Chapter

The Role of the Meiotic Component in Reproduction of B-RAF-Mutated Melanoma: A Review and "Brainstorming" Session

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Abstract

The ectopic expression of cancer testis (CT) antigens and classic meiotic genes is characteristic and a hallmark of poor prognosis of melanoma disease. Here the potential mechanisms of meiotic influence on the cell and life cycle of malignant melanoma are reviewed in the genetic, epigenetic, and evolutionary aspects. The involved mutant B-RAF and N-RAS-induced senescence may be reversed by reprogramming, with stemness linked to meiotic landscape, possibly induced by DNA double-strand breaks at the mutual telomere hot spots. The induced by senescence mitotic slippage (reset of interphase from arrested metaphase) and resulting polyploidy trigger the meiotic ploidy cycle to function for effective DNA recombination repair, genome reduction, and escape of survivors, which enter the mitotic cycle again. The aberrant meiotic pathway in cancer is reviewed in the ancestral asexual variants; inverted meiosis is possible. The conundrum of cancer aneuploidy paradox, selection of fit clones, and the Muller's Ratchet of inevitable accumulation of harmful mutations is discussed. The bioinformatic study of the densely connected protein interaction network of CT antigen expressed genes revealed the melanomagenesis attractor composed of PRAME and small MAGEA group in primary tumors as compared with B-RAF-mutant nevi, restructured stemness network; invasive melanoma further displays the leading role of SPANX CT antigen group; meiotic genes are expressed in all three tissue cohorts.

Keywords: B-RAF-mutant melanoma, reversible senescence, reversible polyploidy, DSB hot spots, ancestral meiosis

1. Introduction

Approximately 50% of melanomas carry mutations in the gene encoding *B-RAF* [1]. Ninety percent of activating *B-RAF* mutations affect the codon 600 and the most common missense change there is V600E [2]. This mutation leads to a constitutive activation of B-RAF, and consequently of the MAPK/ERK pathway,

promoting survival and proliferation of melanoma cells. Other frequent mutations in melanoma include *N-RAS* gene, which is estimated to be present in 13–25% of melanomas [1], and being upstream of the same MAPK/ERK signal transduction pathway. The MAPK/ERK signal transduction pathway involves a signaling cascade initiated by the binding of growth factors or cytokines to their respective receptors, resulting in activation of RAS, which then recruits RAF proteins, a family of protein kinases including B-RAF, to the cell membrane. Phosphorylation of RAF allows the activation of MEK1 [MAP kinase/extracellular signal-regulated kinase 1(ERK1)], which positively regulates the extracellular signal-regulated kinases (ERK). ERK can then directly phosphorylate downstream transcription factors, leading to increased transcription and eventual cell growth and proliferation [3]. Following the discovery of the V600E mutation, the pathway targeting inhibitor drugs was developed [4–10]. However, while initial responses are impressive, therapeutic resistance develops in nearly every patient at a median of 11–15 months of treatment [6, 7, 9, 11, 12].

Human nevi (benign lesions of melanocytes) also frequently harbor V600E mutation in *B-RAF* [13]; however, in spite of the oncogenic nature of this mutation [14], they display classical characteristics of senescence [15] and remain benign in the large majority of cases. At the same time, nevi are supposed to give rise to a quarter of all melanomas [16]. This led to the concept that oncogene induced senescence (OIS) precedes transformation [15, 17, 18], in particular if induced by mutant RAS or *B-RAF*. The expression of mutant RAS in normal human tissues inducing cell proliferation arrest was first described in [19] and further widely used as a model of OIS in normal cells. For a long time, OIS as well as senescence induced either by chemotherapy or oxidative stress (so called accelerated senescence ACS) were assumed as a barrier in premalignant tumor for tumor progression [20]. However, later it was found that senescence has also an opposite side and can reverse, so promoting cancer and metastases development [21–24]. Moreover, the cells that have experienced and evaded cellular senescence are more resistant to therapy than their counterparts [25]. The same group showed also that two different types of histone H3 lysine 9 (H3K9) demethylases, the flavin-dependent amine oxidase LSD1 and the 2-oxoglutarate-dependent Jumonji C family member JMJD2C, epigenetically disable oncogenic RAS- or B-RAF-induced senescence by enabling the expression of E2F target genes, which permits restarting of proliferation cycles. In turn, the inhibition of the H3K9 demethylases restores senescence and controls tumor growth of melanoma [26]. These experiments show the important contribution of the chromatin remodeling in OIS and cancer.

Biochemically, B-RAF has the same kinase activity as the serine-threonine protein kinase MOS [27] that is the main meiotic kinase [28]. Interestingly, proto-oncogenes c-ras and c-raf also participate in gametogenesis and when overexpressed (even non-mutant) can impose the meiotic mechanisms onto somatic cells [29]. In tumors, this pathway elaborating MOS-kinase can be triggered from mitosis through DNA damage checkpoint and senescence, supposedly providing them with the survival advantage [30–33]. At the same time, the expression of many germline proteins specific for meiotic prophase has been found upregulated in cancers [34–36] and in melanoma [37] as well.

