We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 2

Interplay of Epigenetics with Gynecological Cancer

Coralia Bleotu, Demetra Socolov, Mariana Anton, Anca Botezatu, Adriana Plesa, Iulia Virginia Iancu, Lorelei Irina Brasoveanu, Gabriela Anton and Carmen Cristina Diaconu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61032

Abstract

Recent data on the cell deregulation that occurs during the progression to cancer underlines the cooperation between genetic and epigenetic alterations leading to a malignant phenotype. Unlike genetic alterations, the epigenetic changes do not affect the DNA sequence of the genes, but determine the regulation of gene expression acting upon the genome. Moreover, unlike genetic changes, epigenetic ones are reversible, making them therapeutic targets in various conditions in general and in cancer disease in particular. The term *epigenetics* includes a series of covalent modifications that regulate the methylation pattern of DNA and posttranslational modifications of histones. Gene expression can also be regulated at the posttranscriptional level by microRNAs (miRNAs), a family of small noncoding RNAs that inhibit the translation of mRNA to protein. miRNAs can act as 'oncomiRs', as tumor suppressors, or both. In this chapter, we will (1) summarize the current literature on the key processes responsible for epigenetic regulation: DNA methylation, histone modifications and posttranscriptional gene regulation by miRNAs; (2) evaluate aberrant epigenetic modifications as essential players in cancer progression; (3) establish the roles of microenvironment-mediated epigenetic perturbations in the development of gynecological neoplasia; (4) evaluate epigenetic factors involved in drug resistance.

Keywords: Epigenetic, biomarker, gynecological cancer

1. Introduction

1.1. Key processes responsible for epigenetic regulation

Epigenetics could be broadly defined as the sum of cellular and physiological trait variations that are not caused by changes in the DNA sequence. Epigenetic mechanisms are essential for

INTECH
open science | open minds

© 2016 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

the normal development and maintenance of tissue-specific gene expression patterns in mammals. Disruption of epigenetic processes can lead to altered gene function resulting in imprinting disorders, developmental abnormalities and cancer. The epigenetic mechanisms that will be presented in this chapter are (1) DNA methylation, (2) chromatin and histone modifications, and (3) regulatory noncoding RNAs.

1.1.1. DNA methylation

DNA methylation is a biochemical process characterized by the addition of a methyl group especially at the C5 position of cytosine from CpG dinucleotides and is accomplished by two classes of DNA methyltransferases involved in maintenance and *de novo* methylation [1]. CpG dinucleotides are not randomly distributed across the human genome but are found in short CpG-rich DNA sequences called 'CpG islands.' CpG islands are found in regions of large repetitive sequences (e.g. centromeric repeats, retrotransposon elements, rDNA) [2, 3] and in 60% of human gene promoters [4]. Some CpG islands are methylated, whereas the majority of them usually remain unmethylated during development and in differentiated tissues [5]. CpG islands' promoters become methylated during development (imprinted genes, chromosome X inactivation) [2]. Another role of CpG island methylation is to silence noncoding DNA and transposable DNA elements to prevent chromosomal instability by heavy methylation of repetitive sequences [5]. DNA methylation leads to gene silencing by either preventing or promoting the recruitment of regulatory proteins to DNA. Methylation of CpG islands can block the access of transcription factors to the transcription sites [6, 7], or by recruiting methyl-binding domain proteins (MBDs), which can mediate gene repression through interactions with histone deacetylases (HDACs) [8, 9]. This epigenetic modification does not change the DNA sequence, but enhances the stability and chromosome integrity and promotes genome organization into transcriptionally active or silenced regions. DNA methylation at the whole genome level provides a specific global methylation pattern [2, 10] that plays an important role in regulating gene expression (e.g. development and cell-specific gene expression) in association with chromatin-associated proteins. The maintenance of a cell-specific methylation pattern after every cellular DNA replication cycle provides a stable gene-silencing mechanism that plays an important role in regulating gene expression. The maintenance methyltransferase DNMT1 is responsible for copying DNA methylation patterns to the daughter strands during DNA replication, whereas DNMT3a and DNMT3b are *de novo* methyltransferases that establish the methylation patterns early in development [11]. DNMT3L, a homologous protein to other DNMT3s, increases the ability of DNM3a and 3b to bind to DNA, stimulating their activity. Some problems in the establishment of methylation biomarkers in gynecologic cancers, especially in cervical cancer [12], come from the fact that: (1) the extent of methylation across the various CpG sites in a promoter can be rather heterogeneous and consequently, the assay outcome is likely to be influenced by the region of CpGs that is targeted; (2) the distinct levels of background methylation due to differences in cell type composition between cervical tissue samples that can contain substantial amounts of nonepithelial (stromal) cells and cervical scrapings that are enriched in superficial epithelial cells. For this reason, the methylation results obtained from tissue samples may not be directly extrapolated to cervical scrapings [13]. In addition, while the methylation of tumor suppressor' promoters is an early and

frequent alteration in carcinogenesis [14] and, on the other hand, is widespread in the human genome, only a subset of affected loci play critical roles in tumorigenesis [15]. CpG hypermethylation is gene- and cancer type–specific [16, 17, 18, 19], providing a useful signature for tumor diagnosis and prognosis [18] that must be established accurately.

1.1.2. Covalent histone modifications

Mammalian genome represents a highly structured complex comprised of compacted DNA and proteins that can adopt different three-dimensional conformations dependent of nuclear context and biochemical changes present in the genome and at the histone level [20]. At first glance, the chromatin is present in two forms: transcriptionally active euchromatin and more condensed and transcriptionally inactive heterochromatin. In the genome, there are some structural regions (such as centromeres) containing constitutive heterochromatin; others may go through an open conformation to a compact one—optional heterochromatin. These transitions, vital to the establishment of necessary transcriptional various models of embryonic development, growth, and adult life, are under epigenetic control. Nucleosomes form the repetitive fundamental units of the chromatin and are designed to pack the huge eukaryotic genome in the nucleus (mammalian cells contain approximately 2 m of linear DNA wrapped in a core size of 10 μm in diameter) [20]. The nucleosomes in turn are compacted and form the chromosomes. The nucleosomal core consists of approximately 147 base pairs wrapped around a histone octamer made up of two copies of the histones H2A, H2B, H3, and H4. Histone H1 (linker histone) and its isoforms are involved in chromatin compaction underlying nucleosome condensation. Decondensed nucleosomes look like a bead wrapping a DNA molecule [21]. Histone covalent modifications (epigenetic changes) represent important regulatory elements that influence chromatin interactions by structural changes either by electrostatic interactions and recruitment of nonhistone proteins [22].

Histones can undergo a variety of posttranslational modifications at the N-terminus (like acetylation, methylation, phosphorylation, sumoylation, ubiquitination, and ADP-ribosylation) that can alter the DNA–histone interaction, with a major impact on chromatin structure and key cellular processes such as transcription, replication, and repair [20]. The histone code may be transient or stable. The mechanism of inheritance of this histone code is not fully understood. The patterns of histone modifications are specific to each cell type and play a key role in determining cellular identity [23, 24]. In contrast with stem cells, differentiated cells acquire a more rigid chromatin structure, which is important for maintaining cell specialization [23]. Epigenetic regulation mediated by histone modification is a dynamic process. Lysine residue methylation using histone methyltransferase (HMT) is correlated either with transcriptional activation or repression, whereas lysine acetylation correlates with transcriptional activation [25]. Histone methyltransferases (HMTs) and demethylases (HDMs) work in tandem to determine the degree of methylation of the lysine residue [26]. Histone H3 lysine 4 trimethylation (H3K4me3) correlates with euchromatin and gene transcription activation. Histone H3 lysine 27 trimethylation and/or lysine 9 (H3K27me3/H3K9me3) is correlated with the transcriptional repression of heterochromatin and H3K27me3 modification is critical for stem cells; demethylation at this level is correlated with differentiation [27, 28, 29, 30, 31]. These

two modifications represent the main silencing mechanisms in mammalian cells, H3K9me3 working in concert with DNA methylation and H3K27me3 largely working exclusive of DNA methylation [32]. Histone acetylation is one of the histone modifications that have been studied extensively. The two homonymous enzymes that are involved in maintaining a specific profile are histone acetyltransferases (HATs) and histone deacetylases (HDACs) [26]. Generally, the level of histone acetylation correlated with transcriptional activation and deacetylation correlates with transcriptional repression. H3 histone acetylations at lysine 9 (H3K9ac) and lysine 4 to 16 are characteristic euchromatin changes located in regions where genes are actively transcribed. Although histone modifications act mainly by altering the architecture of some modifications (H3K4me3 and H3K9ac) mediates gene regulation by recruiting other proteins involved in chromatin remodeling [33, 34]. Histone modifications and DNA methylation interact with each other at multiple levels to determine gene expression status, chromatin organization, and cellular identity [35]. Several HMTs, including G9a, SUV39H1, and PRMT5, methylate DNA to specific genomic targets recruiting DNA methyltransferases (DNMTs) [36, 37, 38]. In addition, DNMTs may recruit HDACs and methyl-binding proteins to achieve gene silencing and chromatin condensation [8, 9]. DNA methylation can also be established via H3K9 methylation, such as MeCP2, thereby establishing a repressive chromatin state [39]. Recent studies showed that the main chromatin changes that occurs during tumorigenesis are characterized by a global loss of acetylated H4 lysine 16 (H4K16ac) and H4 lysine 20 trimethylation (H4K20me3) [40]. HDACs were found overexpressed in various types of cancer [41, 42] (becoming a major target for epigenetic therapy), along with HATs, whose expression can also be altered in cancer. MOZ, MORF, CBP, and p300 (HATs) may be targets for chromosomal translocations, especially in leukemia [43]. Changes in histone methylation patterns (deregulation of HMTs) are associated with aberrant gene silencing in cancer, and an effective cancer treatment strategy targeting HDMs represents a promising treatment option.

1.2. Posttranscriptional gene regulation by noncoding RNAs

Noncoding RNAs are involved in fundamental processes, such as chromatin dynamics and gene silencing, and their transcripts outnumber the group of protein transcripts. It is well known that the initiation of X-chromosome inactivation is regulated by noncoding RNAs (Xist function) and the noncoding RNAs molecules are also involved in imprinting, suggesting that antisense RNA can induce transcriptional silencing [44, 45, 46]. The characterized noncoding RNA family consists of a large group of small regulatory microRNAs (about 1400 microRNAs in humans) [47].MicroRNAs (miRNAs) are short noncoding RNAs of 20–24 nucleotides that play important roles in virtually all biological pathways in mammals like differentiation and growth control. Based on computer predictions, it was proposed that miRNAs may regulate many cell cycle control genes [48]. miRNAs influence numerous cancer-relevant processes such as proliferation, cell cycle control, apoptosis, differentiation, migration, and metabolism. The key processes of miRNA biogenesis pathways have been characterized. Primary miRNA transcripts are transcribed from separate transcriptional units or embedded within the introns of protein coding genes by RNA polymerase II. Primary miRNA transcripts are processed by a complex formed by RNase III enzyme and Drosha, resulting in a pre-miRNA hairpin that is subsequently exported from the nucleus to the cytoplasm by exportin 5 (XPO5). Further pre-

miRNA molecules are processed by another protein complex, including DICER and TRBP, to produce the single-stranded mature miRNA (ssmiRNA). ssmiRNA is subsequently incorporated in RNA induced silencing complex (RISC), along with key proteins such as AGO2 and GW182. The role of mature miRNA (as part of the RISC) is to induce posttranscriptional gene silencing by complementary sequence motifs to the target mRNAs predominantly found within the 3′ untranslated regions (UTRs) [47, 49, 50]. One specific miRNA may target up to several hundred mRNAs; therefore, a miRNA may silence various genes while a specific mRNA may be targeted by several miRNAs. Aberrant miRNA expression may interfere with gene transcription and influence cancer-related signaling pathways [51, 52, 53].New data are added to decipher the role of miRNAs in normal physiology and pathology. Several microarray expression studies performed on a wide spectrum of cancer types have proved that deregulated miRNAs expression is the rule rather than the exception in cancer [54, 55, 56, 57]. Animal models featuring miRNA overexpression or knock-down have demonstrated the relation between miRNAs and cancer development, thus proposing miRNAs as potential biomarkers and putative therapeutic targets [58]. In addition, since miRNAs were discovered, many researchers focused their interest on identifying miRNAs generated by viruses. Several data support this hypothesis mainly based on miRNA size, which allows them to avoid the immune system but also to be supported by the small size of viral genome. It is not unexpected that many miRNAs encoded by viruses have been discovered, most of them transcribed from double-stranded DNA viruses [59]. miRNAs can regulate the expression of viral genes that are involved in controlling viral replication. It is supposed that these miRNAs might influence viral gene expression in a differentiation-dependent manner by targeting viral transcripts. On the other hand, different hrHPV types have different oncogenic potentials, viral miRNA being considered one of the factors involved in oncogenic regulation; some conserved miRNAs are involved in the switch from HPV productive to transforming infections.

2. Evaluation of aberrant epigenetic modifications as essential players in cancer progression

Normally, evolution and morphological state of genital organs are in close interdependence with hormonal status that is different in different periods: childhood, sexual maturity, climacterium, and menopause. On the other hand, there is an increasing interest in the identification of diagnostic biomarkers and biomarkers able to predict both response to treatment and survival. For an optimal planning of therapeutic strategy in high-risk patients, a close association between biological variables and (epi)genetic profiles associated with aggressive clinical behavior could be useful. Therefore, many cellular changes should be analysed in this context.

Benign tumors of the vulva can be developed from epithelial components (papillomas and warts) mezenchimatos tissue (fibroma, leiomyoma, lipoma, hemangioma, and lymphangioma), and local glands (Bartholin gland cysts or cysts of sweat glands). *Vulvar cancer* is a rare malignant disease accounting for less than 5% of gynecological malignancies [60, 61, 62]. The most common vulvar cancers are epidermoid carcinoma and rarely adenocarcinomas that are

developed in the Bartholin glands or sweat glands. Approximately 20%–40% of vulvar squamous carcinomas are often associated with papilloma virus infection [60 - 66] and are more frequent in young people. Non-HPV vulvar cancers occur in the elderly and are associated with somatic mutations, especially in TP53 [60 - 63, 65, 66]. Tumors harbouring a mutation have a worse prognosis than vulvar squamous cancers without (epi)genetic changes [67 - 70]. However, allelic imbalances seem to occur in both groups and the cumulative number of epigenetic changes increases from dysplasia to cancer [71]. The data with respect to epigenetic changes in vulvar cancer progression is limited to a few articles on DNA hypermethylation but not to chromatin remodeling or histone modifications. This data is presented in Table 1. Hypermethylation seems to be more frequent in vulvar squamous cancers than in vulvar intraepithelial neoplasia, but more studies are needed. Taking into account the existence of two etiological categories of vulvar carcinomas (related or not to HPV), the miRNA signature in these two types of vulvar carcinomas were evaluated [72]. Some miRNAs had lower expression in HPV-positive tumors (miR-1291, miR-342-3p, miR-193a-5p, miR-29c#-, miR-106b#, miR-22#, miR-365, miR-151-5P, miR-144#, miR-125b-1#, miR-519b-3p, miR-26b, miR-19b-1, and miR-1254) and other microRNAs had higher expression in HPV-positive tumors (miR-1274B, miR-142-3p, miR-21, miR-708, miR-16, miR-660, miR-29c, miR-1267, miR-454, and miR-186) [72]. In HPV-negative samples, we observed an association between lymph node metastases with decreased expression of miR-223-5p and miR-19b-1-5p, vascular invasion with decreased expression of miR-100-3p and miR-19b-5p-1, and advanced tumor staging (FIGO IIIA, IIIB, and IIIC) with expression of microRNAs miR-519b-1-5p and miR-133a. In addition, de Melo Maia and collaborators (2013) built a network between miRNA expression profiles and putative target mRNAs (TP53, RB, PTEN, and EGFR) based on prediction algorithms, demonstrating that the evaluated miRNAs can be involved in vulvar cancer progression, thereby providing biomarkers for the establishment of prognostic and predictive values of response to novel targeting therapies in vulvar cancer [72].

The vagina is a fibromuscular tubular organ, which histologically consists of three layers of tissue: (1) an outer layer consisting of fibro-elastic connective tissue; (2) vaginal muscles with a longitudinal outer layer and an inner layer of fibers circularly arranged in a spiral; and (3) Malpighian mucosa, covered by squamous epithelium. The vaginal epithelium undergoes changes in relation to the period of the woman's life and depending on hormonal stimulus. Histological changes are reflected in vaginal cytology. Vaginal epithelium responds to ovarian stimuli through proliferation, differentiation and desquamation. Thus, in adult women, under the action of estrogen during the proliferative phase, vaginal mucosa proliferates and differentiates morphologically and functionally, and later, during the luteal phase, under the action of progesterone, superficial cell layer desquamation occurs. The action of estrogen on the vaginal mucosa is exercised on the epithelium as well as on the subjacent stroma.

Vaginal cancer is also a rare malignancy, accounting for about 2%–3% of all gynecologic cancers [73, 74]. The squamous cell carcinomas (SCC) are more frequent (80%–90%) than adenocarcinomas. If the risk factors linked to vaginal squamous cell carcinoma are smoking, immunosuppression, high number of sexual partners, papillomavirus and history of cervical precancerous and cancerous lesions [75, 76, 77], in the case of the vaginal adenocarcinomas,

particularly clear cell adenocarcinomas, exposure to an antiabortive drug diethylstilbestrol (DES) was incriminated [78, 79, 80]. On the other hand, if squamous vaginal cancer tends to occur more commonly in the proximal third of the vagina, especially the posterior vaginal wall, the adenocarcinomas are mostly seen in the anterior upper vaginal wall [74]. Human papillomaviruses have been also linked to vaginal cancers, HPV prevalence in 2/3 lesions of vaginal intraepithelial neoplasia and invasive vaginal cancer being over 90% and 70%, respectively [81, 82]. The HPV oncogenic transformation has been associated with high levels of E6 and E7 viral oncoproteins in the epithelia that can be achieved by two mechanisms: (1) increased production of E6 and E7 after the loss of E2 (the normal regulator of E6 and E7 expression) during viral integration [83]; (2) methylation of the E2-binding sites (E2BS) in the viral LCR in the region close to the early promoter that could inhibit E6 and E7 transcription [84]. Therefore, HPV16-related integration, methylation in E2BS3 and 4, and viral load may represent different viral characteristics driving vaginal and vulvar carcinogenesis [85].The adverse health outcomes induced by DES exposure during fetal development include infertility, early menopause, and breast cancer, along with a rare form of vaginal adenocarcinoma in adolescent girls [86, 87]. While animal models show an association of early exposure to estrogens with the expression levels of several genes [88, 89, 90] and epigenetic changes, including DNA methylation and histone modifications [91, 92, 93], the first study that evaluates the possible effects of *in utero* DES exposure on genome wide DNA methylation in humans cannot find evidence of large persistent effects of *in utero* DES exposure on blood DNA methylation [94].