Below we review the literature data of the abovementioned meiosis-associated processes and pathways involved in cancer (in the wide sense) and melanoma, in particular.

2. Senescence, TP53 function, and polyploidy in melanoma

Melanomas often derive from nevi, which already contain oncogenic B-RAF and N-RAS mutations. It was shown in several works that the melanoma genesis

from these nevi is associated with the reverse of the OIS induced by these mutations. The mutual feature for all kinds of ACS (OIS, drug-, and oxidative stress-induced) is the introduction of DNA double-strand breaks (DSBs); a persistent DNA damage signaling was shown triggering senescence [38]. The response to the latter includes the activity of tumor suppressor transcription factor p53. Dysfunction of p53 is generally associated with malignant tumors and also with associated overcoming the polyploidy barrier [39]. In relation to melanoma, these issues will be briefly considered below. Wild-type (WT) p53 that is present at undetectable levels in normal tissues, when upregulated by DNA damage, is a potent inducer of apoptosis, cell cycle arrest, and cellular senescence, in general counteracting carcinogenesis [40], but also caring for stem cells by causing transient alternative splicing of POU5F1 in senescent embryonal carcinoma until the repair of DNA damage [41]. The tumor suppressor TP53 is mutated in its DNA binding domain in about half of somatic cancers [42]. In other cases, it is also mostly inactivated in other ways, e.g., by promoter methylation, etc. [43]. TP53 mutants, however, acquire additive functions, e.g., invasive features [44]. Melanoma is not an exclusion: with approximately only 10–19% disabling point mutations, WT p53 is found inactivated in approximately 90% of cases [45, 46]. The low frequency of p53 mutation in melanoma may be due to the overexpression of its counterpart oncoprotein MDM2, which is due to inactivation of *CDKN2A* locus encoding the dual tumor suppressors p16INK4A and p14ARF. Likewise, the most common somatic mutations associated with familial melanoma also disrupt the *CDKN2A* locus [47]. In the presence of oncogenic activation (B-RAF or N-RAS), p14ARF acts to directly inhibit MDM2, the major ubiquitin ligase that normally degrades and inactivates p53 [48]. The cooperation of B-RAF mutations with nonfunctional p53 in melanoma genesis was modeled by Patton and colleagues [49] in p53-deficient Zebrafish, where activated B-RAF induced formation of melanocyte lesions rapidly developed into invasive melanomas, resembling human melanomas and could be serially transplanted. Another tumor suppressor PTEN may also participate in melanoma genesis from B-RAF V600E nevi [50]. TP53 is a barrier to polyploidy [39], the latter is often reached by mitotic slippage (reset of interphase from arrested metaphase with a tetraploid genome). Mitotic slippage and thus polyploidization accompanies OIS or irradiation-drug-induced senescence in tumors with characteristic DNA damage response [51]; however, both senescence and polyploidy, induced by OIS or genotoxic treatments, can be reversed [52–55]. In this prolonged process occupying 7 and more days, the majority of giant cells succumb and the proportion of escape (de-polyploidized) cells may be rather low [56, 57] but they repopulate the tumor in the remote period of time. Mitotic slippage and DNA re-replication resulting in polyploidization was modeled in melanoma by Aurora A-kinase interference [58]. The DNA re-replication stress resulting in the fold-increased amount of DNA DSBs in the polyploidized cells was revealed. MDM2 antagonists relieved it by restoring the functional p53 and its downstream p21, interrupting re-replication of cells. Finally, the same was shown in melanoma: the experiments with prolonged expression of the oncogene N-RAS Q61K in pigment cells showed the induction of senescent multi-nucleated polyploid cells, however further overcoming OIS by the emergence of tumor-initiating mononucleated (de-polyploidized) stem-like cells from senescent cells. This progeny was dedifferentiated, highly proliferative, and anoikis-resistant, and induces fast-growing, metastatic tumors [59].

Besides inducing OIS, *N-RAS* and *B-RAF*-activating mutations can potentially impose meiotic features onto melanocytes (substituting by overexpressed B-RAF of meiotic MOS-MEK-kinase or alternatively triggering its pathway).