The uterus is a hollow organ, in which the product of conception is developed. It consists of three parts: body, isthmus, and cervix. The corpus presents a mucosa (endometrium), muscular wall (myometrium), and serous peritoneal surface. The endometrium is a specialized tissue, particularly receptive to the influence of sex hormones that differs from a histological point of view at prepubertal periods, sexual maturity, and menopause. Also, the uterine mucosa is in constant transformation during menstrual cycles, sexual maturity, growth processes, functional maturation, and regression. Similar risk factors for endometrial cancers were incriminated: adult obesity [95], first-degree family history of endometrial cancer, or colorectal cancer [96]. Nulliparity and infertility appeared to independently contribute to endometrial cancer risk [97]. The endometrium is extremely sensitive to hormones, the estrogen and progesterone being two key regulators of proliferation and differentiation in reproductive tissues [98]. The two isoforms of the progesterone receptor, PRA and PRB, required for endometrial differentiation [99], are generated by alternative transcription and translation from the same gene with the addition of 164 amino acids in the N-terminus sequences of PRB [98] that makes them functionally different [99]. A shift in the estrogen–progesterone balance is the major cause for the development of endometrial cancer [100]. Progesterone is an important inducer of endometrial differentiation and an inhibitor of tumorigenesis because the addition of progestin (synthetic progesterone) can prevent endometrial cancer induced by an excess of estrogens from endogenous sources (e.g., adipose tissue storage of estrogen and with polycystic ovarian syndrome) or from exogenous sources in therapeutic administration [100]. While progestin therapy achieves promising outcomes with early stage endometrial cancer, advanced and recurrent disease has only minor effects. This is due to the fact that in advanced endometrial

cancer, the progesterone receptor is lost but it has been demonstrated that reestablishing progesterone signaling in these cells can inhibit endometrial cancer cell proliferation and invasion and increase sensitivity to apoptotic stimuli [100]. The epigenetic restoration of progesterone receptor expression could result in resensitization of endometrial tumors to progestin therapy. The functional role of epigenetic factors in endometrial cancer development began to be evaluated. A study by Jones and collaborators (2013) emphasizes the role of HAND2 hypermethylation, which is a key step in endometrial carcinogenesis [101]. HAND2 is a basic helix-loop-helix transcription factor and developmental regulator [102], expressed in the normal endometrial stroma. The physiological function of HAND2 is to suppress the production of fibroblast growth factors that mediate the paracrine mitogenic effects of estrogen on the endometrial epithelium [103]. HAND2 is under progesterone regulation [104, 105], entering in the progesterone-mediated suppression of estrogen-induced pathways. Consequently, the methylation of HAND2 is able to predict the response to progesterone [101]. HAND2 methylation is the most common molecular alteration in endometrial cancer and, on the other hand, is an early event in endometrial carcinogenesis that makes it a sensitive test to correctly identify endometrial cancer patients amongst those women who present with postmenopausal bleeding [101].

Histologically, *the cervix* shows mucosa, muscle wall, and the peritoneal serosa. The mucosa of the cervix has an exocervical portion (covered by squamous epithelium, nonkeratinized) and one endocervical (covered by a single-layered cylindrical epithelium, mucus secreting, which contains a small number of ciliated cells, basal stem cells and racemic, tubular, or branched type glands). Cancer of the uterine cervix is the major cause of death from gynecological cancers and in over 90% of cases is associated with high-risk human papilloma virus (hrHPV). Etiological factors include cigarette smoking, impairment of cell-mediated immunity, and long-term estrogen–progestin use [106, 107, 108]. But the main etiological factor of squamous cell carcinoma (that accounts for about 80% of the cases) as well as adenocarcinoma are human papilloma virus infections [109]. The role of other sexually transmitted infections (*Chlamydia trachomatis* and herpes simplex virus) is still unclear [108, 110].In cervical cancer, tumorigenesis of both squamous cell carcinoma and adenocarcinoma is HPV-related [109]. The transforming potential of E6 and E7 viral oncoproteins is based on their numerous actions on cellular proteins, mainly on p53 and pRB tumor suppressors, which are degraded and inactivated, respectively. In addition to the already reported genomic alterations in cervical cancer development by hrHPV, many studies underline the involvement of epigenetic alteration in host cell genes or at the levels of RNA. In order to find some diagnostic and prognostic biomarkers, the methylation of host cell genes and methylation of viral genes were evaluated [12]. The CpG hypermethylation of promoters of tumor suppressor genes, an early and frequent alteration in carcinogenesis, affects all important pathways: cell adhesion (cell adhesion molecule 1 (CADM1)) [13], E-cadherin [111, 112], apoptosis (DAPK, a proapoptotic serine/threonine kinase [113, 114]), cell cycle (cyclin A1 methylation [114, 115]), fragile histidine triad (FHIT) [116], cell signaling pathways (retinoic acid receptor [117], Ras association domain family 1 isoform A (RASSF1) [118]), Wnt/β catenin pathway (adenomatous polyposis coli (APC) [119] and PTEN [120]), p53 signaling pathway (p73 [121]), and DNA repair (O6 methylguanine DNA methyltransferase (MGMT) [113, 122]).For cervical scrapings, some

methylation marker panels of host genes, with sensitivities of over 80% for CIN3+ were evaluated: SOX1/PAX1, SOX1/LMX1A, SOX1/NKX6-1, PAX1/LMX1A; PAX1/NKX6-1, LMX1A/NKX6-1 [123], JAM3/EPB41L3/TERT/C13ORF18 [124], and CADM1/MAL [13, 125], etc. Host gene methylation analysis might be an alternative for hrHPV DNA detection because aberrant methylation can be detected in cervical smears up to 7 years prior to the diagnosis of cervical cancer [126]. On the other hand, for methylation analysis, cervical scrape samples as well as self-collected cervico-vaginal lavage samples can be used [127].As accurate predictor tests, the measurement of DNA methylation in HPV genomes, in certain early (E) and late (L) open reading frames (ORF) as well as in parts of the upstream regulatory region (URR), may have diagnostic value. The hypermethylation in the L1 region was a common feature of cervical cancer but not of CIN induced by HPV16 [128], or HPV18 [129]. But the DNA methylation on multiple CG sites in the L1, L2, E2, and E4 ORFs were significantly associated with CIN2+ after accounting for multiple testing [130]. Some studies have contradictory results because most were quite small and heterogeneous and did not always include (1) comparable sets of specimens (cancer, high-grade CIN, cell lines), (2) exactly the same CG sites, or (3) the same methodology [12]. Overall, as cervical cancer prevention moves to DNA testing methods, DNA-based biomarkers, such as HPV methylation could serve as a reflex strategy to identify women at high risk for cervical cancer [131], but the region with the best predictive value must be established.In addition to the already reported genomic alterations in cervical cancer development by hrHPV, many studies underline the involvement of viral or cellular miRNAs, mainly based on the fact that some RNA micromolecules target transcriptional factors that modulate both cellular and viral gene expression [132, 133].In HPV infection, E6 decreases miR-34a [132, 134], which is a target of p53, thus the effect of E6 on miRNA-34a is mediated by decreased p53 [132,134]. On the other hand, one of the targets of miR-34a is p18Ink4c [135], an inhibitor of CDK4/6 that promotes the cell cycle. E7 decreases miR-203 during keratinocyte differentiation, which is a tumor suppressor and thus increases carcinogenesis [136] through an increase of cell survival targeting antiapoptotic protein bcl-w [137], induction of G1 cell cycle arrest targeting survivin [138], inhibition of migration and invasion targeting LIM and SH3 protein [139]. E7 upregulates miR-15a, miR-15b, and miR-15b through E2F1 and E2F3 [140, 141] and in turn, these miR decrease cyclin E1, leading to cell cycle arrest [142]. A lot of other miRs are upregulated or decreased by virus oncogenes inducing changes in cellular signaling pathways, some of these have not yet been elucidated [143].

Ovaries, paired organs, constitute the female sexual gland with endocrine lunette and also produce ova. The ovary is covered by germinal epithelium (formed from cuboid or cylindrical cells) and subjacent is a thin layer of dense connective tissue. The ovary presents a cortical area (comprised of follicles, corpus luteum, and stroma) and a medulla. Starting from puberty till menopause, there is a growth and maturation of one ovarian follicle during each menstrual cycle and the formation of one corpus luteum after rupture of the follicle and oocyte removal. If the egg is not fertilized, the corpus luteum regresses, undergoes progressive sclerosis forming a hyaline. If the egg is fertilized, the corpus luteum becomes more voluminous and luteal cells increase, constituting the corpus luteum of pregnancy. Ovarian stroma is formed from fibroblastic and mesenchymal cells. Stromal cells present both characters of connective cells and steroid activity (secreting androgens and estrogens). Ovarian medulla consists of lax

connective tissue containing blood and lymph vessels, nerves, and embryonic elements. The growth and development of the follicle during the ovarian cycle are driven by two gonadotrophic hormones, secreted by the anterior pituitary: follicle-stimulating hormone (FSH) and luteinising hormone (LH). Both FSH and LH are under the control of gonadotrophin-releasing hormone (GnRH) secreted by the hypothalamus through negative feedback carried out by estrogens that are secreted by thecal cells of the follicle.

Ovarian cancer ranks second after cervical cancer worldwide. On the other hand, ovarian cancer is in seventh place in terms of incidence among malignant tumors in women and eighth with respect to death due to malignant tumors in women worldwide [144]. If approximately 90% of ovarian cancers arise from epithelial cells, 3% are from germ cells and 7% from granulosa-theca cells. Ovarian cancer comprises different types of tumors with widely differing clinicopathologic features and behaviors. Based on clinicopathologic and molecular genetic studies, two histologic types of epithelial ovarian serous carcinomas were established: low-grade serous carcinomas (LGSCs) and high-grade serous carcinomas (HGSCs) [145]. Although they are developed independently along different molecular pathways, both types develop from fallopian tube epithelium and involve the ovary secondarily. Type I tumors (LGSCs) are comprised of low-grade serous, low-grade endometrioid, mucinous, and clear cell carcinomas; typically present as large cystic masses confined to one ovary; have a relatively indolent course; and are relatively genetically stable being associated with mutations in KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A, and PPP2R1A [146, 147] that perturb signaling pathways. Type II tumors (HGSCs) are composed of high-grade serous, high-grade endometrioid, undifferentiated carcinomas and malignant-mixed mesodermal tumors; clinically aggressive and typically present at an advanced stage, which contributes to their high fatality [148]; at the time of diagnosis, they demonstrate marked chromosomal aberrations but over the course of the disease these changes remain relatively stable [149]; approximately 60% of HGSC have the fallopian tube as the origin of serous tumors [150], because the expression profiles of ovarian HGSCs more closely resemble fallopian tube epithelium than the ovarian surface epithelium [151]; they harbor TP53 mutations in over 95% of cases [152, 153], but rarely harbor the mutations detected in the low-grade serous tumors; another possible origin of HGSC is from inclusion cysts through a process of implantation of tubal (müllerian-type) tissue rather than by a process of metaplasia from ovarian surface epithelium (mesothelial). Hypermethylation has been found to be associated with the inactivation of almost every pathway involved in ovarian cancer development, including DNA repair, cell cycle regulation, apoptosis, cell adherence, and detoxification pathways [154]. Complete or partial inactivation of the BRCA1 gene through hypermethylation of its promoter has been reported in 15% of sporadic ovarian tumors [155, 156], 31% of carcinomas but not in the benign or borderline tumors [157], or in the hereditary type of the disease, nor in samples from women with a germ line BRCA1 mutation [158, 159]. On the other hand, hypermethylation of BRCA1 was detected at a significantly higher frequency in serous carcinomas than in tumors of the other histological types [160]. The homeobox genes (HOX), a family of transcription factors that function during embryonic development and control pattern formation, differentiation, and proliferation [161] was associated with ovarian cancers [162]. In addition, based on the high percentage of methylation of the HOXA9 gene observed in 95% of patients with high-grade serous ovarian

carcinoma [163, 164], it has been suggested that the methylation status of HOXA9 and HOXAD11 genes may serve as potential diagnostic and prognostic biomarkers [163,164]. Some other genes found hypomethylated were associated with progression towards cancer: LINE-1 elements [165], SNGG (synucelin-γ), encoding an activator of the MAPK and Elk-1 signaling cascades [166, 167], etc. Overall, DNA hypomethylation may promote tumorigenesis by transcriptional activation of proto-oncogenes and on the other hand loss of imprinting or genomic instability. DNA hypermethylation predisposes to gene mutation because the methylated cytosines are often deaminated and converted to thymine leading to inactivation of tumor suppressor genes. However, these phenomena deregulate the main functions of gynecological cancer cells (Figure 1 and Table 1).

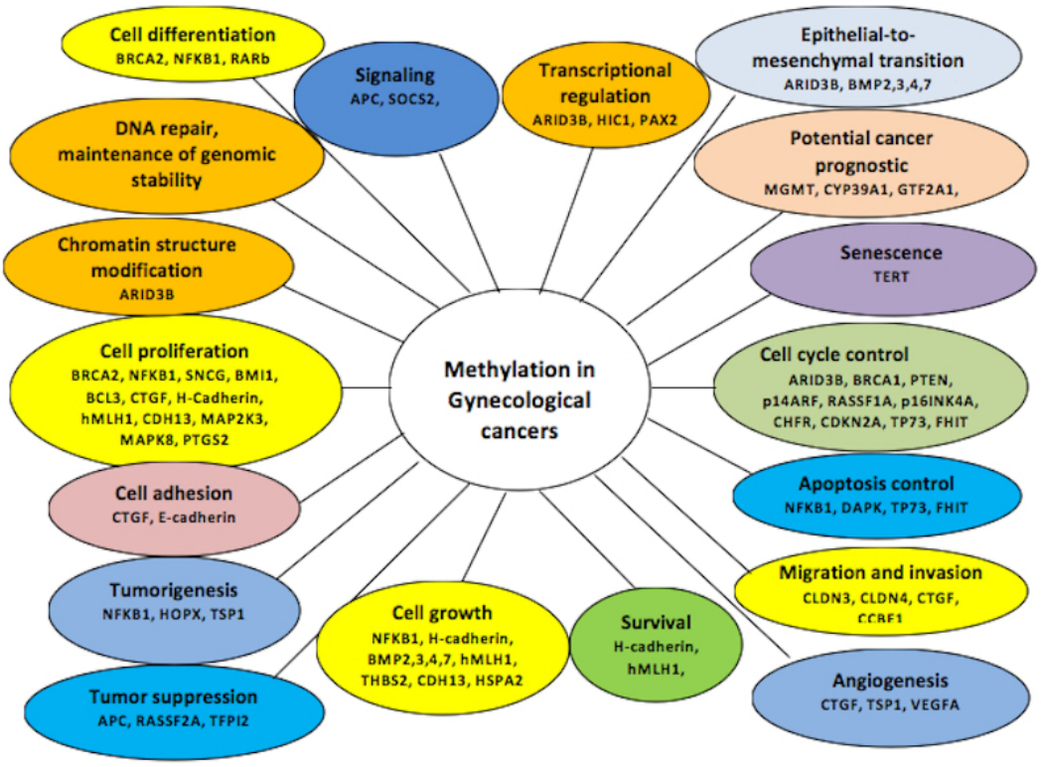

Figure 1. Biological functions influenced by alterations of DNA methylation in gynecological cancers.

	Genes	Functions	Expression change	Epigenetic regulation	References
Ovarian cancer	*BRCA2*	Cell proliferation and differentiation	Overexpression	Hypomethylation	168, 169
	CLDN3;CLDN4	Migration and invasion	Overexpression	DNA hypomethylation, H3 acetylation; Loss of repressive histone modifications	170, 171, 172

Genes	Functions	Expression change	Epigenetic regulation	References
HOXA10 *HOXA11*	Fertility, embryo viability, regulation of hematopoietic lineage commitment; regulation of uterine development and is required for female fertility	Overexpression	DNA hypomethylation/ hypermethylation	164, 173, 174, 175
MAL	Formation, stabilization and maintenance of glycosphingolipid-enriched membrane microdomains	Overexpression	Hypomethylation	176
NFKB1	Cell proliferation; Inflammation, immunity, differentiation, cell growth, tumorigenesis, and apoptosis	Overexpression	miR-9 downregulation	177
SNCG	Cell proliferation	Overexpression	DNA hypomethylation	167
BMI1	Cell proliferation	Overexpression	miR-15a and miR-16 down regulation	178
TUBB3	Taxane drug resistance	Overexpression	DNA hypomethylation, chromatin acetylation	179
ARID3B	Epithelial-to-mesenchymal transition; Embryonic patterning, cell lineage gene regulation, cell cycle control, transcriptional regulation and possibly in chromatin structure modification	Overexpression	miR-125a downregulation via EGFR signaling	180
BCL3	Cell proliferation, tumorigenesis	Overexpression	miR-125b downregulation	181
BRCA1	DNA repair, cell cycle checkpoint control, and maintenance of genomic stability	Overexpression	Hypermethylation	182
PTEN, *p14ARF*	Cell cycle regulation	Overexpression	Hypermethylation	182
DAPK	Regulator of programmed cell death	Overexpression	Hypermethylation	182
RASSF1A	Negative regulator of cell proliferation through inhibition of G1/S-phase progression	Overexpression	Hypermethylation	159,182, 183
p16INK4A	Cell cycle regulation	Overexpression	Hypermethylation	183
APC	Tumor suppression by antagonizing the WNT.	Overexpression	Hypermethylation	159, 183

http://dx.doi.org/10.5772/61032

	Genes	Functions	Expression change	Epigenetic regulation	References
	CTGF	Cell adhesion, migration, proliferation, angiogenesis	Overexpression	Hypermethylation	184
	CCBE1	Extracellular matrix remodeling and migration	Overexpression	Hypermethylation	185
	HIC1	Transcription factor	Overexpression	Hypermethylation	159
	RARb	Cell differentiation	Overexpression	Hypermethylation	183
	E-cadherin	Cell adhesion		Hypermethylation	183
	H-cadherin	Regulation of cell growth, survival and proliferation	Overexpression	Hypermethylation	183
	hMLH1	Regulation of cell growth, survival and proliferation DNA mismatch repair	Overexpression	Hypermethylation	186, 187, 188
	GSTP1	Detoxification	Overexpression	Hypermethylation	189
	MGMT	Potential prognostic cancer	Overexpression	Hypermethylation	187,188
	CYP39A1	Potential prognostic cancer	Overexpression	Hypermethylation	190
	GTF2A1, FOXD4L4, EBP	Potential prognostic cancer	Overexpression	Hypermethylation	190
	HAAO	Potential prognostic cancer	Overexpression	Hypermethylation	190
Endometrial cancer	*BMP2,3,4,7*	Cell growth and EMT	Overexpression	Hypomethylation	191
	SOX4	Prognosis	Overexpression	miR-129-2 downregulation by DNA hypermethylation	192
	hMLH1	Regulation of cell growth, survival and proliferation; DNA mismatch repair		Hypermethylation	193, 194
	RASSF1A	Negative regulator of cell proliferation through inhibition of G1/S-phase progression		Hypermethylation	195, 196, 197
	CHFR	Regulates progression of the cell cycle		Hypermethylation	198, 199
	APC	Signaling and intracellular adhesion		Hypermethylation	200
	THBS2	Inhibitor of tumor growth and angiogenesis		Hypermethylation	201
	p16INK4A	Cell cycle regulation		Hypermethylation	202
	PTEN	Cell cycle regulation		Hypermethylation	203

	Genes	Functions	Expression change	Epigenetic regulation	References
	PER1	Cells circadian rhythms maintenance; cancer development		Hypermethylation	204
	HOPX	Tumorigenesis		Hypermethylation	205
	CDH13	Regulation of cell growth, survival and proliferation		Hypermethylation	206
	HSPA2, MLH1	Regulation of cell growth		Hypermethylation	206
	SOCS2	Cytokine-inducible negative regulators of cytokine signaling		Hypermethylation	206
	PAX2	Transcriptional factor		Hypomethylation	207
Vulvar cancer	*CDKN2A*	Cell cycle regulation		Hypermethylation	208, 209
	MGMT	Potential prognostic cancer		Hypermethylation	210
	RASSF2A	Tumor suppressor gene		Hypermethylation	210
	RASSF1A	Negative regulator of cell proliferation through inhibition of G1/S-phase progression		Hypermethylation	210
	TERT	Cellular senescence		Hypermethylation	209
	TSP1	Platelet aggregation, angiogenesis, and tumorigenesis		Hypermethylation	210
	TFPI2	Tumor suppressor gene		Hypermethylation	209
	TP73, FHIT	Cell cycle regulation; apoptosis		Hypermethylation	211
	TSLC-1			Hypermethylation	212
Cervical cancer	*CAGE*	RNA processing	Overexpression	Hypomethylation	213
	MAP2K3	Cell proliferation	Overexpression	miR-214 downregulation	177
	MAPK8	Cell proliferation	Overexpression	miR-214 downregulation	177
	PTGS2	Cell proliferation, migration, invasion	Overexpression	miR-101 downregulation	214
	SERPINH1	Metastasis	Overexpression	miR-29a downregulation	215
	VEGFA	Tumor growth, angiogenesis	Overexpression	miR-203 downregulation by DNA hypermethylation	216

Table 1. Altered DNA methylation in gynecological cancer

http://dx.doi.org/10.5772/61032

miRNA as key players in cell fate decisions are strongly linked to gynecological cancer. But, although the methods to discover miRNA were improved, research is still in progress. Some of these miRNA that have been associated with gynecologic cancers are shown in Figure 2 and Table 2.

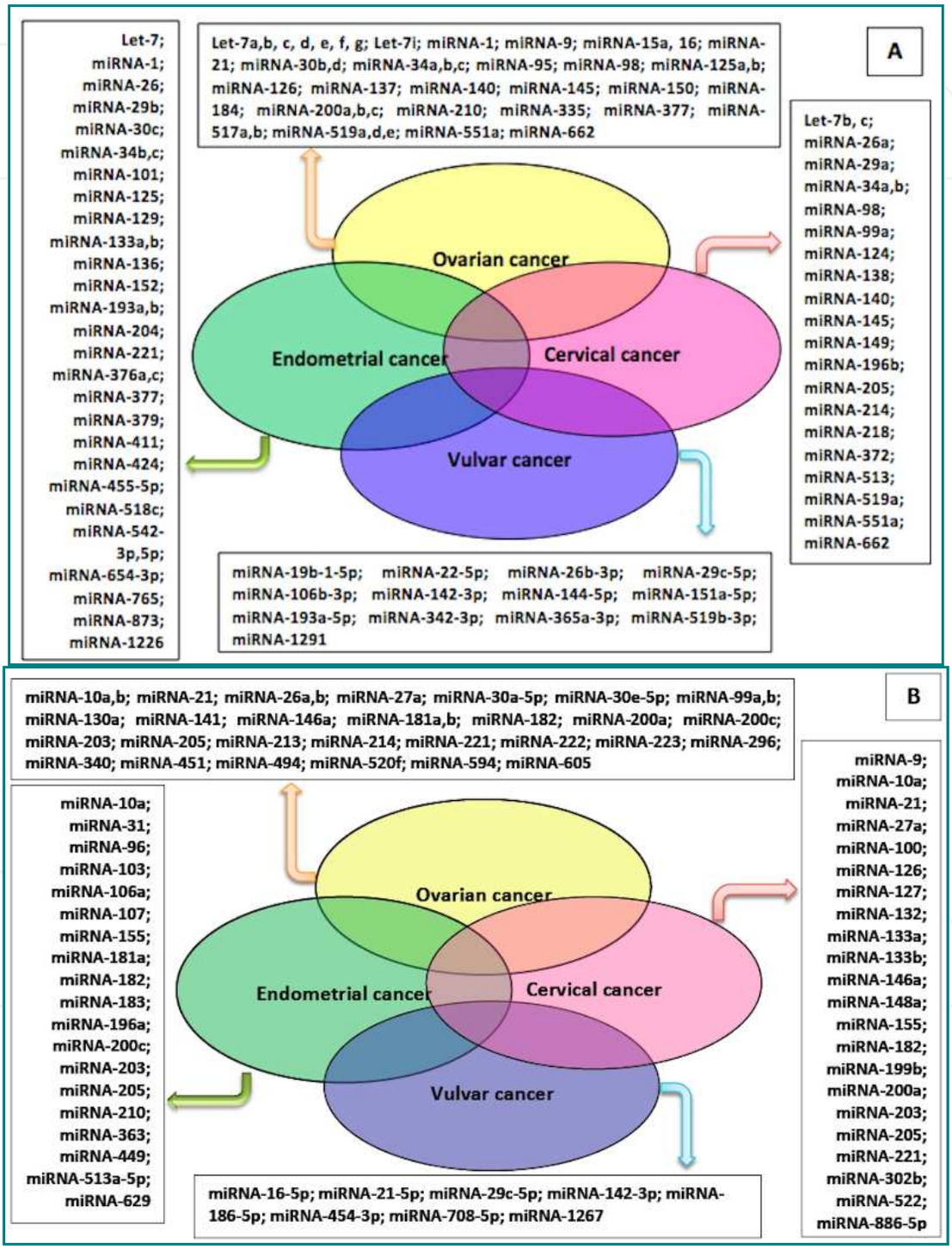

Figure 2. Venn diagram showing dysregulated miRNAs in gynecological cancers. (A) miRNAs downregulated, (B) miRNAs upregulated. Common miRNAs dysregulated signature between ovarian and other cancers are shown in red.

Specific miRNAs have effects on various molecular pathways, and specific miRNA expression signatures in gynecological cancers can be associated with diagnosis, prognosis, and therapy response. miRNAs can regulate a large number of target genes and Table 2 lists the estimated targets.

	miRNA(s)	Expression (Up/ downregulated)	Estimated target(s)	References
Ovarian cancer	Let-7a,b, c, d, e, f, g	Down	c-Myc, KRAS, HMGA2, IL-6, LIN28B, HIC2	217, 218
	Let-7i	Down	HMGA2, LIN28Bm TRIM71,IGF2BP1	219
	1	Down	FOXP1, HDAC4 c-Met, Pim1, HAND2	220
	9	Down	NF-kB, Bcl2, Bcl6, FGF, b-Raf	220, 221
	15a, 16	Down	BMI1	178
	21	Down	PTEN	222
	30b,d	Down	Unknown	223, 224
	34a,b,c	Down	SIRT1, MYC, NOTCH, BCL2, CCND1,WNT3	222, 223, 225
	95	Down	AIB1, GNAI2	226
	98	Down	HMGA2, LIN28B, HIC2	223
	125a, b	Down	ARID3B, LIN28b, Akt3, ETS1ARID3B, RBB2, ERBB3, TNFa, BMPR1B	223, 227, 228
	126	Down	SPRED1, PIK3R2, RGS4, RGS5, PI3K	229
	137	Down	CDK6, MITF, KLF12, PDLIM3	2
	140	Down	c-SRK, MMP13, FGF2	220,230
	145	Down	MAP3K3, MAP4K4, SOX2, OCT4, KLF4, c-myc	220, 230, 231
	150	Down	c-Myb, MAK9, Akt3, MAP2K4	230
	184	Down	TTK69, K10, Sax(A)	230
	200a,b,c	Down	ZEB1, ZEB2, FN1, PPM1E, EXOC5, GATA4, GATA6, TUBB3, TNC, TGF-b	219 ; 232, 233
	210	Down	E2F3, EFNA3, HoxA1, HoxA9	226, 234, 235, 236
	335	Down	P18SRP, HLF, CALU, MAX, HOXD8, SOX4, JAG1, TNC, c-Met, TNC	223, 228
	377	Down	REST, SOD1	230, 237
	517a, b	Down	CREAP-1, MAPKAPK5, NFKBIE, PTK2B	238
	519a, d,e	Down	FLJ31818, TGFBR2, HuR, EIF2C1, ARID4B, GATA2BD, SUV39H1	223,238, 239

http://dx.doi.org/10.5772/61032

miRNA(s)	Expression (Up/ downregulated)	Estimated target(s)	References
551a	Down	LPHN1, ERBB4, ZFP36	223
662	Down	NEGR1, MKX, CSF3	223
10a,b	Up	USF2, HOXA1, HOXD10, HOXB1, HOXB3, RB1CC1 and ribosomal proteins (enhances translation)	223,237,238, 240
21	Up	PDCD4, RPS7, NCAPG, TPM1, PTEN	222, 224, 228, 229, 238, 240
26a,b	Up	PTEN, IL6, KPNA6, CTDSPL, ITGA5, EZH2	230,237,238
27a	Up	ZBTB10, Myt-1, HMGB2, HOXA2, CYP1B1	226, 242
30a-5p, 30e-5p	Up	Unknown	223
99a,b	Up	SLC6A7, AIFM2, DNPEP, HS3ST2, DOHH	223, 229
130a	Up	MCSF, GAX, HOXA5	243, 244
141	Up	ZEB1, ZEB2	245
146a	Up	BRCA1, BRCA2	246
181a,b	Up	HOXA11, GATA6, NLK, CDX2, TBL1X, DPP6,KLF2	238, 247, 248
182	Up	FoxO3, FoxO1	238, 244, 249
200a	Up	ZEB1, ZEB2	245
200c	Up	TUBB3, ZEB1, ZEB2	245, 250
203	Up	p63, SOCS-3, ABL1, MCEF, ADAMTS6	220, 238
205	Up	ZEB1, ZEB2, E2F1, ERBB3, PKCe, SHIP2	220, 238,251
213	Up	APP, SATB2	252
214	Up	SLC2AB, KSR1, JMJD2B, EZH1, PLXNB3, NARG1, PTEN	226, 244
221	Up	CDKN1B (p27), CDKN1C (p57)	223, 235
222	Up	CDKN1B (p27), CDKN1C (p57)	253
223	Up	SEPT6, MMP9, USF2, KRAS, EGF	224,237, 254
296	Up	LYPLA2, IQSEC2, RNF44, HGS	223, 255
340	Up	PAM, RTN3, PPL, RNF34, ZNF513	252
451	Up	ZBTB10, Myt-1, HMGB2, HOXA2, CYP1B1	226, 242
494, 594	Up	Unknown	223
520f	Up	ZNF443, AK2, NFYA,TCERG1	247
605	Up	VGLL3, PHACTR2, SCAMP1, SEC24D	223, 256

	miRNA(s)	Expression (Up/ downregulated)	Estimated target(s)	References
Endometrial cancer	1	Down	c-Met, TIMP-3, TRIM2, ITGB3, ZNF264	257, 258
	Let-7	Down	KRAS, c-Myc, HMG2A, IL-6, HIC2	229
	26	Down	SMAD1, SOX2, Bcl6, SMAD4, BCL2,KLF4	229
	29b	Down	IGF1, Mcl-1	257
	30c	Down	MYH11, GPRASP2, DDR2, CKS2,C5	250
	34b,c	Down	NOTCH, BCL2, CCND1, WNT3, MYC, SIRT1	257, 259
	101	Down	COX2, EZH2	257
	125	Down	LIN28, ERBB2, ERBB3, Akt3 and ETS1	229
	129-2	Down	SOX4	192
	133a,b	Down	PKM2, Mcl-1,Bcl2l2	257
	136	Down	Rtl1	257
	152	Down	ENPP2, SNCAIP, LTBP4, MLH1,Bcl2l11	259, 260
	193a,b	Down	KIT, RAMP1, TSPYL5, ERBB4, ROBO4, UPA	250, 261
	204	Down	Ezrin, ESR1, CHD5, CAMTA1	261
	221	Down	LMOD, p27Kip1, p57Kip2, c-Kit	260
	376a,c	Down	PRPS1, BMPR2, KLF15,GRIK2	257, 262
	377	Down	ETS1, XIAP, RNF38	257
	379	Down	FOXP2, MTMR2, HLCS,CCNB1	257
	411	Down	MAP3K1, SP2, CDH2, FOXO1, SMAD4,SET	257
	424	Down	CCNE1, CCND1,NFI-A	257
	455-5p	Down	PP1R12A, KDR, SUZ12, FOXN3,PTPRJ	257, 263
	518c	Down	ID-1, HOXA3,HOXC8,RAP1B,ABCG2,HLA-G	245,257
	542-3p,5p	Down	COX-2, HSPG2, ZNF618, CREB5	257, 264
	654-3p	Down	KLF12, SORBS1, WDR26, RNF145, AP1S3	229, 265
	765	Down	KLK4, POU2F2, TIMP3, ADAM19, BCL6B	257
	873	Down	FOXK2, TBL1X, TMOD2, BMPR2, SFRS1	257
	1226	Down	MARCH9, PPFIBP1	257
	10a	Up	USF2, HOXA1, HOXD10, HOXB1, HOXB3, RB1CC1 and ribosomal proteins	250
	31	Up	FOXCP2, FOXP3	261
	96	Up	CHES1, FOXO1, FOXO3A	261, 266

http://dx.doi.org/10.5772/61032

	miRNA(s)	Expression (Up/ downregulated)	Estimated target(s)	References
	103	Up	GPD1, cdc5A, cdk6, cyclin D2, ENPP2, TIMP3	260, 268
	106a	Up	TGFB1I1, CNN1, OLFML2A, Rbp1-like, FOXA1, KIF1A, ZIC1	257, 260
	107	Up	ENPP2, CDK2, HIF1a	267
	142-5p	Up	E2F7, EGR3, IGF1, SOX11, SOX5, TGFBR2	257
	155	Up	UBE2J1, DCAF7, RAB34, SH3BP4	261
	181a	Up	GPRASP1, TBL1X, DPP6, KLF2, HOXA11, GATA6, NLK, CDX2	260, 268
	182, 183	Up	FOXO1, FOXO3, CASP3, CASP2, Fas	257, 260, 261, 266, 268
	196a	Up	ANXA1, HOXB8, HOXA7, HOXC8, HOXD8	269
	200c	Up	TUBB3	250
	203	Up	JPH4, ZIC1, CDK6, ABCE1, SMYD3, p63	257, 268
	205	Up	E2F1, ERBB3, JPH4, S100A2, ZEB1, ZEB2	257, 268
	210	Up	DCHS1, ENPP2, MYH11, KCNMB1, MNT, BDNF, PTPN1	257,260, 261, 268
	363	Up	CUL3, CXCL5, AGGF1, CIT, DUSP6, EPS8	261, 270
	449	Up	WISP2, MUC5B, EFNB1, VAMP2	261
	513a-5p	Up	CCRL1, MCHR2, CD274, RGS5, EPS8	257
	629	Up	LRP6, TCF4, SEPT1, ZNF436, SLC1A7	257
Cervical cancer	Let -7b, c	Down	Unknown	271
	29a	Down	Neurotrophin/TRK signaling	272, 273
	26a	Down	Unknown	274
	34a,b	Down	p18Ink4c, CDK4, CDK6, Cyclin E2, 2F1, E2F3, BCL2, BIRC3	199, 275
	99a	Down	IGF-1, BCL2L2, VEGFA CDK6	274
	124	Down	IGFBP7, CDK6	276
	138	Down	hTERT	277
	145	Down	IGF-1	274
	149,196b	Down	Unknown	271, 278
	205	Down	ZEB1, ZEB2, SIP1	279
	214	Down	MEK3, JNK1	175

	miRNA(s)	Expression (Up/ downregulated)	Estimated target(s)	References
	218	Down	LAMB3	280
	372	Down	CDK2, Cyclin A1	281
	513	Down	IGF-1, BCL2L2, VEGFA CDK6	274
	519a	Down	HuR	282
	9	Up	Unknown	283
	10a	Up	(HOX) genes	274
	21	Up	PTEN,TPM1, PDCD4	271, 284
	27a	Up	Unknown	285
	100	Up	PLK1	286
	126, 127	Up	Unknown	278, 287
	132	Up	(HOX) genes	274
	133a	Up	Unknown	278
	133b	Up	MST2,CDC42, RHOA,MAPK1,AKT1	288
	146a	Up	Unknown	285
	148a	Up	PTEN, P53INP1 and TP53INP2	274
	155	Up	Unknown	272, 278
	182, 199b	Up	Unknown	278, 280
	200a	Up	MYH10, ZEB1, DCP2, YWHAG, KIDINS220, ZEB2, TGFB2, RANBP5, EXOC5	283
	203	Up	p63	136
	205, 221	Up	Unknown	272, 285
	302b, 522	Up	Unknown	274
	886-5p	Up	BAX	289
Vulvar cancer	19b-1-5p; 22-5p; 26b-3p; 29c-5p; 106b-3p; 142-3p; 144-5p; 151a-5p; 193a-5p; 342-3p; 365a-3p; 519b-3p; 1291	Down	Unknown	72
	16-5p; 21-5p; 29c-5p; 142-3p; 186-5p; 454-3p; 708-5p; 1267	Up	Unknown	72

Table 2. Dysregulated miRNAs in gynecological cancer.

http://dx.doi.org/10.5772/61032

Specific biological functions affected by histone modifications in gynecological cancers are presented in Table 3.