The possibility of imposing the meiotic (oocyte maturation) program by overexpressed RAS and RAF onto somatic cells was reported in literature [29, 60, 61]. Such trigger can supposedly favor the reduction division of polyploidized tumor cells [31–33] and likely also, in collaboration with REC8, the monopolar spindle of meiotic prophase [62]. In irradiated lymphoma cell lines, MOS was activated through polyploidy only in TP53-mutants, not their WT TP53 counterparts [30], where neither polyploidy nor MOS was induced. MOS protein was shown expressed in 20 types of cancer, including melanoma (https://www.proteinatlas.org/ENSG00000172680-MOS/pathology). As shown by more recent data on OIS in melanoma [58], the persistence of DNA damage in the absence of p53 function may be a bridge to invasive melanoma. And the persistent DNA DSBs in senescing polyploid cells, in turn, may be also a bridge from the G2M DNA damage checkpoint and/or mitotic slippage to the meiotic-type recombinative prophase possessing the same molecular background [33] (see also below in the section about SPO11 nuclease). So, B-RAF and N-RAS mutation, senescence with DDR signaling, deficiency of p53 function (upregulation of MDM2), induced and reversible polyploidy, and trigger to meiotic prophase are all molecularly related and this network can be potentially involved in melanoma genesis.

3. Cancer testis (CT) genes

CT genes were first defined as a group of tumor antigens that elicit a cytosolic T cell response and are expressed in male germ cells in the testis and various malignancies [63–65]. The first CT antigen identified was melanoma antigen 1 (MAGEA-1) [66]. Using the melanoma cell line MZ2-MEL and autologous cytotoxic T-lymphocyte (CTL) clones cytolytic to this line, MAGE-1 (subsequently re-named as MAGEA1, melanoma antigen A1) was identified as the target antigen for one of the CTL clones. This represented the first immunogenic tumor antigen shown to have elicited autologous cytotoxic T-lymphocyte responses in a cancer patient. Pursuing the same strategy, a range of other tumor-antigen genes, including MAGE-A3, another member of the MAGE-A family, as well as two additional families of antigens, namely the BAGE and GAGE gene families, were identified [64, 67–69]. The next huge step toward the identification of tumor antigens came from the screening of cDNA expression libraries with antibodies, the technology called SEREX (serological analysis of cDNA expression libraries) [70]. Very soon SEREX led to the identification of several categories of tumor antigens. To date, more than 80 families of CT genes are recognized and defined as germline restricted genes with evaluated expression in cancer [71]. As per today's definition, CT gene should simply exhibit a biased expression in the testis, ovaries [72], or the placenta [73], and in cancer.

CT genes can be divided between those that are encoded in the X chromosome (CT-X genes) and those that are distributed throughout the genome (non-X CT genes). CT-X genes are mostly members of gene families organized into complex direct and inverted repeats, and are expressed in testes primarily during the spermatogonial stage of spermatogenesis [74]. Annotation of the sequence of the human X chromosome has revealed that as many as 10% of all genes present on the chromosome are members of known CT families [75]. Further analysis of the expression patterns of genes of unknown function located in these repeated regions could even increase this estimate [76]. Melanoma has been found to have one of the highest CT antigens frequency expressions among other cancers. Moreover, higher frequency of CT antigens expression in melanoma is also correlated with worse disease outcome [77–80].

Our analyses of the NCBI's Gene Expression Omnibus [81] GSE98394 dataset including a cohort of 27 B-RAF-mutant nevi and 51 melanoma, described in details in [81] revealed the stark upregulation of many CT antigens in primary melanoma compared to nevi (Appendix Table 1). The densely connected component of protein-protein interactions (PPI) network of the upregulated melanoma CT antigens genes constructed using String Server [82] revealed the melanoma network module composed of 25 nodes, with a carcass of MAGEA-group hubs connected with the cohesin subunit SA-2 (STAG2) and the inhibitor of the differentiation-inducing retinoid acid receptor (PRAME) [83] hubs indicating to the acquired stemness (**Figure 1**). The high average node connectivity degree (5.84, PPI enrichment p-value <1.0e-16) characterizes this module as a CT antigen attractor of melanoma genesis from B-RAF-mutant nevi.

Similar upregulation of many CTA, however, different from those, occurs when the primary melanoma progresses and metastasis are formed as revealed in the TCGA-SKCM dataset that includes 103 primary melanoma and 368 melanoma metastases (https://www.cancer.gov/tcga) (Appendix Table 2).

The biological role of CT genes, particularly CT-X genes (a majority of them are CT antigens), in both germline tissues and tumors remains not well understood. However, studies have provided some evidence that MAGE gene expression may protect cells from programmed cell death and contribute to the development of malignancies by promoting survival [84]. It has also been shown that MAGE A2 is a strong inhibitor of the p53 tumor suppressor through histone deacetylase (HDAC)3 recruitment. In human primary melanoma cells, Mage A2 expression confers resistance to chemotherapeutic drugs by interfering with p53 acetylation [85]. Mage A2 interferes with p53 acetylation at promyelocytic leukemia (PML)-nuclear bodies (NBs) and with PMLIV-dependent activation of p53 through an HDAC-dependent mechanism, so downregulating it [86]. Usually, p53 is recruited to PML-NBs where it becomes acetylated and activated, and participates in the triggering of cellular senescence [87], a critical barrier against cell transformation (discussed above).