	Genes	Functions	Expression Up/ downregulate	References
Ovarian cancer	EZH2	Lysine methyltransferase; Transcription regulator that acts in gene silencing and embryonic development;	Up	290
	SMYD2 (KMT3C)	Lysine methyltransferases; methylates both histones and nonhistone proteins, including p53/TP53 and RB1.	Up	291
	KDM4A	A demethylase that binds to androgen receptor and represses transcription; may play a role in regulation of cell cycle	Up	292
	EP300	Histone acetyltransferase that regulates transcription via chromatin remodeling	Down	293
	hMOF (KAT8)	Histone acetyltransferase which may be involved in transcriptional activation.	Down	294, 295
	CREBBP (KAT3A)	Plays critical roles in embryonic development, growth control, and homeostasis by coupling chromatin remodeling to transcription factor recognition.	Down	296
Endometrial cancer	HDAC1	Histone deacetylase 1, a transcriptional regulator that mediates histone deacetylation, antiapoptosis, synapse maturation, and hippocampus development	Up	297
	KDM4A	A demethylase that binds to androgen receptor and represses transcription; may play a role in regulation of cell cycle	Up	298
	EZH2	Transcription regulator that acts in gene silencing and embryonic development;	Up	299
Cervical cancer	KDM5B	Histone demethylase and transcription repressor that acts in regulation of Notch signaling, stem cell maintenance, and cell differentiation	Up	300
	EZH2	Transcription regulator that acts in gene silencing and embryonic development	Up	301
	KDM5C	A putative transcription regulator that may act in chromatin remodeling and brain development	Down	302
	KDM6A	Demethylates histone H3 lysine 27; induced expression by papillomavirus E7 oncoprotein results in epigenetic reprogramming	Up	303
	KDM6B	A transcription repressor that plays a role in gonad and lung development and defense response to Gram-positive	Up	303

Genes	Functions	Expression Up/ downregulate	References
	bacteria, regulates histone methylation, macrophage differentiation, and protein localization		
EP300	Histone acetyltransferase and regulates transcription via chromatin remodeling	Up	304
pCAF (KAT2B)	Histone acetyltransferase (HAT) to promote transcriptional activation	Up	305
HDAC1	Histone deacetylase 1; a transcriptional regulator that mediates histone deacetylation, antiapoptosis, synapse maturation, and hippocampus development	Up	306, 307
HDAC2	Histone deacetylase 2; a histone deacetylase and a transcriptional corepressor that acts in chromatin remodeling, inflammatory response, and regulation of translation	Up	307

Table 3. Histone modifications in gynecological cancer.

3. The roles of microenvironment-mediated epigenetic perturbations in the development of gynecological neoplasia

The complexity that governs the tumor phenotype cannot be explained only at the genetic level, as genetic abnormalities occur with low frequency. Therefore, major attention was focused on the study of the role of tumor microenvironment (TME) not only in tumor initiation but also in progression and metastasis. The hypothesis of cancer cell development and proliferation only in a conducive environment has been made by Paget since 1889 [308]. While Paget suggested that the microenvironment facilitates or inhibits metastasis through growth-promoting/ inhibiting factors, recent research sustains that the tumor is directed into one or several possible molecular evolution pathways by signals originating in native and/or modified microenvironmental factors [309]. The tumor microenvironment consists of epithelial cells, vascular endothelial cells, fibroblasts and myofibroblasts, macrophages, leukocytes, and the extracellular matrix (ECM). Together with the ECM, these nonmalignant cell types constitute the stromal tissue of the tumor that secretes ECM components, cytokines, and growth factors involved in tumor growth and invasion. All these components are dynamically interconnected around the tumor. In the tumorigenesis process, studies have shown the critical role of chronic inflammation by hyperexpression of the inflammatory mediators in the microenvironment. The inflammatory microenvironment is both the result of genetic alterations in cancer cells and of the tumor-infiltrating cells that produce inflammatory mediators [310].

While normal fibroblasts prevent tumor progression, cancer-associated fibroblasts (CAFs) that display a different secretory pattern generate an environment that favors tumor growth and

invasiveness. Tumor formation is characterized by changes in cell behavior, like accelerated growth with loss of tissue architecture and epithelial dysfunction, angiogenesis, stromal activation, and migratory and invasive features. Therefore, dysfunction in the tumor microenvironment, in addition to epithelial dysfunction, is crucial for carcinogenesis as altering its components leads to impaired immune response. TME promotes tumorigenesis through new blood vessel formation. Although studies have suggested that some cells in TME contained mutations, recent data pointed, first, to the presence of mutations only in tumorigenic cells and second, to the contribution of these mutations to epigenetic changes in both nontumorigenic cells and TME. In turn, the cells in the microenvironment produce epigenetic changes in tumor cells reflected in their pattern of differentiation [311] and animal models demonstrate that the tumor microenvironment can induce epigenetic alterations and changes in gene expression in tumors [312].

It was suggested that the epigenome serves as the interface between the genome and the environment [313, 314]. The epigenetic role of TME in growth induction seems to be linked with transforming growth factor (TGF)-β and its receptor, whose expressions are regulated through chromatin remodeling [315], although no research on stromal fibroblasts was performed. TGFβ pathways are involved in the oncogenesis process, acting either as tumor suppressor or as tumor promotor, depending on TME crosstalk in the tumor microenvironment [316]. In malignant progression, epigenetic changes in the expression of 12 genes responsive to the TME stress suggest that coordinated transcriptional response of eukaryotic cells to microenvironment might be correlated with chemotherapy resistance of solid tumors [317]. Since tumor development is lead by physiological responses to an aberrant stromal environment, the interaction between the tumor and stromal cells determines tumoral progression [318]. In the chemokine network, epigenetic silencing of CXCR4 in SDF-1α/CXCR4 signaling of tumor microenvironment of cervical cancer cell lines and primary biopsy samples limited the cell response to the paracrine source of SDF-1α, which lead to loss of cell adhesion and disease progression [319]. Other authors reported miRNA's contribution to cancer progression and metastasis. While extracellular miRNAs are involved in cell–cell communication and stromal remodeling [320], specific intracellular ones lead to cell proliferation through cancer-associated fibroblast activation [321].

The acquisition of invasive properties in tumor cells seems to be partially linked to epithelial-mesenchymal transition by abrogation of homotypic cell–cell adhesion due to the absence of E-cadherin expression. Starting from the important role of transient E-cadherin expression in neoplasia, DesRoches and collaborators investigated its regulation by the microenvironment. Using 3D human tissue constructs, the authors suggested the role of epigenetic changes (DNA methylation, chromatin remodeling, and specific miRNA regulation) in the plasticity of E-cadherin-mediated adhesion in different tissue microenvironments during tumor cell invasion and metastasis [322]. The entry of the epithelial cells into the stroma is promoted through the E-cadherin intercellular junction disruption by MMP-3 and break down of the ECM collagen fibers by MMP-2 and MMP-9 [323]. MicroRNA suppression also influences the changes involved in epithelial–mesenchymal transition [324]. Reexpression of E-cadherin might reestablish cell–cell adhesion and may result in a mesenchymal–epithelial transition that might lead to proliferative growth of metastases.

Metastasis, as a multistage process (tumor cell migration from primary tumor, invasion of the surrounding tissues, intravasation into the circulation or the lymphatic system metastasis) involves communication with surrounding nonneoplastic cells [325] that can be epigenetically modulated to lead to ECM remodeling. Also, the epigenetic changes in the microenvironment have a significant impact on distant metastasis. In order to create a favorable local environment for cell proliferation in the metastatic sites, carcinoma cells induce epigenetic changes in both the stromal cells and bone marrow–derived cells [326]. The bone marrow cells are mobilized by the primary tumors to the metastatic sites before the actual metastasis creating a suitable microenvironment for metastasis [315, 327].

Due to their reversal character, epigenetic changes of TME might be targeted for controlling diseases and for therapeutic approach as drug resistance seems to also depend on TME. But, chemotherapeutic drug resistance depends at least partly on the TME rather than the tumor itself [328] and the combined treatment of both the tumor and the TME may be more efficient in the fight with cancer [315].

4. Molecular and epigenetic factors involved in drug resistance

Chemotherapy success is challenged by a multitude of intrinsic or acquired, molecular, genetic and epigenetic factors involved in drug transport, detoxification, signal transduction, gene expression, DNA repair, and programmed cell death. Drug resistance is a major challenge that chemotherapy should overcome. Even if the drug itself is efficient in destroying cancer cells, it is much more complicated to avoid triggering resistance than might appear at different levels of interaction between the drug and its cellular components.

The efflux mechanism is considered to be mainly responsible for the multiple drug resistance phenotypes in gynecologic cancers as well as in all types of cancers [329]. The process may be managed by cancer cells at the genetic and/or epigenetic level. While the genetic modifications of MDR1 and related multidrug resistance proteins were intensely explored over the past few decades, the contribution of epigenetic modification to the expression of MDR1 remains insufficiently explored in human gynecological cancers. It was observed that MDR1 was hypermethylated in 100% of ovarian cancer cell lines, and in 5 out of 13 (38%) primary ovarian cancers associated with loss of MDR1 mRNA expression in ovarian cancer cell lines, sustaining the importance role of epigenetic regulation in the expression of MDR1 and clinical treatment outcomes in human ovarian cancer [330]. However, in six ovarian cancer cell lines—W1MR, W1CR, W1DR, W1VR, W1TR, and W1PR that are respectively resistant to methotrexate, cisplatin, doxorubicin, vincristine, topotecan, and paclitaxel, P-gp is responsible for chemoresistance and, in the case of methotrexate, was found to have a relation between the MRP2 transcript level and drug resistance [331]. Among inhibitors of Pgp MDR, valspodar, an analog of cyclosporine A, showed no clinical benefit in a phase III trial with paclitaxel and carboplatin [332], because while these agents can block drug efflux at the cellular level, the effects are not tumor specific, requiring a reduction in dosage for minimizing the side effects but also the therapeutic advantage. On the other hand, miRNA was involved in resistance through the

http://dx.doi.org/10.5772/61032

regulation of MDR proteins at a posttranscriptional level. The interaction of miRNAs with the targeted mRNA can downmodulate MDR proteins improving the response to anticancer drugs. It was described [329] that miR-223 can downregulate ABCB1 and mRNA levels. miR-124a and miR-506 significantly decreased the protein level of MRP4 (ABCC4), which is another efflux membrane transporter; however, these miRNAs did not change the gene transcription levels [333]. In addition, although there are many modalities acting on efflux proteins in order to circumvent drug resistance, their effective action can be compromised due to the diversity of signal transduction pathways involved in transporter-mediated MDR, such as MAPK, JNK, PI3K, among others; as well as some transcription factors, like NF-κB, TNF-α, and PTEN that could influence the levels of carrier proteins in different conditions [334].

Also, the signal transduction pathways can be involved in drug resistance. The Wnt signaling pathway, which is regulated by a multiprotein complex consisting of, among others, members of β-catenin, adenomatous polyposis coli APC, Axin, and GSK-3β [335], are involved in calcium-dependent cell adhesion due to the interaction between β-catenin and cadherin [336]. Different mutations in APC, promotes β-catenin proteolysis and reduces its transcriptional activity. PTEN, a lipid and protein phosphatase that is a negative regulator of phosphatidylinositol 3 (PI-3) kinase-dependent signaling interacts with the WNT pathway by impeding activation of integrin-linked kinase (ILK), which inhibits GSK-3β and thus causes accumulation of β-catenin [337]. The WNT signaling pathway is the most frequently altered pathway in the majority of cancers; therefore, individual components of the pathway are interesting targets for epigenetic inactivation. PI3K/Akt is another signaling pathway that is involved in acquired resistance of many cancers including gynecological ones. All of its isoforms (Akt1, Akt2, and Akt3) are activated (phosphorylated) by phosphatidylinositol 3-kinase (PI3-K) in response to growth factors and promote cell survival. It was demonstrated that the Akt pathway is directly related to the resistance of cancers against different drugs like sorafenib, trastuzumab, and erlotinib [329]. The epigenetic control of Akt and NF-κB is important for the establishment of drug resistance. RUNX3 suppresses Akt1 transcription by directly binding to the Akt1 promoter, and methylation of RUNX3 induces activation of the Akt signaling pathway [329].

Acquired resistance may develop additionally as blockage of apoptotic pathways or defective apoptotic signaling, often associated with loss of tumor suppressor protein p53, but also independent of p53, alteration of the control points of the cell cycle, increased ability to repair DNA, increased DNA damage tolerance, oncogene induction, and downmodulation of tumor suppressor genes. Eluding the normal process of programmed cell death is already known as a crucial strategy for cancer development and progression, but even more importantly, its participation in the intrinsic or acquired resistance of cancer cells to chemotherapy and radiation. Identification of the points of therapeutic intervention could potentially open up more efficient treatment opportunities. Epigenetic strategies might also be a feasible strategy to reactivate apoptosis or on the contrary to inactivate apoptosis-related genes that inhibit the process. However, it has now been demonstrated that inhibitors of DNA methylation and histone deacetylases can reactivate expression of tumor suppressor genes and induce histone hyperacetylation in the tumors of patients with cervical cancer after treatment with these agents. Preclinical studies have suggested a multitude of strategies to prevent or overcome resistance, but these approaches have not successfully translated to clinical practice yet [338].

5. Conclusions

This chapter underlined the importance of epigenetic events in gynecological cancer. Deciphering the relevant epigenetic changes associated with each step of tumor development might improve molecular diagnostic and cancer risk assessment. Advances in elucidating epigenetic regulation in cancer disease, as well as in the development of technology, lead to the identification of potential biomarkers for diagnostic screening. As epigenetic changes occur early in neoplastic process, epigenetic biomarkers seem to be more sensitive and specific in cancer detection and some have already been tested for several types of cancer, alone or in combination with traditional biomarkers. Unlike genetic changes, epigenetic alterations are essentially reversible and allow plasticity. These features are exploited and new therapeutic agents targeting epigenetic processes have been developed. The epigenetic changes of the transformed cells or TME can be modified by chemotherapeutic drugs and this epigenetic reversal therapy has potential in the future. In addition, miRNAs should be heavily explored as they might represent future alternatives for combined therapy of cancer. Many epigenetic targets are druggable and in order to overcome drug resistance, epigenetic therapy might also be a feasible strategy for induced cell death. Moreover, epigenetic patterns might be useful tools for therapy response prediction.

Author details

Coralia Bleotu[1*], Demetra Socolov[2], Mariana Anton[3], Anca Botezatu[1], Adriana Plesa[1], Iulia Virginia Iancu[1], Lorelei Irina Brasoveanu[1], Gabriela Anton[1] and Carmen Cristina Diaconu[1]

*Address all correspondence to: cbleotu@yahoo.com

1 Stefan S Nicolau Institute of Virology, Bucharest, Romania

2 University of Medicine and Pharmacy "Gr. T. Popa", Iassy, Romania

3 Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

References

[1] Siedlecki P, Zielenkiewicz P. Mammalian DNA methyltransferases. Acta Biochim Pol. 2006;53(2):245–256.

[2] Bird AP. DNA methylation patterns and epigenetic memory. Genes Dev. 2002;16(1): 6–21.DOI: 10.1101/gad.947102.

[3] Takai D, Jones PA. Comprehensive analysis of CpG islands in human chromosomes 21 and 22. Proc Natl Acad Sci U S A. 2002;99:3740–3745. DOI: 10.1073/pnas.052410099.

[4] Wang Y, Leung FC. An evaluation of new criteria for CpG islands in the human genome as gene markers. Bioinformatics. 2004;20:1170–1177. DOI: 10.1093/bioinformatics/bth059.

[5] Suzuki MM, Bird A. DNA methylation landscapes: provocative insights from epigenomics. Nat Rev Genet. 2008;9:465–476. DOI: 10.1038/nrg2341.

[6] Prendergast GC, Ziff EB. Methylation-sensitive sequence-specific DNA binding by the c-Myc basic region. Science. 1991;251:186–189.DOI: 10.1126/science.1987636.

[7] Watt F, Molloy PL. Cytosine methylation prevents binding to DNA of a HeLa cell transcription factor required for optimal expression of the adenovirus major late promoter. Genes Dev. 1988;2:1136–1143. DOI: 10.1101/gad.2.9.1136.

[8] Jones PL, Veenstra GJ, Wade PA, Vermaak D, Kass SU, *et al*. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat Genet. 1988;19:187–191. DOI: 10.1038/561.

[9] Nan X, Ng HH, Johnson CA, Laherty CD, Turner BM, *et al*. Transcriptional repression by the methyl-CpG binding protein MeCP2 involves a histone deacetylase complex. Nature. 1998;393:386–389. DOI:10.1038/30764.

[10] Bird AP, Taggart MH, Nicholls RD, Higgs DR, Non-methylated CpG-rich islands at the human alphaglobin locus: Implications for evolution of the alpha-globin pseudogene. The EMBO J. 1987;6(4):999–1004.

[11] Lan J, Hua S, He X, Zhang Y. DNA methyltransferases and methyl-binding proteins of mammals. Acta Biochim Biophys Sin. 2010;42(4):243–252. DOI: 10.1093/abbs/gmq015.

[12] Cuzick J, Bergeron C, von Knebel Doeberitz M, Gravitt P, *et al*. New technologies and procedures for cervical cancer screening. Vaccine. 2012;30S:F107–F116.

[13] Overmeer RM, Henken FE, Snijders PJ, Claassen-Kramer D, Berkhof J, *et al.* Association between dense CADM1 promoter methylation and reduced protein expression in high-grade CIN and cervical SCC. J Pathol. 2008;215(4):388–397.

[14] Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007;128:683–692.

[15] Yang HJ. Aberrant DNA methylation in cervical carcinogenesis. Chin J Cancer. 2013;32:42–48.

[16] Esteller M, Corn PG, Baylin SB, *et al*. A gene hypermethylation profile of human cancer. Cancer Res. 2001;61:3225–3229.

[17] Esteller M. Epigenetics in cancer. N Engl J Med. 2008;358:1148–1159.

[18] Mulero Navarro S, Esteller M. Epigenetic biomarkers for human cancer: the time is now. Crit Rev Oncol Hematol. 2008;68:1–11.

[19] Qureshi SA, Bashir MU, Yaqinuddin A. Utility of DNA methylation markers for diagnosing cancer. Int J Surg. 2010;8:194–198.

[20] Kouzarides T. Chromatin modifications and their function. Cell. 2007;128:693–705:DOI: http://dx.doi.org/10.1016/j.cell.2007.02.005.

[21] Caterino TL, Hayes JJ. Chromatin structure depends on what's in the nucleosome's pocket. Nat Struct Mol Biol. 2007;14:1056–1058. DOI:10.1038/nsmb1107-1056.

[22] Shogren-Knaak M, Ishii H, Sun JM, Pazin MJ, Davie JR, *et al*. Histone H4-K16 acetylation controls chromatin structure and protein interactions. Science. 2006;311(5762): 844–847. DOI: 10.1126/science.1124000.

[23] Mikkelsen TS, Ku M, Jaffe DB, Issac B, Lieberman E, *et al*. Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature. 2007;448:553–560. DOI: 10.1038/nature06008.

[24] Ringrose L, Paro R. Polycomb/trithorax response elements and epigenetic memory of cell identity. Development. 2007;134:223–232. DOI: 10.1242/dev.02723.

[25] Kouzarides T. Histone methylation in transcriptional control. Curr Opin Genet Dev. 2002;12(2):198–209. DOI: 10.1016/S0959-437X(02)00287-3.

[26] Zardo G, Cimino G, Nervi C. Epigenetic plasticity of chromatin in embryonic and hematopoietic stem/progenitor cells: therapeutic potential of cell reprogramming. Leukemia. 2008;22(8):1503–1518. DOI: 10.1038/leu.2008.141.