The mechanisms involved in the regulation of CT antigens expression appears to be promoted by DNA demethylation. Methylation of CpG islands within gene promoters is responsible for gene silencing due to both its effect on chromatin structure

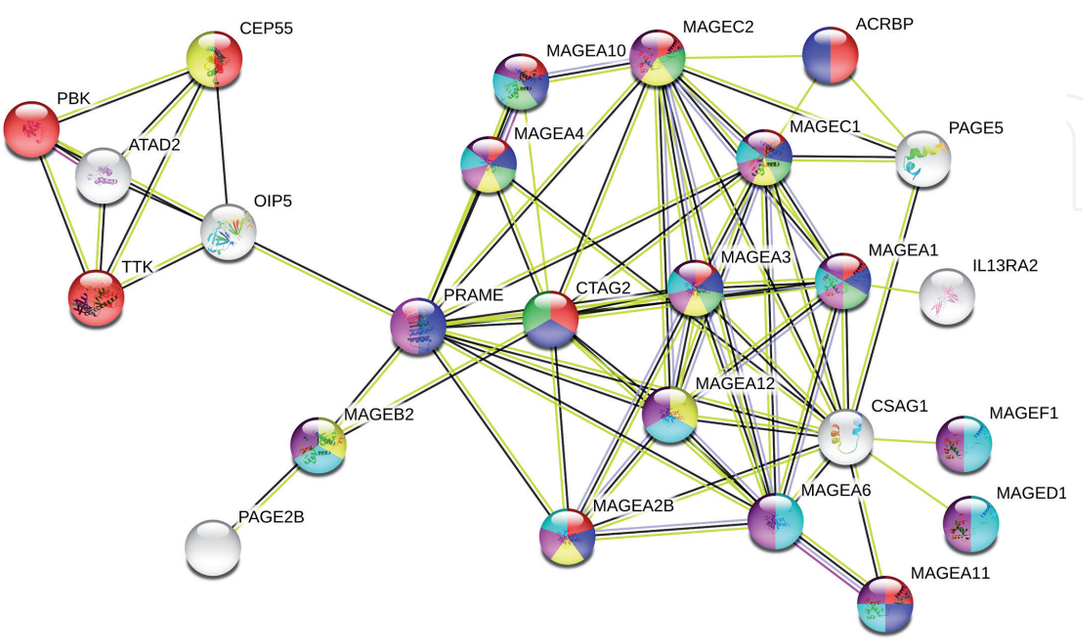

Figure 1.
The densely connected component of protein-protein interactions (PPI) network of the upregulated melanoma CT antigens constructed using String server [82].

and binding of transcription factors [88]. "Epigenetic reprogramming," consisting of concerted DNA pan-demethylation and corresponding chromatin remodeling, occurs twice in the human life cycle: during early embryogenesis and gametogenesis of primordial germ cells (PGC) [89]. So far, all CT antigens studied have methylated CpG islands in normal somatic tissues and are activated by demethylation during spermatogenesis [90]. Experimental demethylation of CT antigens promoters induces antigen expression in cells that do not normally produce them [91]. It has been proposed that the activation of CT antigens in cancer is a consequence of the ectopic induction of gametogenic program [74, 92, 93], which thus includes the meiotic component.

As recently found, all MAGEs contain a conservative E-ring domain and assemble with E3 RING ubiquitin ligases to form MAGE-RING ligases (MRLs) that act as regulators of ubiquitination by modulating E-ring-ligase activity [94]. The latter are acting at the cross-roads between tumor suppression and oncogenesis [95]. In addition, a majority of the CT antigens [96, 97] are intrinsically disordered proteins (IDPs). IDPs lack rigid 3D structures either along their entire length or in localized regions. Despite the lack of structure, most IDPs can transit from disorder to order upon binding to various biological targets [98]. Protein intrinsic disorder can serve as the structural basis for hub protein promiscuity; thus, CT antigens proteins can provide flexible linkers between functional domains [99]. Many normal cellular processes are associated with the presence of the right amount of precisely activated IDPs at right places and at the right time, those may be altered in disease, including cancer [100, 101]. The IDPs—features of the X-linked CT antigen-encoded genes, which can change their targets, as well as the relation of the MAGE group to ubiquitin-ligases suggest their highly adaptive post-translation functions for the cancer genome and proteome networks. This property is consistent with their activation by CTCF inhibitor and pan-genome activator, the CT gene Brother of Regulator of Imprinted Sites (BORIS) located at the chromosome region 20q13.2. This region is commonly amplified in human cancers [102, 103]. BORIS expression is normally restricted to testis and becomes aberrantly expressed in different types of cancer [104]. In melanoma, BORIS expression was observed in 59% of melanoma cell lines, in 16% of primary melanomas and in 34% of melanoma metastases [105].