[27] Schwartz YB, Pirrotta V. Polycomb silencing mechanisms and the management of genomic programmes. Nat Rev Genet. 2007;8(1):9–22.DOI: 10.1038/nrg1981.

[28] Simon JA, Kingston RE. Mechanisms of polycomb gene silencing: knowns and unknowns. Nat Rev Mol Cell Biol. 2009;10(10):697–708. DOI: 10.1038/nrm2763.

[29] Agger K, Cloos PA, Christensen J, Pasini D, Rose S, *et al.* UTX and JMJD3 are histone H3K27 demethylases involved in HOX gene regulation and development. Nature. 2007;449(7163):731–734. DOI: 10.1038/nature06145.

[30] De Santa F, Totaro MG, Prosperini E, Notarbartolo S, Testa G, *et al*. The histone H3 lysine-27 demethylase JMJD3 links inflammation to inhibition of polycombmediated gene silencing. Cell. 2007;130(6):1083–1094. DOI: http://dx.doi.org/10.1016/j.cell. 2007.08.019.

[31] Lan F, Bayliss PE, Rinn JL, Whetstine JR, Wang JK, *et al.* A histone H3 lysine 27 demethylase regulates animal posterior development. Nature. 2007;449(7163):689–694. DOI: 10.1038/nature06192.

[32] Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010;31(1):27–36. DOI: 10.1093/carcin/bgp220.

[33] Zhao XD, Han X, Chew JL, Liu J, Chiu KP, *et al.* Whole-genome mapping of histone H3 Lys4 and 27 trimethylations reveals distinct genomic compartments in human embryonic stem cells. Cell Stem Cell. 2007;1(3):286–298. DOI: 10.1016/j.stem.2007.08.004.

[34] Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, *et al.* A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell. 2006;125(2):315–326. DOI: http://dx.doi.org/10.1016/j.cell.2006.02.041.

[35] Cedar H, Bergman Y. Linking DNA methylation and histone modification: patterns and paradigms. Nat Rev Genet. 2009;10:295–304. DOI: 10.1038/nrg2540.

[36] Tachibana M, Matsumura Y, Fukuda M, Kimura H, Shinkai Y. G9a/GLP complexes independently mediate H3K9 and DNA methylation to silence transcription. EMBO J. 2008;27:2681–2690. DOI: 10.1038/emboj.2008.192.

[37] Lehnertz B, Ueda Y, Derijck AA, Braunschweig U, Perez-Burgos L, *et al*. Suv39h-mediated histone H3 lysine 9 methylation directs DNA methylation to major satellite repeats at pericentric heterochromatin. Curr Biol. 2003;13:1192–1200. DOI: http://dx.doi.org/10.1016/S0960-9822(03)00432-9.

[38] Zhao Q, Rank G, Tan YT, Li H, Moritz RL, Simpson RJ, *et al*. PRMT5-mediated methylation of histone H4R3 recruits DNMT3A, coupling histone and DNA methylation in gene silencing. Nat Struct Mol Biol. 2009;16:304–311. DOI: 10.1038/nsmb.1568.

[39] Fuks F, Hurd PJ, Wolf D, Nan X, Bird AP, *et al*. The methyl-CpG-binding protein MeCP2 links DNA methylation to histone methylation. J. Biol. Chem. 2003;278:4035–4040. DOI: 10.1074/jbc.M210256200.

[40] Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, *et al*. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nat Genet. 2005;37:391–400. DOI: 10.1038/ng1531.

[41] Halkidou K, Gaughan L, Cook S, Leung HY, Neal DE, *et al*. Upregulation and nuclear recruitment of HDAC1 in hormone refractory prostate cancer. Prostate. 2004;59:177–189. DOI: 10.1002/pros.20022.

[42] Song J, Noh JH, Lee JH, Eun JW, Ahn YM, *et al*. Increased expression of histone deacetylase 2 is found in human gastric cancer. APMIS. 2005;113:264–268. DOI: 10.1111/j.1600-0463.2005.apm_04.x.

[43] Yang XJ. The diverse superfamily of lysine acetyltransferases and their roles in leukemia and other diseases. Nucleic Acids Res. 2004;32:959–976. DOI: 10.1093/nar/gkh252.

[44] Rougeulle C, Heard E. Antisense RNA in imprinting: spreading silence through air. Trends Genet. 2002;18:434–437. DOI: http://dx.doi.org/10.1016/S0168-9525(02)02749-X.

[45] Sleutels F, Zwart R, Barlow DP. The non-coding Air RNA is required for silencing autosomal imprinted genes. Nature. 2002;415:810–813. DOI:10.1038/415810a.

[46] Plath K, Mlynarczyk-Evans S, Nusinow DA, Panning B. Xist RNA and the mechanism of X chromosome inactivation. Annu. Rev. Genet. 2002;36:233–278. DOI: 10.1146/annurev.genet.36.042902.092433.

[47] Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell. 2004;116:281–297. DOI: http://dx.doi.org/10.1016/S0092-8674(04)00045-5.

[48] Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. Cell. 2003;115:787–798. DOI: http://dx.doi.org/10.1016/S0092-8674(03)01018-3.

[49] Fabian MR, Sonenberg N. The mechanics of miRNA-mediated gene silencing: a look under the hood of miRISC. Nat Struct Mol Biol. 2012;19:586–593. DOI: 10.1038/nsmb.2296.

[50] Saj A, Lai EC. Control of microRNA biogenesis and transcription by cell signaling pathways. Curr Opin Genet Dev. 2011;21:504–551. DOI: 10.1016/j.gde.2011.04.010.

[51] Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science. 2001;294:853–858. DOI: 10.1126/science.1064921.

[52] Lau NC, Lim LP, Weinstein EG, Bartel DP. An abundant class of tiny RNAs with probable regulatory roles in *Caenorhabditis elegans*. Science. 2001;294:858–862. DOI: 10.1126/science.1065062.

[53] Lee RC, Ambros V. An extensive class of small RNAs in *Caenorhabditis elegans*. Science. 2001;294:862–864. DOI: 10.1126/science.1065329.

[54] Croce CM. Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet. 2009;10:704–714. DOI: 10.1038/nrg2634.

[55] Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, *et al.* MicroRNA expression profiles classify human cancers. Nature 2005;435:834–838. DOI: 10.1038/nature03702.

[56] Munker R, Calin GA. MicroRNA profiling in cancer. Clin Sci (Lond). 2011;121:141–158. DOI: 10.1042/CS20110005.

[57] Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, *et al*. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006;103:2257–2261. DOI: 10.1073/pnas.0510565103.

[58] Iorio MV, Croce CM. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. EMBO Mol Med. 2012;4:143–159. DOI: 10.1002/emmm.201100209.

[59] Seo GJ, Fink LH, O'Hara B, Atwood WJ, Sullivan CS. Evolutionarily conserved function of a viral microRNA. J Virol. 2008 82(20), 9823–9828.

[60] Del Pino M, Rodriguez-Carunchio L, Ordi J. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology 2013;62(1):161–175.

[61] Gadducci A, Tana R, Barsotti C, Guerrieri ME, Genazzani AR. Clinico-pathological and biological prognostic variables in squamous cell carcinoma of the vulva. Crit Rev Oncol Hematol 2012;83(1):71–83.

[62] van der Avoort IA, Shirango H, Hoevenaars BM, Grefte JM, de Hullu JA, *et al*. Vulvar squamous cell carcinoma is a multifactorial disease following two separate and independent pathways. Int J Gynecol Pathol. 2006;25(1):22–29.

[63] Schuurman MS, van den Einden LC, Massuger LF, Kiemeney LA, van der Aa MA, *et al*. Trends in incidence and survival of Dutch women with vulvar squamous cell carcinoma. Eur J Cancer. 2013;49(18):3872–3880.

[64] van de Nieuwenhof HP, Massuger LF, van der Avoort IA, Bekkers RL, Casparie M, *et al.* Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age. Eur J Cancer 2009;45(5):851–856.

[65] McCluggage WG. Premalignant lesions of the lower female genital tract: cervix, vagina and vulva. Pathology 2013;45(3):214–328.

[66] Raspollini MR, Asirelli G, Moncini D, Taddei GL. A comparative analysis of lichen sclerosus of the vulva and lichen sclerosus that evolves to vulvar squamous cell carcinoma. Am J Obstet Gynecol. 2007;197(6):592–595.

[67] Sliutz G, Schmidt W, Tempfer C, Speiser P, Gitsch G, *et al*. Detection of p53 point mutations in primary human vulvar cancer by PCR and temperature gradient gel electrophoresis. Gynecol Oncol. 1997;64(1):93–98.

[68] Chulvis do Val IC, Almeida Filho GL, Valiante PM, Gondim C, Takiya CM, *et al*. Vulvar intraepithelial neoplasia p53 expression, p53 gene mutation and HPV in recurrent/progressive cases. J Reprod Med. 2004;49(11):868–874.

[69] Aulmann S, Schleibaum J, Penzel R, Schirmacher P, Gebauer G, *et al*. Gains of chromosome region 3q26 in intraepithelial neoplasia and invasive squamous cell carcinoma of the vulva are frequent and independent of HPV status. J Clin Pathol. 2008;61(9):1034–1037.

[70] Lavorato-Rocha AM, De Melo MB, Rodrigues IS, Stiepcich MMA, Baiocchi G, *et al*. Prognostication of vulvar cancer based on p14ARF status: molecular assessment of transcript and protein. Ann Surg Oncol. 2013; 20(1):31–39.

[71] Trietsch MD, Nooij LS, Gaarenstroom KN, van Poelgeest MIE. Genetic and epigenetic changes in vulvar squamous cell carcinoma and its precursor lesions: a review of the current literature. Gynecol Oncol. 2015; 136: 143–157.

[72] de Melo Maia B, Lavorato-Rocha AM, Rodrigues LS, Coutinho-Camillo CM, Baiocchi G, *et al*. microRNA portraits in human vulvar carcinoma. Cancer Prev Res (Phila). 2013;6(11):1231–1241. doi: 10.1158/1940-6207.CAPR-13-0121.

[73] de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, *et al*. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13:607–615.

[74] Rajaram S, Maheshwari A, Srivastava A. Staging for vaginal cancer. Best Pract Res Clin Obstet Gynaecol. 2015. http://dx.doi.org/10.1016/j.bpobgyn.2015.01.006.

[75] Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370(9581):59–67.

[76] Hellman K, Silfverswärd C, Nilsson B, Hellström AC, Frankendal B, *et al*. Primary carcinoma of the vagina: factors influencing the age at diagnosis. The Radiumhemmet series 1956–96. Int J Gynecol Cancer. 2004;14(3):491–501.

[77] Daling JR, Madeleine MM, Schwartz SM, Shera KA, Carter JJ, *et al*. A population-based study of squamous cell vaginal cancer: HPV and cofactors. Gynecol Oncol 2002;84(2):263–270.

[78] Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284(15):878–881.

[79] Mittendorf R. Teratogen update: carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) *in utero*. Teratology 1995;51(6):435–445.

[80] Treffers PE, Hanselaar AG, Helmerhorst TJ, Koster ME, van Leeuwen FE. Consequences of diethylstilbestrol during pregnancy; 50 years later still a significant problem. Ned Tijdschr Geneeskd. 2001;145(14):675–680.

[81] De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124(7):1626–1636.

[82] Alemany L, Saunier M, Tinoco L, Quirós B, Alvarado-Cabrero I, *et al*. HPV VVAP Study Group. Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples. Eur J Cancer. 2014; 50:2846–2854.

[83] Thierry F. Transcriptional regulation of the papillomavirus oncogenes by cellular and viral transcription factors in cervical carcinoma. Virology. 2009; 384:375–379.

[84] Thain A, Jenkins O, Clarke AR, Gaston K. CpG methylation directly inhibits binding of the human papillomavirus type 16 E2 protein to specific DNA sequences. J Virol 1996; 70: 7233–7235.

[85] Lillsunde Larsson G, Helenius G, Sorbe B, Karlsson MG. Viral load, integration and methylation of E2BS3 and 4 in human papilloma virus (HPV) 16-positive vaginal and vulvar carcinomas. PLoS ONE. 2014; 9(11): e112839. doi:10.1371/journal.pone.0112839.

[86] Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, *et al*. Prenatal diethylstilbestrol exposure and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15: 1509–1514.

[87] Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, *et al*. Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med. 2011; 365: 1304–1314. doi: 10.1056/NEJMoa1013961.

[88] Block K, Kardana A, Igarashi P, Taylor HS. In utero diethylstilbestrol (DES) exposure alters Hox gene expression in the developing mullerian system. FASEB J. 2000; 14:1101–1108.

[89] Newbold RR, Jefferson WN, Grissom SF, Padilla-Banks E, Snyder RJ, *et al*. Developmental exposure to diethylstilbestrol alters uterine gene expression that may be associated with uterine neoplasia later in life. Mol Carcinog. 2007; 46: 783–796.

[90] Vanhees K, Coort S, Ruijters EJ, Godschalk RW, van Schooten FJ, *et al*. Epigenetics: prenatal exposure to genistein leaves a permanent signature on the hematopoietic lineage. FASEB J. 2011; 25: 797–807. doi: 10.1096/fj.10-172155.

[91] Bromer JG, Wu J, Zhou Y, Taylor HS. Hypermethylation of homeobox A10 by *in utero* diethylstilbestrol exposure: an epigenetic mechanism for altered developmental programming. Endocrinology. 2009; 150: 3376–3382. doi: 10.1210/en.2009-0071.

[92] Li S, Washburn KA, Moore R, Uno T, Teng C, *et al*. Developmental exposure to diethylstilbestrol elicits demethylation of estrogen-responsive lactoferrin gene in mouse uterus. Cancer Res. 1997; 57: 4356–4359.

[93] Li S, Hursting SD, Davis BJ, McLachlan JA, Barrett JC. Environmental exposure, DNA methylation, and gene regulation: Lessons from diethylstilbesterol-induced cancers. Ann N Y Acad Sci. 2003; 983: 161–169.

[94] Harlid S, Xu Z, Panduri V, D'Aloisio AA, DeRoo LA, *et al*. In utero exposure to diethylstilbestrol and blood DNA methylation in women ages 40–59 years from the Sister Study. PLoS ONE. 2015; 10(3): e0118757. doi:10.1371/journal.pone.0118757.

[95] Dougan MM, Hankinson SE, Vivo I, Tworoger SS, Glynn RJ, *et al*. Prospective study of body size throughout the life-course and the incidence of endometrial cancer among premenopausal and postmenopausal women. Int J Cancer. 2015. doi: 10.1002/ijc.29427.

[96] Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. Obstet Gynecol. 2015;125(1):89–98. doi: 10.1097/AOG.0000000000000563.

[97] Yang HP, Cook LS, Weiderpass E, Adami HO, Anderson KE, *et al*. Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). Br J Cancer. 2015;112(5):925–933.

[98] Graham JD, Clarke CL. Physiological action of progesterone in target tissues. Endocr Rev. 1997;18(4):502–519.

[99] Conneely OM, Lydon JP. Progesterone receptors in reproduction: functional impact of the A and B isoforms. Steroids. 2000;65(10–11):571–577.

[100] Yang S, Thiel KW, De Geest K, Leslie KK. Endometrial cancer: reviving progesterone therapy in the molecular age. Discov Med. 2011;12(64):205–212.

[101] Jones A, Teschendorff AE, Li Q, Hayward JD, Kannan A, *et al*. Role of DNA methylation and epigenetic silencing of HAND2 in endometrial cancer development. PLoS Med. 2013;10(11):e1001551. doi: 10.1371/journal.pmed.1001551.

[102] Srivastava D, Thomas T, Lin Q, Kirby ML, Brown D, *et al*. Regulation of cardiac mesodermal and neural crest development by the bHLH transcription factor, dHAND. Nat Genet. 1997;16: 154–160. doi:10.1038/ng0697-154.

[103] Li Q, Kannan A, DeMayo FJ, Lydon JP, Cooke PS, *et al*. The antiproliferative action of progesterone in uterine epithelium is mediated by Hand2. Science. 2011;331:912–916. doi:10.1126/science.1197454.

[104] Bagchi IC, Li Q, Cheon YP, Mantena SR, Kannan A, *et al*. Use of the progesterone receptor antagonist RU 486 to identify novel progesterone receptor-regulated pathways in implantation. Semin Reprod Med. 2005;23:38–45. doi:10.1055/s-2005-864032.

[105] Dassen H, Punyadeera C, Kamps R, Klomp J, Dunselman G, *et al*. Progesterone regulation of implantation-related genes: new insights into the role of oestrogen. Cell Mol Life Sci. 2007;64: 1009–1032. doi:10.1007/s00018-007-6553-9.

[106] Deacon JM, Evans CD, Yule R, *et al*. Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case–control study nested within the Manchester Cohort. Br J Cancer. 2000;83:1565–1572.

[107] Klumb EM, Araújo Jr ML, Jesus GR, *et al*. Is higher prevalence of cervical intraepithelial neoplasia in women with lupus due to immunosuppression? J Clin Rheumatol. 2010;16:153–157.

[108] Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A. Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature. Gynecol Endocrinol. 2011;27: 597–604.

[109] Lax S. Histopathology of cervical precursor lesions and cancer. Acta Dermatovenerol Alp Panonica Adriat. 2011;20:125–133.

[110] Kwasniewska A, Korobowicz E, Zdunek M, *et al*. Prevalence of *Chlamydia trachomatis* and herpes simplex virus 2 in cervical carcinoma associated with human papillomavirus detected in paraffin sectioned samples. Eur J Gynaecol Oncol. 2009;30:65–70.

[111] Chen CL, Liu SS, Ip SM, *et al*. E-cadherin expression is silenced by DNA methylation in cervical cancer cell lines and tumours. Eur J Cancer. 2003;39:517–523.

[112] Shivapurkar N, Sherman ME, Stastny V, *et al*. Evaluation of candidate methylation markers to detect cervical neoplasia. Gynecol Oncol. 2007;107:549–553.

[113] Kim JH, Choi YD, Lee JS, *et al*. Assessment of DNA methylation for the detection of cervical neoplasia in liquid based cytology specimens. Gynecol Oncol. 2010;116:99–104.

[114] Yang N, Nijhuis ER, Volders HH, *et al*. Gene promoter methylation patterns throughout the process of cervical carcinogenesis. Cell Oncol. 2010;32:131–143.

[115] Kitkumthorn N, Yanatatsanajit P, Kiatpongsan S, *et al*. Cyclin A1 promoter hypermethylation in human papillomavirus associated cervical cancer. BMC Cancer, 2006;6:55.

[116] Ki KD, Lee SK, Tong SY, *et al*. Role of 5'CpG island hypermethylation of the FHIT gene in cervical carcinoma. J Gynecol Oncol, 2008;19:117-122.

[117] Jha AK, Nikbakht M, Parashar G, *et al*. Reversal of hypermethylation and reactivation of the RARbeta2 gene by natural compounds in cervical cancer cell lines. Folia Biol (Praha). 2010;56:195–200.