Normally, BORIS plays a major role in regulating de-repressing, de-methylation processes during spermatogenesis—it removes imprinting from genes during the last mitotic division of type B spermatogonia producing the first spermatocyte [106]. In particular, in melanoma, BORIS binds near the promoter of transforming growth factor-beta 1 (TFGB1), a well-recognized factor involved in the transition toward an invasive state, activating it through transcriptional reprogramming [107]. BORIS is a paralog and antagonist of CTCF. A primary role for CTCF in the global organization of chromatin architecture was shown, which suggests that CTCF may be a heritable topological repressive component of an epigenetic system regulating the interplay between DNA methylation, higher-order chromatin structure, and lineage-specific gene expression [108, 109]. Nowadays, multiple studies have indicated an oncogenic role for BORIS [110–112]. Notably, emerging evidence has shown that BORIS functions as an epigenetic modifier in modulating the whole genome gene expression [113–115], including expression of other CT genes [116, 117]. BORIS was also found to be expressed in embryonal carcinoma, ovarian cancer [118] as well as cancer stem cell (CSC)-enriched populations isolated from epithelial cancer cells [119, 120]. The mRNA isoforms of BORIS genes are expressed in normal ovary and in the altered pattern, in epithelial ovarian cancer [121]. An association of BORIS expression with CSC-like properties was also observed [119, 120]. Moreover, it has been shown that BORIS association with the CSC-like traits occurs through the epigenetic regulation of *POU5F1/OCT4* [112]. OCT4 is

considered a master regulator in the maintenance of stem cell pluripotency. Many studies have demonstrated a correlation between OCT4 and CSCs in many cancers, including melanoma [122–124].

In relation to metastatic melanoma, using the TCGA database (https://www.cancer.gov/tcga), we assessed the expression of a number of genes selected from the POU, SOX, SALL, and NANOG gene families with relation to stemness in normal and cancer stem cells [125] and noted an increase in stemness during transition from primary melanoma to metastases. Moreover, the heat map shows the reconstruction of the landscape in the expression of stemness-associated genes indicating to the whole genome rearrangement (**Figure 2**).

Melanocytes originate from the neural crest developing in embryo very early (as the fourth germ layer) and is associated with intensive cell migration. Melanomas in patients or cell constructs upregulating the Wnt pathway, associated with neural crest development, display epithelial-to-mesenchyme-transition (EMT) phenotype, worse prognoses in patients, and resistance to drugs in vitro [129]. The role of the neural crest development factors in ectopic regulation of melanoma was also investigated in [130]. Likely, because of the origin, nearly the root of the ontogenetic tree, melanoma is so invasive and malignant.

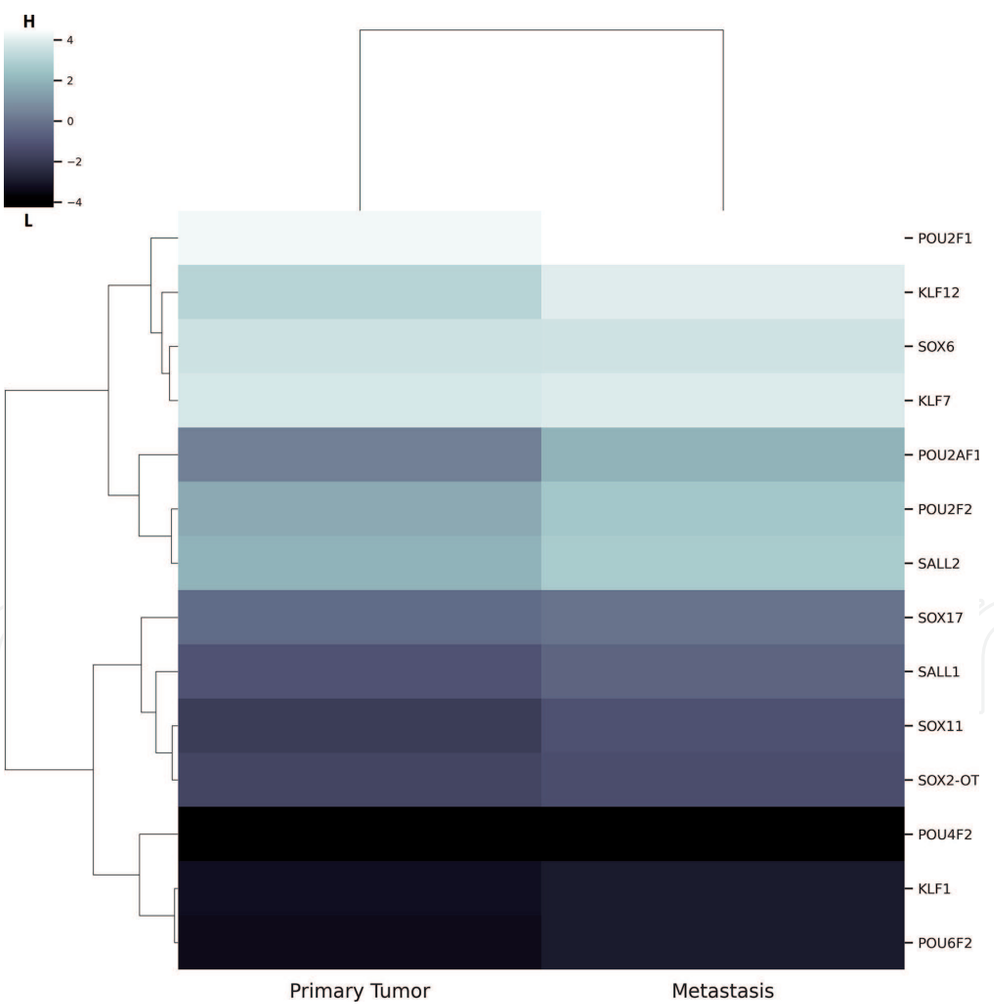

Figure 2.
Gene expression (in log2CPM values) of stemness genes in the cohort of 368 melanoma metastases compared to 103 primary melanoma from the TCGA-SKCM dataset (https://www.cancer.gov/tcga). The data was extracted from the TCGA database using the TCGA Biolinks Bioconductor package [126]. EdgeR [127] was used to perform differential expression analysis through the generalized linear model approach. The differentially expressed genes (DEGs) which were upregulated in metastatic melanoma (log2FC > 0, p < 0.01) were filtered for genes from the POU, SOX, SALL, and NANOG gene families with relation to stemness. Seaborn [128] was used to construct the heat map.

The particular interest for carcinogenesis represents the non-X CT genes or germline restricted genes that normally mediate meiotic program [30, 34–37, 131] and therefore are denoted by some authors, the meiosis-specific CT (meiCT) genes [36].

4. Conventional meiosis: in brief

The conventional meiotic progression is well described [28] and has been recently updated by Feichtinger and McFarlane [35]. Thus, only a short recitation of some of the main points is provided here.

Meiosis is a special mode of cell division that naturally occurs in mammalian only in the germ cells—in the male testis and female ovary. During meiosis, diploid germ cells undergo a single round of premeiotic DNA replication (4n), followed by two chromosome segregation events, meiosis I (reductional) and meiosis II (equational), creating haploid (1n) gametes. Meiosis I is marked by a prolonged prophase that is subdivided into five stages: leptotene, zygotene, pachytene, diplotene, and diakinesis, where during the first three stages, there occurs the formation of DSBs, homologous chromosome pairing, and synapsis and reciprocal homologous recombination (HR) between them. The initiation of meiosis is not fully understood in mammals, but it is thought that meiotic entry is initiated by upregulation of the stimulated by retinoic acid 8 (STRA8) gene expression—transcription activator that binds directly to the promoter regions of meiosis-specific genes [124–126].

During premeiotic DNA replication, a ring of specific cohesins is formed that holds newly formed sister chromatids together [127]. In meiosis I prophase, HR program is initiated by the generation of DNA DSBs along the chromosome axis in specific hotspots [128]. This is initiated by a protein complex, which consists of SPO11 and TOPOVIBL [129]. Generated DSBs serve as the substrates for the recombinase RAD51 and its meiosis-specific paralogue DMC1 acting as a heterodimer [130]. The hot spot selection in mammals mediates the zinc finger histone methyltransferase, PR domain containing 9 (PRDM9), which primes the DNA for DSB and exchange of DNA between chromosomes [131, 132]. Of note, in the case of meiosis, DNA DSBs are obligatory rather than the result of accidental damage, as in the mitotic cell cycle, and the recombination partners are homologous chromosomes in meiosis, whereas they are sister chromatids in DNA repair during mitosis. As the homologous chromosome bivalents after HR align on the metaphase I plate, the centromeres of sister chromatids form monopolar spindle associations. Loss of sister cohesion in the arm regions of chromosomes, but not the centromeric regions, occurs on entry into meiotic anaphase I permitting reductional segregation of homologous chromosomes. During meiosis II, centromeric cohesion is broken down and an equational segregation of the chromatids, like in mitosis, occurs [127].