[118] Hesson LB, Cooper WN, Latif F. The role of RASSF1A methylation in cancer. Dis Markers. 2007;23:73–87.

[119] Dong SM, Kim HS, Rha SH, *et al*. Promoter hypermethylation of multiple genes in carcinoma of the uterine cervix. Clin Cancer Res, 2001;7:1982-1986.

[120] Cheung TH, Lo KW, Yim SF, Chan LK, Heung MS, *et al*. Epigenetic and genetic alternation of PTEN in cervical neoplasm. Gynecol Oncol. 2004;93:621–627.

[121] Liu SS, Leung RC, Chan KY, *et al*. p73 expression is associated with the cellular radiosensitivity in cervical cancer after radiotherapy. Clin Cancer Res. 2004;10:3309–3316.

[122] Wentzensen N, Sherman ME, Schiffman M, *et al*. Utility of methylation markers in cervical cancer early detection: appraisal of the state of the science. Gynecol Oncol. 2009;112: 293–299.

[123] Lai HC, Lin YW, Huang RL, Chung MT, Wang HC, *et al*. Quantitative DNA methylation analysis detects cervical intraepithelial neoplasms type 3 and worse. Cancer. 2010;116(18):4266–4274.

[124] Eijsink JJ, Lendvai A, Deregowski V, Klip HG, Verpooten G, *et al*. A four gene methylation marker panel as triage test in hr-HPV positive patients. Int J Cancer. 2012;130(8):1861–1869.

[125] Hesselink AT, Heideman DA, Steenbergen RD, Coupé VM, Overmeer RM, Rijkaart D, *et al*. Combined promoter methylation analysis of CADM1 and MAL: an objective triage tool for high-risk human papillomavirus DNA-positive women. Clin Cancer Res. 2011;17(8): 2459–2465.

[126] Steenbergen RD, Kramer D, Braakhuis BJ, Stern PL, Verheijen RH, *et al*. TSLC1 gene silencing in cervical cancer cell lines and cervical neoplasia. J Natl Cancer Inst. 2004;96(4):294–305.

[127] Eijsink JJ, Yang N, Lendvai A, Klip HG, Volders HH, *et al*. Detection of cervical neoplasia by DNA methylation analysis in cervico-vaginal lavages, a feasibility study. Gynecol Oncol. 2011;120(2):280–283.

[128] Kalantari M, Calleja-Macias IE, Tewari D, Hagmar B, Lie K, *et al*. Conserved methylation patterns of human papillomavirus type 16 DNA in asymptomatic infection and cervical neoplasia. J Virol. 2004;78: 12762–12772.

[129] Turan T, Kalantari M, Calleja-Macias IE, Villa LL, Cubie HA, *et al*. Methylation of the human papillomavirus-18 L1 gene: A biomarker of neoplastic progression? Virology. 2006;349:175–183.

[130] Mirabello L, Sun C, Ghosh A, Rodriguez AC, Schiffman M, *et al.* Methylation of the HPV16 genome is associated with disease progression in a prospective population-based cohort. J Natl Cancer Inst. 2012;104(7):556–565.

[131] Mirabello L, Frimer M, Harari A, McAndrew T, Smith B, Chen Z, *et al*. HPV16 methyl-haplotypes determined by a novel next-generation sequencing method are associated with cervical precancer. Int J Cancer. 2015;136(4):E146-53. doi: 10.1002/ijc.29119.

[132] Zheng ZM, Wang X, Regulation of cellular miRNA expression by human papillomaviruses, Biochim Biophys Acta, 2011; 668–677.

[133] Skalsky RL, Cullen BR, Viruses, microRNAs, and host interactions. Annu Rev Microbiol. 2010;64:123–141.

[134] Wang X,Wang H-K, McCoy JP, *et al.* Oncogenic HPV infection interrupts the expression of tumor-suppressive miR-34a through viral oncoprotein E6. RNA. 2009;15:637–647.

[135] Wang X, Meyers C, Guo M, Zheng ZM. Upregulation of p18Ink4c expression by oncogenic HPV E6 via p53-miR-34a pathway. Int J Cancer. 2011;129:1362–1372.

[136] Melar-New M, Laimins LA. Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins. J Virol. 2010;84:5212–5221.

[137] Bo J, Yang G, Huo K, *et al*. microRNA-203 suppresses bladder cancer development by repressing bcl-w expression. FEBS J. 2011;278:786–792.

[138] Bian K, Fan J, Zhang X, *et al*. MicroRNA-203 leads to G1 phase cell cycle arrest in laryngeal carcinoma cells by directly targeting survivin. FEBS Lett. 2012;586:804–809.

[139] Takeshita N, Mori M, Kano M, *et al*. miR-203 inhibits the migration and invasion of esophageal squamous cell carcinoma by regulating LASP1. Int J Oncol. 2012;41:1653–1661.

[140] Ofir M, Hacohen D, Ginsberg D. MiR-15 and miR-16 are direct transcriptional targets of E2F1 that limit E2F-induced proliferation by targeting cyclin E. Mol Cancer Res. 2011;9:440–447.

[141] Myklebust M, Bruland O, Fluge O, Skarstein A, Balteskard L, *et al*. MicroRNA-15b is induced with E2F controlled genes in HPV-related cancer. Br J Cancer. 2011;105:1719–1725.

[142] Wang F, Fu X-D, Zhou Y, Zhang Y. Downregulation of the cyclin E1 oncogene expression by microRNA-16-1 induces cell cycle arrest in human cancer cells. BMB Rep. 2009;42:725–730.

[143] Chen J. Signaling pathways in HPV-associated cancers and therapeutic implications. Rev Med Virol. 2015;25 Suppl 1:24-53. doi: 10.1002/rmv.1823.

[144] Chudecka-Głaz, AM, ROMA, an algorithm for ovarian cancer. Clin Chim Acta. 2015;440:143–151.

[145] May T, Shoni M, Crum CP, Xian W, Vathipadiekal V, *et al*. Low-grade and high-grade serous Mullerian carcinoma: review and analysis of publicly available gene expression profiles. Gynecol Oncol. 2013;128(3):488-92. doi: 10.1016/j.ygyno.2012.12.009.

[146] Shih I, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004; 164:1511–1518.

[147] Wiegand KC, Shah SP, Al-Agha OM, *et al*. ARID1A mutations in endometriosis associated ovarian carcinomas. N Engl J Med. 2010;363:1532–1543.

[148] Kurman RJ, Shih I. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. Hum Pathol. 2011;42:918–931.

[149] Kurman RJ. Origin and molecular pathogenesis of ovarian high-grade serous carcinoma, Ann Oncol. 2013;24 (Supplement 10): x16–x21; doi:10.1093/annonc/mdt463.

[150] Przybycin CG, Kurman RJ, Ronnett BM, *et al.* Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol. 2010;34:1407–1416.

[151] Tone AA, Begley H, Sharma M., *et al*. Gene expression profiles of luteal phase fallopian tube epithelium from BRCA mutation carriers resemble high-grade serous carcinoma. Clin Cancer Res. 2008;14:4067–4078.

[152] Kuhn E, Kurman RJ, Vang R., *et al*. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma—evidence supporting the clonal relationship of the two lesions. J Pathol. 2012;226:421–426.

[153] Cancer Genome Atlas Res Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474:609–615.

[154] Koukoura O, Spandidos DA, Daponte A, Sifakis S, DNA methylation profiles in ovarian cancer: implication in diagnosis and therapy (Review). Mol Med Rep. 2014;10:3–9.

[155] Baldwin RL, Nemeth E, Tran H, *et al*. BRCA1 promoter region hypermethylation in ovarian carcinoma: a population-based study. Cancer Res. 2000;60:5329–5333.

[156] Strathdee G, Appleton K, Illand M, *et al*. Primary ovarian carcinomas display multiple methylator phenotypes involving known tumor suppressor genes. Am J Pathol. 2001;158:1121–1127.

[157] Wang C, Horiuchi A, Imai T, *et al*. Expression of BRCA1 protein in benign, borderline, and malignant epithelial ovarian neoplasms and its relationship to methylation and allelic loss of the BRCA1 gene. J Pathol. 2004;202:215–223.

[158] Bol GM, Suijkerbuijk KP, Bart J, Vooijs M, van der Wall E, *et al*. Methylation profiles of hereditary and sporadic ovarian cancer. Histopathology. 2010;57:363–370.

[159] Rathi A, Virmani AK, Schorge JO, Elias KJ, Maruyama R et *al*. Methylation profiles of sporadic ovarian tumors and nonmalignant ovaries from high-risk women. Clin. Cancer Res. 2002;8(11):3324–3331.

[160] Yang HJ, Liu VW, Wang Y, Tsang PC, Ngan HY. Differential DNA methylation profiles in gynecological cancers and correlation with clinico-pathological data. BMC Cancer. 2006;6:212.

[161] Samuel S, Naora H. Homeobox gene expression in cancer: insights from developmental regulation and deregulation. Eur J Cancer. 2005;41:2428–2437.

[162] Kelly ZL, Michael A, Butler-Manuel S, Pandha HS, Morgan RG, HOX genes in ovarian cancer. J Ovarian Res. 2011;4:16.

[163] Montavon C, Gloss BS, Warton K, *et al*. Prognostic and diagnostic significance of DNA methylation patterns in high grade serous ovarian cancer. Gynecol Oncol. 2012;124:582–588.

[164] Widschwendter M, Apostolidou S, Jones AA, *et al*. HOXA methylation in normal endometrium from premenopausal women is associated with the presence of ovarian cancer: a proof of principle study. Int J Cancer. 2009;125: 2214–2218.

[165] Pattamadilok J, Huapai N, Rattanatanyong P, *et al*. LINE-1 hypomethylation level as a potential prognostic factor for epithelial ovarian cancer. Int J Gynecol Cancer. 2008;18:711–717.

[166] Woloszynska-Read A, James SR, Link PA, Yu J, Odunsi K, and Karpf AR. DNA methylation-dependent regulation of BORIS/CTCFL expression in ovarian cancer. Cancer Immun. 2007;7:21.

[167] Gupta A, Godwin AK, Vanderveer L, Lu A, Liu J. Hypomethylation of the synuclein gamma gene CpG island promotes its aberrant expression in breast carcinoma and ovarian carcinoma. Cancer Res. 2003;63:664–673.

[168] Chan KY, Ozçelik H, Cheung AN, Ngan HY, Khoo US. Epigenetic factors controlling the BRCA1 and BRCA2 genes in sporadic ovarian cancer. Cancer Res. 2002;62:4151–4156.

[169] Dann RB, DeLoia JA, Timms KM, Zorn KK, Potter J, *et al*. BRCA1/2 mutations andexpression:response to platinum chemotherapy in patients with advanced stage epithelial ovariancancer. Gynecol Oncol. 2012;125:677–82. DOI: 10.1016/j. ygyno. 2012.03.006.

[170] Kwon MJ, Kim SS, Choi YL, Jung HS, Balch C, *et al*. Derepression of CLDN3 and CLDN4 during ovarian tumorigenesisis associated with loss of repressive histone modifications. Carcinogenesis. 2010;31:974–983. DOI:10.1093/carcin/bgp336.

[171] Honda H, Pazin MJ, Ji H, Wernyj RP, Morin PJ. Crucial roles of Sp1 and epigenetic modifications in the regulation of the CLDN4 promoter in ovarian cancer cells. J Biol Chem. 2006;281:21433–21444. DOI:10.1074/jbc. M603767200.

[172] Honda H, Pazin MJ, D'Souza T, Ji H, Morin PJ. Regulation of the CLDN3 gene in ovarian cancer cells. Cancer Biol Ther. 2007;6:1733–1742. DOI:10.4161/cbt.6.11.4832.

[173] Cheng W, Jiang Y, Liu C, Shen O, Tang W, *et al*. Identification of aberrant promoter hypomethylation of HOXA10 in ovarian cancer. J Cancer Res Clin Oncol. 2010;136:1221–1227. doi:10.1007/s00432-010-0772-4.

[174] Fiegl H, Windbichler G, Mueller-Holzner E, Goebel G, Lechner M, *et al*. HOXA11 DNA methylation—a novel prognostic biomarker in ovarian cancer. Int J Cancer. 2008;123(3):725–729. DOI: 10.1002/ijc.23563.

[175] Frasco MA, Ayhan A, Zikan M, Cibula D, Iyibozkurt CA, Yavuz E, *et al*. HOXA methylation in normal endometrium from premenopausal women is associated with the presence of ovarian cancer: a proof of principle study. Int J Cancer. 2009;125(9): 2214–2218. DOI: 10.1002/ijc.24599.

[176] Lee PS, Teaberry VS, Bland AE, Huang Z, Whitaker RS, *et al*. Elevated MAL expression is accompanied by promoter hypomethylation and platinum resistance in epithelial ovarian cancer. Int J Cancer. 2010;126:1378–1389. DOI:10.1002/ijc.24797.

[177] Yang Z, Chen S, Luan X, Li Y, Liu M, *et al*. Micro RNA-214 is aberrantly expressed in cervical cancers and inhibits the growth of HeLa cells. IUBMB Life. 2009;61:1075–82. DOI:10.1002/iub.252.

[178] Bhattacharya R, Nicoloso M, Arvizo R, Wang E, Cortez A, *et al*. MiR-15a and MiR-16 control Bmi-1 expression in ovarian cancer. Cancer Res. 2009;69:9090–9095. DOI: 10.1158/0008-5472.CAN-09-2552.

[179] Izutsu N, Maesawa C, Shibazaki M, Oikawa H, Shoji T, *et al*. Epigenetic modification is involved inaberrant expression of class III beta-tubulin, TUBB3; in ovarian cancer cells. Int J Oncol. 2008;32:1227. DOI:10.3892/ijo_ 32_6_1227.

[180] Dahl KDC, Dahl R, Kruichak JN, Hudson LG. The epidermal growth factor receptor responsive miR25 are presses mesenchymal morphology in ovarian cancer cells. Neoplasia. 2009;11:1208. DOI:10.1593/neo.09942.

[181] GuanY, Yao H, Zheng Z, Qiu G, Sun K. MiR-125b targets BCL3 and suppresses ovarian cancer proliferation. Int J Cancer. 2011;128:2274–2283. DOI:10.1002/ijc.25575

[182] Ibanez de Caceres I, Battagli C, Esteller M, Herman JG, Dulaimi E, Edelson MI, *et al*. Tumor cell-specific BRCA1 and RASSF1A hypermethylation in serum, plasma, and peritoneal fluid from ovarian cancer patients. Cancer Res. 2004;64(18):6476–6481. DOI: 10.1158/0008-5472.CAN-04-1529.

[183] Makarla PB, Saboorian MH, Ashfaq R, Toyooka KO, Toyooka S, *et al*. Promoter hypermethylation profile of ovarian epithelial neoplasms. Clin. Cancer Res. 2005;11(15): 365–369. DOI: 10.1158/1078-0432.CCR-04-2455.

[184] Widschwendter M, Apostolidou S, Jones AA, Fourkala EO, Arora R, *et al*. Promoter hypermethylation contributes to frequent inactivation of a putative conditional tumor suppressor gene connective tissue growth factor in ovarian cancer. Cancer Res. 2007;67(15):7095–7105. DOI: 10.1158/0008-5472.CAN-06-4567.

[185] Barton CA, Gloss BS, Qu W, Statham AL, Hacker NF, *et al*. Collagen and calcium-binding EGF domains 1 is frequently inactivated in ovarian cancer by aberrant promoter hypermethylation and modulates cell migration and survival. Br J Cancer. 2010;102(1):87–96. DOI: 10.1038/sj.bjc.6605429.

[186] Gifford G, Paul J, Vasey PA, Kaye SB, Brown R. The acquisition of hMLH1 methylation in plasma DNA after chemotherapy predicts poor survival for ovarian cancer patients. Clin Cancer Res. 2004;10(13):4420–4426. DOI: 10.1158/1078-0432.CCR-03-0732.

[187] Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol. 2006;24(29):4783–4791. DOI 10.1200/JCO.2006.06.7173.

[188] Zhou XC, Dowdy SC, Podratz KC, Jiang SW. Epigenetic considerations for endometrial cancer prevention, diagnosis and treatment. Gynecol Oncol. 2007;107(1):143–153. DOI: http://dx.doi.org/10.1016/j.ygyno.2007.06.019.

[189] Barton CA, Hacker NF, Clark SJ, O'Brien PM. DNA methylation changes in ovarian cancer: implications for early diagnosis, prognosis and treatment. Gynecol Oncol. 2008;109(1):129–139. DOI 10.1016/j.ygyno.2007.12.017.

[190] Huang YW, Jansen RA, Fabbri E, Potter D, Liyanarachchi S, Chan MW, *et al*. Identification of candidate epigenetic biomarkers for ovarian cancer detection. Oncol Rep. 2009;22(4):853–861. DOI: 10.3892/or_00000509.

[191] Hsu YT, Gu F, Huang YW, Liu J, Ruan J, *et al*. Promoter hypomethylation of EpCAM regulated bone morphogenetic protein gene family in recurrent endometrial cancer. Clin Cancer Res. 2013;19:6272–6285. DOI:10.1158/1078-0432.CCR-13-1734.

[192] Huang YW, Liu JC, Deatherage DE, Luo J, Mutch DG, *et al*. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 oncogene in endometrial cancer. Cancer Res. 2009;69:9038–9046. DOI:10.1158/ 0008-5472.CAN-09-1499.

[193] Muraki Y, Banno K, Yanokura M, Kobayashi Y, Kawaguchi M, *et al*. Epigenetic DNA hypermethylation: clinical applications in endometrial cancer. Oncol Rep. 2009;22:967–972. DOI: 10.3892/or_00000523.

[194] Banno K, Yanokura M, Iida M, Masuda K, Aoki D. Carcinogenic mechanisms of endometrial cancer:Involvement of genetics and epigenetics. J Obstet Gynaecol Res. 2014;40(8): 1957–1967. DOI:10.1111/jog.12442.

[195] Pallarés J, Velasco A, Eritja N, Santacana M, Dolcet X, Cuatrecasas M, *et al*. Promoter hypermethylation and reduced expression of RASSF1A are frequent molecular alterations of endometrial carcinoma. Mod Pathol. 2008;21: 691–699. DOI 0.1038/modpathol.2008.38.

[196] Jo H, Kim JW, Kang GH, Park NH, Song YS, *et al*. Association of promoter hypermethylation of the RASSF1A gene with prognostic parameters in endometrial cancer. Oncol Res. 2006;16(4):205–209. DOI: http://dx.doi.org/10.3727/000000006783981125.

[197] Kang S, Kim JW, Kang GH, Lee S, Park NH, *et al*. Comparison of DNA hypermethylation patterns in different types of uterine cancer: cervical squamous cell carcinoma, cervical adenocarcinoma and endometrial adenocarcinoma. Int J Cancer. 2006;118(9): 2168–2171. DOI: 10.1002/ijc.21609.

[198] Toyota M, Sasaki Y, Satoh A, Ogi K, Kikuchi T, *et al*. Epigenetic inactivation of CHFR in human tumors. Proc Natl Acad Sci U S A. 2003;100(13): 7818–7823. DOI: 10.1073/pnas.1337066100.

[199] Wang X, Yang Y, Xu C, Xiao L, Shen H, *et al.* CHFR suppression by hypermethylation sensitizes endometrial cancer cells to paclitaxel. Int J Gynecol Cancer. 2011;21(6): 996–1003. DOI: 10.1097/IGC.0b013e31821e05e8.

[200] Ignatov A, Bischoff J, Ignatov T, Schwarzenau C, Krebs T, *et al*. APC promoter hypermethylation is an early event in endometrial tumorigenesis. Cancer Sci. 2010;101:321–327. DOI 10.1111/j.1349-7006.2009.01397.x.

[201] Whitcomb BP, Mutch DG, Herzog TJ, Rader JS, Gibb RK, *et al.* Frequent HOXA11 and THBS2 promoter methylation, and a methylator phenotype in endometrial adenocarcinoma. Clin Cancer Res. 2003;9(6):2277–2287.

[202] Wong YF, Chung TK, Cheung TH, Nobori T, Yu AL, *et al*. Methylation of p16INK4A in primary gynecologic malignancy. Cancer Lett.1999;136(2):231–235. DOI: http://dx.doi.org/10.1016/S0304-3835(98)00327-9.

[203] Salvesen HB, MacDonald N, Ryan A, Jacobs IJ, Lynch ED, *et al*. PTEN methylation is associated with advanced stage and microsatellite instability in endometrial carcinoma. Int J Cancer. 2001;91(1):22–26. DOI: 10.1002/1097-0215(20010101)91:1<22::AID-IJC1002>3.0.CO;2-S.

[204] Yeh KT, Yang MY, Liu TC, Chen JC, Chan WL, *et al*. Abnormal expression of period 1 (PER1) in endometrial carcinoma. J Pathol. 2005;206(1):111–120. DOI: 10.1002/path.1756.

[205] Yamaguchi S, Asanoma K, Takao T, Kato K, Wake N. Homeobox gene HOPX is epigenetically silenced in human uterine endometrial cancer and suppresses estrogen-stimulated proliferation of cancer cells by inhibiting serum response factor. Int J Cancer. 2009;124(11):2577–2588. DOI: 10.1002/ijc.24217.

[206] Fiegl H, Gattringer C, Widschwendter A, Schneitter A, Ramoni A, *et al*. Methylated DNA collected by tampons—a new tool to detect endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2004;13(5):882–888.

[207] Wu H, Chen Y, Liang J, Shi B, Wu G, *et al*. Hypomethylation-linked activation of PAX2 mediates tamoxifen-stimulated endometrial carcinogenesis. Nature. 2005;438(7070):981–987 (2005). DOI: 10.1038/nature04225.

[208] Soufir N, Queille S, Liboutet M, Thibaudeau O, Bachelier F, *et al*. Inactivation of the CDKN2A and the p53 tumour suppressor genes in external genital carcinomas and their precursors. Br J Dermatol. 2007;156(3):448–53. DOI: 10.1111/j.1365-2133.2006.07604.x.

[209] Oonk MH, Eijsink JJ, Volders HH, Hollema H, Wisman GB, *et al*. Identification of inguinofemoral lymph node metastases by methylation markers in vulvar cancer. Gynecol Oncol. 2012;125(2):352–357. DOI: 10.1016/j.ygyno.2012.01.013.

[210] Guerrero D, Guarch R, Ojer A, Casas JM, Méndez-Meca C, *et al*. Differential hypermethylation of genes in vulvar cancer and lichen sclerosus coexisting or not with vulvar cancer. Int J Cancer. 2011;128(12):2853–2864. DOI: 10.1002/ijc.25629.

[211] Stephen JK, Chen KM, Raitanen M, Grénman S, Worsham MJ. DNA hypermethylation profiles in squamous cell carcinoma of the vulva. Int J Gynecol Pathol. 2009;28(1):63–75. doi: 10.1097/PGP.0b013e31817d9c61.

[212] Guerrero-Setas D, Perez-Janices N, Ojer A, Blanco-Fernandez L, Guarch-Troyas C, *et al*. Differential gene hypermethylation in genital lichen sclerosus and cancer: a comparative study. Histopathology. 2013;63(5):659–669.

[213] Lee TS, Kim JW, Kang GH, Park NH, Song YS, *et al*. DNA hypomethylation of CAGE promoters in squamous cell carcinoma of uterine cervix. Ann N Y Acad Sci. 2006;1091:218–224. DOI:10.1196/annals.1378.068.

[214] Huang F, Lin C, Shi YH, Kuerban G. Micro RNA-101 inhibits cell proliferation, invasion, and promotes apoptosis by regulating cyclooxygenase-2 in Hela cervical carcinoma cells. Asian Pac J Cancer Prev. 2013;14:5915–5920. DOI:10.7314/APJCP.2013.14.10.5915.

[215] Yamamoto N, Kinoshita T, Nohata N, Yoshino H, Itesako T, *et al*. Tumor-suppressive microRNA-29a inhibits cancer cell migration and invasion via targeting HSP47in cervical squamous cell carcinoma. Int J Oncol. 2013;43:1855–1863. DOI:10.3892/ijo.2013.2145.

[216] Zhu X, Er K, Mao C, Yan Q, Xu H, *et al*. miR-203 suppresses tumor growth and angiogenesis by targeting VEGFA in cervical cancer. Cell Physiol Biochem. 2013;32:64–73. DOI:10.1159/000350125.

[217] Shell S, Park SM, Radjabi AR, Schickel R, Kistner EO, *et al*. Let-7 expression defines two differentiation stages of cancer. Proc Natl Acad Sci U S A. 2007;104(27):11400–11405. DOI: 10.1073/pnas.0704372104.

[218] Poleshko A, Einarson MB, Shalginskikh N, Zhang R, Adams PD, *et al.* Identification of a functional network of human epigenetic silencing factors. J Biol Chem. 2010;285(1):422–433. DOI: 10.1074/jbc.M109.064667.

[219] Yang N, Kaur S, Volinia S, Greshock J, Lassus H, *et al.* MicroRNA microarray identifies Let-7i as a novel biomarker and therapeutic target in human epithelial ovarian cancer. Cancer Res. 2008;68(24):10307-14. DOI: 10.1158/0008-5472.CAN-08-1954.

[220] Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, *et al.* MicroRNA signatures in human ovarian cancer. Cancer Res. 2007;67(18):8699–8707. DOI: 10.1158/0008-5472.CAN-07-1936.

[221] Guo LM, Pu Y, Han Z, Liu T, Li YX, *et al*. MicroRNA-9 inhibits ovarian cancer cell growth through regulation of NF-kappaB1. FEBS J. 2009;276(19):5537–5546. DOI: 10.1111/j.1742-4658.2009.07237.x.

[222] Nam EJ, Yoon H, Kim SW, Kim H, Kim YT, *et al*. MicroRNA expression profiles in serous ovarian carcinoma. Clin Cancer Res. 2008;14(9):2690–2695. DOI: 10.1158/1078-0432.CCR-07-1731.

[223] Dahiya N, Sherman-Baust CA, Wang TL, Davidson B, Shih IeM, *et al*. MicroRNA expression and identification of putative miRNA targets in ovarian cancer. PLoS ONE. 2008;3(6):e2436. DOI: 10.1371/journal.pone.0002436.

[224] Laios A, O'Toole S, Flavin R, Martin C, Kelly L, Ring M, *et al*. Potential role of miR-9 and miR-223 in recurrent ovarian cancer. Mol Cancer. 2008;7:35. DOI 10.1186/1476-4598-7-35.

[225] Corney DC, Flesken-Nikitin A, Godwin AK, Wang W, Nikitin AY. MicroRNA-34b and microRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth. Cancer Res. 2007;67(18):8433–8438. DOI: 10.1158/0008-5472.CAN-07-1585.

[226] Zhang L, Huang J, Yang N, Greshock J, Megraw MS, *et al*. microRNAs exhibit high frequency genomic alterations in human cancer. Proc Natl Acad Sci U S A. 2006;103(24),9136–9141. DOI: 10.1073/pnas.0508889103.

[227] Cowden Dahl KD, Dahl R, Kruichak JN, Hudson LG. The epidermal growth factor receptor responsive miR-125a represses mesenchymal morphology in ovarian cancer cells. Neoplasia. 2009;11(11):1208–1215. DOI 10.1593/neo.09942.

[228] Sorrentino A, Liu CG, Addario A, Peschle C, Scambia G, *et al*. Role of microRNAs in drug-resistant ovarian cancer cells. Gynecol Oncol. 2008;111(3):478–486. DOI: 10.1016/j.ygyno.2008.08.017.

[229] Resnick KE, Alder H, Hagan JP, Richardson DL, Croce CM, *et al*. The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform. Gynecol Oncol. 2009;112(1):55–59. DOI: 10.1016/j.ygyno.2008.08.036.

[230] Zhang L, Volinia S, Bonome T, Calin GA, Greshock J, *et al*.Genomic and epigenetic alterations deregulate microRNA expression in human epithelial ovarian cancer. Proc Natl Acad Sci U S A. 2008;105(19):7004–7009. DOI: 10.1073/pnas.0801615105.

[231] Papagiannakopoulos T, Pan G, Thomson JA, Kosik KS. MicroRNA-145 regulates OCT4; SOX2; and KLF4 and represses pluripotency in human embryonic stem cells. Cell. 2009;137(4):647–658. DOI: 10.1016/j.cell.2009.02.038.

[232] Hu X, Macdonald DM, Huettner PC, Feng Z, *et al*. miR-200 microRNA cluster as prognostic marker in advanced ovarian cancer. Gynecol Oncol. 2009;114(3):457–464. DOI 10.1016/j.ygyno.2009.05.022.

[233] Shimono Y, Zabala M, Cho RW, Lobo N, Dalerba P, Qian D, *et al*. Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells. Cell. 2009;138(3): 592–603. DOI: 10.1016/j.cell.2009.07.011.

[234] Choi YL, Kim J, Kwon MJ, Choi JS, Kim TJ, Bae DS, *et al*. Expression profile of tight junction protein claudin 3 and claudin 4 in ovarian serous adenocarcinoma with prognostic correlation. Histol Histopathol. 2007;22(11):1185–1195. DOI: http://www.hh.um.es.

[235] Fasanaro P, Greco S, Lorenzi M, Pescatori M, Brioschi M, *et al*. An integrated approach for experimental target identification of hypoxia-induced miR-210. J Biol Chem. 2009;284(50):35134–35143. DOI: 10.1074/jbc.M109.052779.

[236] Giannakakis A, Sandaltzopoulos R, Greshock J, Liang S, Huang J, Hasegawa K, *et al*. miR-210 links hypoxia with cell cycle regulation and is deleted in human epithelial ovarian cancer. Cancer Biol Ther. 2008;7(2):255–264. DOI: 10.4161/cbt.7.2.5297.

[237] Wyman SK, Parkin RK, Mitchell PS, Fritz BR, O'Briant K, Godwin AK, *et al*. Repertoire of microRNAs in epithelial ovarian cancer as determined by next generation sequencing of small RNA cDNA libraries. PLoS One. 2009;4(4): E5311. DOI: 10.1371/journal.pone.0005311.

[238] Lee CH, Subramanian S, Beck AH, Espinosa I, Senz J, *et al*. MicroRNA profiling of BRCA1/2 mutation-carrying and non-mutation-carrying high-grade serous carcinomas of ovary. PLoS One. 2009;4(10):E7314. DOI: 10.1371/journal.pone.0007314.

[239] Abdelmohsen K, Srikantan S, Kuwano Y, Gorospe M. miR-519 reduces cell proliferation by lowering RNA-binding protein HuR levels. Proc Natl Acad Sci U S A. 2008;105(51):20297–20302. DOI: 10.1073/pnas.0809376106.

[240] Bearfoot JL, Choong DY, Gorringe KL, Campbell IG. Genetic analysis of cancer-implicated microRNA in ovarian cancer. Clin. Cancer Res. 2008;14(22):7246–7250. DOI: 10.1158/1078-0432.CCR-08-1348.

[241] Yang Y, Chaerkady R, Beer MA, Mendell JT, Pandey A. Identification of miR-21 targets in breast cancer cells using a quantitative proteomic approach. Proteomics. 2009;9(5):1374–1384. DOI: 10.1002/pmic.200800551.

[242] Shibata D, Mori Y, Cai K, Zhang L, Yin J, *et al*. RAB32 hypermethylation and microsatellite instability in gastric and endometrial adenocarcinomas. Int J Cancer. 2006;119(4), 801–806. DOI: 10.1002/ijc.21912.

[243] Eitan R, Kushnir M, Lithwick-Yanai G, David MB, Hoshen M, Glezerman M, *et al*. Tumor microRNA expression patterns associated with resistance to platinum based chemotherapy and survival in ovarian cancer patients. Gynecol Oncol. 2009;114(2): 253–259. DOI: 10.1016/j.ygyno.2009.04.024.

[244] Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. Gynecol Oncol. 2008;110(1):13–21. DOI: 10.1016/j.ygyno.2008.04.033.

[245] Bendoraite A, Knouf EC, Garg KS, Parkin RK, Kroh EM, *et al*. Regulation of miR-200 family microRNAs and ZEB transcription factors in ovarian cancer: evidence supporting a mesothelial-to-epithelial transition. Gynecol Oncol. 2010;116(1):117–125. DOI: 10.1016/j.ygyno.2009.08.009.

[246] Shen J, Ambrosone CB, DiCioccio RA, Odunsi K, Lele SB, Zhao H. A functional polymorphism in the miR-146a gene and age of familial breast/ovarian cancer diagnosis. Carcinogenesis. 2008;29(10):1963–1966. DOI: 10.1093/carcin/bgn172.

[247] Risinger JI, Maxwell GL, Chandramouli GV, Aprelikova O, Litzi T, *et al*. Gene expression profiling of microsatellite unstable and microsatellite stable endometrial cancers

indicates distinct pathways of aberrant signaling. Cancer Res. 2005;65(12):5031–5037. DOI: 10.1158/0008-5472.CAN-04-0850.

[248] Ji J, Yamashita T, Budhu A, Forgues M, Jia HL, *et al*. Identification of microRNA-181 by genome-wide screening as a critical player in EpCAM-positive hepatic cancer stem cells. Hepatology. 2009;50(2):472–480. DOI: 10.1002/hep.22989.

[249] Zhu H, Wu H, Liu X, Evans BR, Medina DJ, *et al*. Role of microRNA miR-27a and miR-451 in the regulation of MDR1/P-glycoprotein expression in human cancer cells. Biochem Pharmacol. 2008;76(5):582–588. DOI: 10.1016/j.bcp.2008.06.007.

[250] Cochrane DR, Spoelstra NS, Howe EN, Nordeen SK, Richer JK. MicroRNA-200c mitigates invasiveness and restores sensitivity to microtubule-targeting chemotherapeutic agents. Mol Cancer Ther. 2009;8(5):1055–1066. DOI: 10.1158/1535-7163.MCT-08-1046.

[251] Yu J, Ryan DG, Getsios S, Oliveira-Fernandes M, Fatima A, Lavker RM. MicroRNA-184 antagonizes microRNA-205 to maintain SHIP2 levels in epithelia. Proc Natl Acad Sci U S A. 2008;105(49):19300–19305. DOI: 10.1073/pnas.0803992105.

[252] Boren T, Xiong Y, Hakam A, Wenham R, Apte S, Chan G, *et al*. MicroRNAs and their target messenger RNAs associated with ovarian cancer response to chemotherapy. Gynecol Oncol. 2009;113(2):249–255. DOI: 10.1016/j.ygyno.2009.01.014.

[253] Wurz K, Garcia RL, Goff BA, Mitchell PS, Lee JH, *et al*. MiR-221 and MiR-222 alterations in sporadic ovarian carcinoma: relationship to CDKN1B, CDKNIC and overall survival. Genes Chromosomes Cancer. 2010;49(7):577–584. DOI: 10.1002/gcc.20768.

[254] Fukao T, Fukuda Y, Kiga K, Sharif J, Hino K, *et al*. An evolutionarily conserved mechanism for microRNA-223 expression revealed by microRNA gene profiling. Cell. 2007;129(3):617–631. DOI: http://dx.doi.org/10.1016/j.cell.2007.02.048.

[255] Würdinger T, Tannous BA, Saydam O, Skog J, Grau S, Soutschek J, *et al*. miR-296 regulates growth factor receptor overexpression in angiogenic endothelial cells. Cancer Cell. 2008;14(5):382–393. DOI: 10.1016/j.ccr.2008.10.005.

[256] Yang WT, Lewis MT, Hess K, Wong H, Tsimelzon A, Karadag N, *et al*. Decreased TGFb signaling and increased COX2 expression in high risk women with increased mammographic breast density. Breast Cancer Res Treat. 2010;119(2):305–314. DOI: 10.1007/s10549-009-0350-0.

[257] Hiroki E, Akahira J, Suzuki F, Nagase S, Ito K, *et al*. Changes in microRNA expression levels correlate with clinicopathological features and prognoses in endometrial serous adenocarcinomas. Cancer Sci. 2009;101(1):241–249. DOI: 10.1111/j.1349-7006.2009.01385.x.

[258] Dalmay T, Edwards DR. MicroRNAs and the hallmarks of cancer. Oncogene. 2006;25(46):6170–6175. DOI: 10.1038/sj.onc.1209911.

[259] Lujambio A, Calin GA, Villanueva A, Ropero S, Sánchez-Céspedes M, *et al*. A microRNA DNA methylation signature for human cancer metastasis. Proc Natl Acad Sci U S A. 2008;105(36):13556–13561. DOI: 10.1073/pnas.0803055105.

[260] Boren T, Xiong Y, Hakam A, Wenham R, Apte S, *et al*. MicroRNAs and their target messenger RNAs associated with endometrial carcinogenesis. Gynecol Oncol. 2008;110(2):206–215. DOI: 10.1016/j.ygyno.2008.03.023.

[261] Wu W, Lin Z, Zhuang Z, Liang X. Expression profile of mammalian microRNAs in endometrioid adenocarcinoma. Eur J Cancer Prev. 2009;18(1):50–55. DOI: 10.1097/CEJ.0b013e328305a07a.

[262] Kawahara Y, Zinshteyn B, Sethupathy P, Iizasa H, Hatzigeorgiou AG, Nishikura K. Redirection of silencing targets by adenosine-to-inosine editing of miRNAs. Science. 2007;315(5815):1137–1140. DOI: 10.1126/science.1138050.

[263] Mayr D, Kanitz V, Anderegg B, Luthardt B, Engel J, *et al*. Analysis of gene amplification and prognostic markers in ovarian cancer using comparative genomic hybridization for microarrays and immunohistochemical analysis for tissue microarrays. Am J Clin Pathol. 2006;126(1):101–109. DOI: 10.1309/N6X5MB24BP42KP20.