5. Melanoma and meiosis specific CT (meiCT) genes

HR sites resulting in crossovers are initiated by the creation of DSBs in the leptotene prophase stage catalyzed by the protein Spo11 [132]. Spo11 is an homolog of the A subunit of type II DNA topoisomerase that together with TOPOVIBL, an homolog of B subunit, forms protein complex. The MREII exonuclease creates DNA nicks guiding the SPO11-TOPOVIBL complex to accurately catalyze DSBs along the genome in specific hotspots [133, 134]. Aberrant expression of SPO11 has been found in cell lines of melanoma and also lung cancer [135], see **Figure 3**, acute myeloid leukemia (AML) [136], cutaneous T-cell lymphoma (CTCL) [137] as well

as in patient samples of melanoma, [135, 138], cervical cancer [135], gastric cancer [138], and CTCL [139]. Although the exact mechanism of SPO11 reactivation in cancer cells remains elusive, it has been shown that in CTCL, it is regulated epigenetically and temporary expressed at the onset of the cell division in G1/S phase transition [139]. This expression before DNA replication seems unrelevant but, indeed, it appears that SPO11 expression in B-RAF- and TP-53 mutant melanoma may be not dependent on the cell cycle phase (**Figure 3**).

SPO11 expression in CTCL cell lines decreased after cell line treatment with histone deacetylase (HDAC) inhibitors, e.g., Vorinostat and Romidepsin [137]. Moreover, SPO11-introduced DNA DSBs have also been shown to increase the risk of genome rearrangements and mutations in the germline [140]—a potential source of the idiopathic male infertility, which is associated with the 20-fold increased risk of the germline cancer [141]. Spo11 appears to be present in all sequenced eukaryotic genomes, and indeed it may be the only truly universal meiotic protein. At the same time, in many organisms, the recombination defect in Spo11 mutants can rescue meiosis by production of DSBs from an exogenous source such as ionizing radiation [142, 143]. On the other side, SPO11 was also found in species and tissues undergoing asexual life-cycles [143] or DNA recombination for nonsexual function. e.g., SPO11 was revealed in mouse germinal center B cells undergoing