[264] Toloubeydokhti T, Pan Q, Luo X, Bukulmez O, Chegini N. The expression and ovarian steroid regulation of endometrial micro-RNAs. Reprod Sci. 2008;15(10):993–1001. DOI: 10.1177/1933719108324132.

[265] Kim JY, Tavare S, Shibata D. Counting human somatic cell replications: methylation mirrors endometrial stem cell divisions. Proc Natl Acad Sci U S A. 2005;102(49):17739–17744. DOI: 10.1073/pnas.0503976102.

[266] Myatt SS, Wang J, Monteiro LJ, Christian M, Ho KK, *et al*. Definition of microRNAs that repress expression of the tumor suppressor gene FOXO1 in endometrial cancer. Cancer Res. 2010;70:367–377. DOI: 10.1158/0008-5472.CAN-09-1891.

[267] Orom UA, Nielsen FC, Lund AH. MicroRNA-10a binds the 5′UTR of ribosomal protein mRNAs and enhances their translation. Mol Cell. 2008;30(4):460–471. DOI: 10.1016/j.molcel.2008.05.001.

[268] Chung TK, Cheung TH, Huen NY, Wong KW, Lo KW, Yim SF, *et al*. Dysregulated microRNAs and their predicted targets associated with endometrioid endometrial adenocarcinoma in Hong Kong women. Int J Cancer. 2009;124(6):1358–1365. DOI: 10.1002/ijc.24071.

[269] Luthra R, Singh RR, Luthra MG, Li YX, Hannah C, *et al*. MicroRNA-196a targets annexin A1: a microRNA-mediated mechanism of annexin A1 downregulation in cancers. Oncogene. 2008;27(52):6667–6678. DOI: 10.1038/onc.2008.256.

[270] Kim YK, Yu J, Han TS, Park SY, Namkoong B, Kim DH, Hur K, Yoo MW, Lee HJ, Yang HK, Kim VN. Functional links between clustered microRNAs: suppression of

cell-cycle inhibitors by microRNA clusters in gastric cancer. Nucleic Acids Res. 2009;37(5):1672–1681. DOI: 10.1093/nar/gkp002.

[271] Lui WO, Pourmand N, Patterson BK, Fire A. Patterns of known and novel small RNAs in human cervical cancer. Cancer Res. 2007;67(13):6031–6043. DOI: 10.1158/0008-5472.CAN-06-0561.

[272] Wang X, Tang S, Le SY, Lu R, Rader JS, *et al*. Aberrant expression of oncogenic and tumor-suppressive microRNAs in cervical cancer is required for cancer cell growth. PLoS ONE. 2008;3(7):e2557. DOI: 10.1371/journal.pone.0002557.

[273] Torres A, Torres K, Maciejewski R, Harvey WH. Micro-RNAs and their role in gynecological tumors. Med Res Rev. 2011;31(6):895–923. DOI: 10.1002/med.20205.

[274] Pereira PM, Marques JP, Soares AR, Carreto L, Santos MA. MicroRNA expression variability in human cervical tissues. PLoS One. 2010;5(7):e11780. DOI: 10.1371/journal.pone.0011780.

[275] Botezatu A, Goia-Rusanu CD, Iancu IV, Huica I, Plesa A, *et al*. Quantitative analysis of the relationship between microRNA-124a, -34b and -203 gene methylation and cervical oncogenesis. Mol Med Rep. 2011;4(1):121–128. DOI: 10.3892/mmr.2010.394.

[276] Wilting SM, van Boerdonk RA, Henken FE, Meijer CJ, Diosdado B, Meijer GA, *et al*. Methylation-mediated silencing and tumour suppressive function of hsa-miR-124 in cervical cancer. Mol Cancer. 2010;9:167–181. DOI: 10.1186/1476-4598-9-167.

[277] Chakrabarti M, Banik NL, Ray SK. miR-138 overexpression is more than hTERT knockdown to potentiate apigenin for apoptosis in neuroblastoma in vitro and *in vivo*. Expl Cell Res. 2013;319(10);1575–1585. DOI: 10.1016/j.yexcr.2013.02.025.

[278] Lee JW, Choi CH, Choi JJ, Park YA, Kim SJ, *et al*. Altered MicroRNA expression in cervical carcinomas. Clin Cancer Res. 2008;14: 2535–2542. DOI: 10.1158/1078-0432.CCR-07-1231.

[279] Gregory PA, Bracken CP, Bert AG, Goodall GJ. MicroRNAs as regulators of epithelial–mesenchymal transition. Cell Cycle. 2008;7(20):3112-8. DOI:10.4161/cc.7.20.6851.

[280] Martinez I, Gardiner AS, Board KF, Monzon FA, Edwards RP, Khan SA. Human papillomavirus type 16 reduces the expression of microRNA-218 in cervical carcinoma cells. Oncogene. 2008;27(18):2575–2582. DOI:10.1038/sj.onc.1210919.

[281] Tian RQ, Wang XH, Hou LJ, Jia WH, Yang Q, *et al*. MicroRNA-372 is down-regulated and targets cyclin-dependent kinase 2 (CDK2) and cyclin A1 in human cervical cancer, which may contribute to tumorigenesis. J Biol Chem. 2011;286(29):25556–25563. DOI: 10.1074/jbc.M111.221564.

[282] Abdelmohsen K, Kim MM, Srikantan S, Mercken EM, Brennan SE, *et al*. miR-519 suppresses tumor growth by reducing HuR levels. Cell Cycle. 2010;9(7):1354–1359. DOI: 10.4161/cc.9.7.11164.

[283] Hu X, Schwarz JK, Lewis JS Jr, Huettner PC, Rader JS, *et al*. A microRNA expression signature for cervical cancer prognosis. Cancer Res. 2010;70(4):1441–1448. DOI: 10.1158/0008-5472.CAN-09-3289.

[284] Yao Q, Xu H, Zhang QQ, Zhou H, Qu LH. MicroRNA-21 promotes cell proliferation and down-regulates the expression of programmed cell death 4 (PDCD4) in HeLa cervical carcinoma cells. Biochem Biophys Res Commun. 2009;388(3):539-42. DOI: 10.1016/j.bbrc.2009.08.044.

[285] Gocze K, Gombos K, Juhasz K, Kovacs K, Kajtar B, *et al*. Unique microRNA expression profiles in cervical cancer. Anticancer Res 2013;33(6):2561–2567.

[286] Li BH, Zhou JS, Ye F, Cheng XD, Zhou CY, *et al*. Reduced miR-100 expression in cervical cancer and precursors and its carcinogenic effect through targeting PLK1 protein. Eur J Cancer. 2011;47(14):2166–2174. DOI: 10.1016/j.ejca.2011.04.037.

[287] Gilad S, Meiri E, Yogev Y, Benjamin S, Lebanony D, Yerushalmi N, *et al*. Serum microRNAs are promising novel biomarkers, PLoS One. 2008;3(9):e3148. DOI: 10.1371/journal.pone.0003148.

[288] Qin W, Dong P, Ma C, Mitchelson K, Deng T, Zhang L, *et al*. MicroRNA-133b is a key promoter of cervical carcinoma development through the activation of the ERK and AKT1 pathways. Oncogene. 2011;31(36):4067–4075. DOI: 10.1038/onc.2011.561.

[289] Li JH, Xiao X, Zhang YN, Wang YM, Feng LM, *et al*. MicroRNA miR-886-5p inhibits apoptosis by down-regulating Bax expression in human cervical carcinoma cells. Gynecol Oncol. 2011;120(1):145–151. doi:10.1016/j.ygyno.2010.09.009.

[290] Li H, Zhang R. Role of EZH2 in epithelial ovarian cancer: from biological insights to therapeutic target. FrontOncol. 2013; 3:47. DOI:10.3389/fonc.2013.00047.

[291] Scoumanne A, Chen X. Protein methylation: a new mechanism of p53 tumor suppressor regulation. Histol Histopathol. 2008; 23: 1143–1149.

[292] Black JC, Manning AL, Van Rechem C, Kim J, Ladd B, *et al*. KDM4A lysine demethylase induces site-specific copy gain and rereplication of regions amplified in tumors. Cell. 2013;154:541–555. DOI: 10.1016/j.cell.2013.06.051.

[293] Bryan EJ, Jokubaitis VJ, Chamberlain NL, Baxter SW, Dawson E, *et al*. Mutation analysis of EP300 in colon, breast and ovarian carcinomas. Int J Cancer. 2002;102:137–141. DOI: 10.1002/ijc.10682.

[294] Cai M, Hu Z, Liu J, Gao J, Tan M, *et al*. Expression of hMOF in different ovarian tissues and its effects on ovarian cancer prognosis. Oncol Rep. 2015;33(2):685–692. DOI: 10.3892/or.2014.3649.

[295] Liu N, Zhang R, Zhao X, Su J, Bian X, *et al.* A potential diagnostic marker for ovarian cancer: involvement of the histone acetyltransferase, human males absent on the first. Oncol Lett. 2013;2:393–400. DOI:10.3892/ol.2013.1380.

[296] Ward R, Johnson M, Shridhar V, van Deursen J, Couch FJ. CBP truncating mutations in ovarian cancer. J Med Genet. 2005;42:514–518. DOI: 10.1136/jmg.2004.025080.

[297] Weichert W, Denkert C, Noske A, Darb-Esfahani S, Dietel M, *et al*. Expression of class I histone deacetylases indicates poor prognosis in endometrioid subtypes of ovarian and endometrial carcinomas. Neoplasia. 2008;10(9):1021–1027. DOI: 0.1593/neo.08474

[298] Wang HL, Liu MM, Ma X, Fang L, Zhang ZF, *et al*. Expression and effects of JMJD2A histone demethylase in endometrial carcinoma. Asian Pac J Cancer Prev. 2014;15:3051–3056.

[299] Bachmann IM, Halvorsen OJ, Collett K, Stefansson IM, Straume O, *et al*. EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate,and breast. J Clin Oncol. 2006;24:268–273. DOI: 10.1200/JCO.2005.01.5180.

[300] Hayami S, Yoshimatsu M, Veerakumarasivam A, Unoki M, Iwai Y, Tsunoda T, *et al*. Overexpression of the JmjC histone demethylase KDM5B in human carcinogenesis: involvement in the proliferation of cancer cells through the E2F/RB pathway. Mol Cancer. 2010;9:59. DOI: 10.1186/1476-4598-9-59.

[301] Hyland PL, McDade SS, McCloskey R, Dickson GJ, Arthur K, *et al*. Evidence for alteration of EZH2; BMI1; and KDM6A and epigenetic reprogramming in human papillomavirus type 16 E6/E7-expressing keratinocytes. J Virol. 2011;85(21):10999–11006. DOI: 10.1128/JVI.00160-11.

[302] Smith JA, White EA, Sowa ME, Powell ML, Ottinger M, *et al*. Genome-wide siRNA screen identifies SMCX, EP400; and Brd4 as E2-dependent regulators of human papillomavirus oncogene expression. Proc Natl Acad Sci U S A. 2010;107(8):3752-7.DOI: 10.1073/pnas.0914818107.

[303] McLaughlin-Drubin ME, Crum CP, Münger K. Human papillomavirus E7 oncoprotein induces KDM6A and KDM6B histone demethylase expression and causes epigenetic reprogramming. Proc Natl Acad Sci U S A. 2011;108(5):2130–2135. DOI: 10.1073/pnas.1009933108.

[304] Bernat A, Avvakumov N, Mymryk JS, Banks L. Interaction between the HPV E7 oncoprotein and the transcriptional coactivator p300. Oncogene. 2003;22:7871–7881. DOI: 10.1038/sj.onc.1206896.

[305] Avvakumov N, Torchia J, Mymryk JS. Interaction of the HPV E7 proteins with the pCAF acetyltransferase. Oncogene. 2003;22:3833–3841. DOI: 10.1038/sj.onc.1206562.

[306] Longworth MS, Laimins LA. The binding of histone deacetylases and the integrity of zinc finger-like motifs of the E7 protein are essential for the life cycle of human papillomavirus type 31. J Virol. 2004;78:3533–3541. DOI: 10.1128/JVI.78.7.3533-3541.2004.

[307] Brehm A, Nielsen SJ, Miska EA, McCance DJ, Reid JL, *et al*. The E7 oncoprotein associates with Mi2 and histone deacetylase activity to promote cell growth. EMBO J. 1999;18:2449–2458. DOI: 10.1093/emboj/18.9.2449.

[308] Westhoff MA, Brühl O, Debatin KM. Cancer therapy: know your enemy? Mol Cell Pediatr. 2014; 1:10. http://www.molcellped.com/content/1/1/10.

[309] Witz IP, The tumor microenvironment: the making of a paradigm. Cancer Microenviron. 2009;S1:9–17. doi: 10.1007/s12307-009-0025-8.

[310] Tsai MJ, Chang WA, Huang MS, Kuo PL. Tumor microenvironment: a new treatment target for cancer. ISRN Biochem. 2014. http://dx.doi.org/10.1155/2014/351959.

[311] Ma XJ, Dahiya S, Richardson E, Erlander M, Sgroi DC. Gene expression profiling of the tumor microenvironment during breast cancer progression. Breast Cancer Res. 2009;11(1):R7.

[312] Hamm CA, Stevens JW, Xie H, Vanin EF, Morcuende JA, *et al*. Microenvironment alters epigenetic and gene expression profiles in Swarm rat chondrosarcoma tumors. BMC Cancer. 2010;10:471.

[313] Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet. 2011;13:97–109. doi: 10.1038/nrg3142.

[314] Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet. 2007;8: 253–262.

[315] Dey P. Epigenetics meets the tumor microenvironment. Med Epigenet. 2013; 31–36. DOI: 10.1159/000354283.

[316] Bierie B, Moses HL. Tumour microenvironment: TGFβ: the molecular Jekyll and Hyde of cancers. Nat Rev Cancer 2006; 6:506–520. doi:10.1038/nrc1926.

[317] Denko N, Schindler C, Koong A, Laderoute K, Green C, *et al*. Epigenetic regulation of gene expression in cervical cancer cells by the tumor microenvironment. Clin Cancer Res. 2000;6(2): 480–487.

[318] Kiaris H, Trimis G, Papavassiliou AG. Regulation of tumor-stromal fibroblast interactions: implications in anticancer therapy. Curr Med Chem. 2008;15:3062–3067.

[319] Yadav SS, Prasad SB, Das M, Kumari S, Pandey LK, *et al*. Epigenetic silencing of CXCR4 promotes loss of cell adhesion in cervical cancer. BioMed Res Int. 2014; doi.org/10.1155/2014/581403.

[320] Rusek AM, Abba M, Eljaszewicz A, Moniuszko M, Niklinski J, *et al*. MicroRNA modulators of epigenetic regulation, the tumor microenvironment and the immune system in lung cancer. Mol Cancer. 2015; 14:34. DOI 10.1186/s12943-015-0302-8.

[321] Mitra AK, Zillhardt M, Hua Y, Tiwari P, Murmann AE, *et al*. MicroRNAs reprogram normal fibroblasts into cancer-associated fibroblasts in ovarian cancer. Cancer Discov. 2012;2:1100–1108.

[322] DesRochers TM, Shamis Y, Alt-Holland A, Kudo Y, Takata T, *et al*. The 3D tissue microenvironment modulates DNA methylation and E-cadherin expression in squamous cell carcinoma. Epigenetics. 2012;7(1): 34–46.

[323] Li JR, Li MQ, Bao JT, Li JZ: Correlation between expression of metastasis-associated gene 1 and matrix metalloproteinase 9 and invasion and metastasis of breast cancer. Zhonghua Yi Xue Za Zhi. 2008;88:2278–2280.

[324] Talbot LJ, Bhattacharya SD, Kuo PC. Epithelial–mesenchymal transition, the tumor microenvironment, and metastatic behavior of epithelial malignancies. Int J Biochem Mol Biol. 2012;3(2):117–136.

[325] Ungefroren H, Sebens S, Seidl D, Lehnert H, Hass R. Interaction of tumor cells with the microenvironment. Cell Commun Signal. 2011;9:18. http://www.biosignaling.com/content/9/1/18.

[326] Kaplan RN, Rafii S, Lyden D. Preparing the 'soil': the premetastatic niche. Cancer Res. 2006; 66: 11089–11093.

[327] Schedin P, Elias A. Multistep tumorigenesis and the microenvironment. Breast Cancer Res. 2004; 6: 93–101.

[328] Farmer P, Bonnefoi H, Anderle P, Cameron D, Wirapati P, *et al.* A stroma related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. Nat Med. 2009; 15: 68–74.

[329] Niero EL, Rocha-Sales B, Lauand C, Cortez BA, Medina de Souza M, *et al*. The multiple facets of drug resistance: one history, different approaches. J Exp Clin Cancer Res. 2014; 33:37. doi:10.1186/1756-9966-33-37.

[330] Kawakami Y, Miyamoto K, Takehara K, Kumagai M, Samura O, *et al*. Down-regulation of MDR1 by epigenetic alteration in human epithelial ovarian cancer cells. J Clin Oncol. 27; 2009 (suppl; abstr e16556).

[331] Januchowski R, Wojtowicz K, Sujka-Kordowska P, Andrzejewska M, Zabel M. MDR gene expression analysis of six drug-resistant ovarian cancer cell lines. Biomed Res Int. 2013;2013:241763. doi: 10.1155/2013/241763.

[332] Lhomme´ C, Joly F, Walker JL *et al*. Phase III study of valspodar (PSC 833) combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone in patients with stage IV or suboptimally debulked stage III epithelial ovarian cancer or primary peritoneal cancer. J Clin Oncol. 2008;26:2674–2682.

[333] Markova SM, Kroetz DL. ABCC4 is regulated by microRNA-124a and microRNA-506. Biochem Pharmacol. 2014;87:515–522.

[334] Sui H, Fan Z-Z, Li Q. Signal transduction pathways and transcriptional mechanisms of ABCB1/Pgp-mediated multiple drug resistance in human cancer cells. J Int Med Res 2012; 40:426–435.

[335] Uthoff SM, Eichenberger MR, McAuliffe TL, Hamilton CJ, Galandiuk S. Wingless-type frizzled protein receptor signaling and its putative role in human colon cancer. Mol Carcinogen. 2001;31:56–62.

[336] Hajra KM, Fearon ER. Cadherin and catenin alterations in human cancer. Genes Chromosomes Cancer 2002; 34:255–268.

[337] Persad S, Troussard AA, McPhee TR, Mulholland DJ, Dedhar S. Tumor suppressor PTEN inhibits nuclear accumulation of beta-catenin and T cell/lymphoid enhancer factor 1-mediated transcriptional activation. J Cell Biol. 2001;153:1161–1174.

[338] Bookman MA. The addition of new drugs to standard therapy in the first-line treatment of ovarian cancer. Ann Oncol. 2010;21(Supplement 7): vii211–vii217. doi: 10.1093/annonc/mdq368.

IntechOpen

IntechOpen

IntechOpen