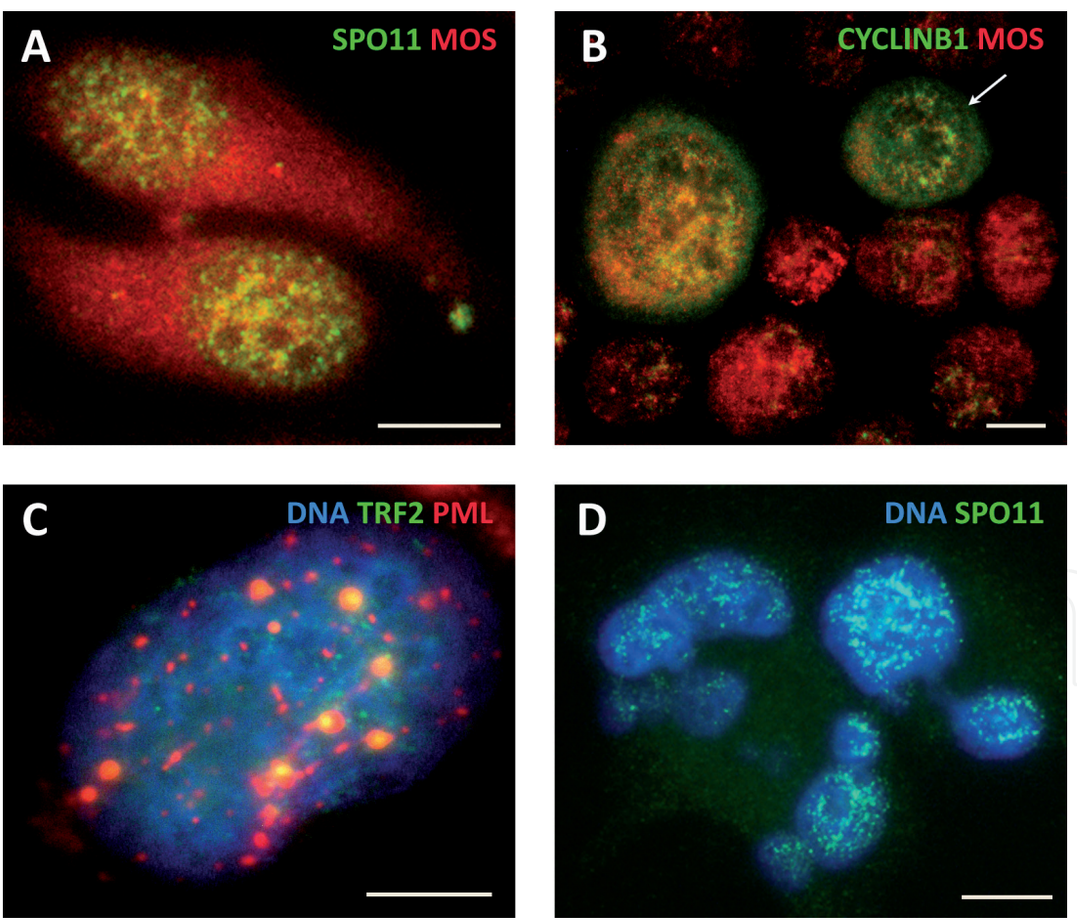

Figure 3.
Meiotic genes, alternative telomere lengthening, and mitotic slippage in B-RAF V600E and TP53-mutant melanoma SkMel28 cell line: (A) the expression of the meiotic MOS-kinase (sc-28,789) and recombination endonuclease SPO11 (sc-377,161) in cell nuclei of non-treated cells; (B) co-expression of MOS and cyclin B1 (sc-245) in rare polyploid cells and some metaphases [14] of nontreated control; (C) the polyploid cell on day 7 after doxorubicine treatment (500 nM for 24 h) maintains telomeres (marked by TRF2, 05-521, millipore) by alternative lengthening of telomeres (ALT) in promyelocytic leukemia (PML) (PA5-80910, thermo fisher scientific) bodies; and (D) two giant cells resistant to B-RAF inhibitor vemurafenib (50 nM for 24 h), with signs of mitotic slippage and multinucleation on day 21 after treatment show positivity for SPO11. Bars = 10 μm.

immunoglobulin gene diversification and class switch recombination, but mice lacking Spo11 had no detectable immune system defects [144]. SPO11 introduces meiotic recombination breaks in the chromosome DSB hotspots [145]. So, it is possible that senescence-associated DDR affecting the DSB hot spots (at least, in p53-nonfunctional tumors) can upregulate and attract SPO11. Localized clustered hotspots are a feature of meiotic recombination in *S. pombe*, mouse, and humans as well, but the factors that determine whether a given DNA sequence will be a DSB hotspot are not well understood in any organism. Such hotspots may appear due to underreplication of DNA in the heterochromatin, particularly in telomeres, e.g., in the drug-induced senescence of tumor cells [146]. Depletion of the H3K9me3 chromatin repressive hallmarks seems rather decisive for attraction of SPO11 to the hot spots [147]. This data shows that execution of the very definitive molecular biochemical mechanism of SPO11 is dependent on the permissive epigenetic chromatin organization of the very general character. Therefore, it is interesting to highlight the breaking through report showing the reset of senescence and abrogation of invasive growth achieved in melanoma by inhibition of the DNA demethylases [26].

Spo11 is the catalytic center of the meiotic recombination initiation mechanism, but it is not sufficient to generate DSBs: numerous additional proteins are also required; the main of them is Mre11-Rad50-Xrs2 (MRX). These proteins form a complex with multiple roles in many different aspects of DNA metabolism, including DNA repair, telomere maintenance, and checkpoint signaling. Mutant MRX complex leaves SPO11 accumulated to telomere ends with the nonreleased terminal chiasmata [148]. Although the SPO11 catalytic gene part is conserved, the proteins involved in meiotic recombination are generally among the more rapidly evolving of all cellular proteins: major challenges for them represent the whole genome duplications (WGDs) and the difficulties of auto- and allo-polyploids in the meiotic reduction divisions [149, 150].

The meiosis-specific histone methyltransferase gene PRDM9 has also been reported to be activated in melanoma alongside with other cancers, like embryonal carcinoma, astrocytoma, leukemia, colon, prostate, breast, and ovary cancers [151].

Another meiosis-specific gene involved in SPO11-mediated recombination regulation, TEX15, has been reported to be overexpressed in melanoma and other cancers including bladder, head and neck, and lung carcinomas, neuroblastomas, prostate tumors, and sarcomas [152].

The synapsis of homologous chromosomes in conventional meiotic prophase is marked by synaptonemal complex (SC). SC is a large zipper-like protein complex that connects one pair of sister chromatids to the homologous pair, so stabilizing the tetrad and ensuring proper homolog pairing. SC formation starts with the formation of axial element that consists from SC proteins 2 and 3 (SCP2 and SCP3). Then, the axial elements (at this point referred lateral elements) are joined by the transverse filaments formed by the SC protein 1 (SCP1) [153–155]. The central elements consists of SC central element 1 and 2 (encoded by SYCE1 and SYCE2) [156]. Notably, SYCP1 and SYCP3 genes both have been implicated in cancer. Both mRNA are expressed in a variety of cancers and cancer cell lines including melanoma [30, 31, 157, 158]. Moreover, SCP3 protein expression correlated with activated AKT (pAKT) signaling [159]. Overexpression of SCP3 was shown prognostically unfavorable for lung cancer [160].

HORMA domain containing 1 (Hormad1) is another protein associated with SC axis. It has multiple roles, but in general it coordinates DSB formation with synapsis and the timely progression of DSB repair through HR [161]. Hormad1 is significantly upregulated in several cancers and noted also in melanoma [37, 162]. Although the mechanism of its reactivation remains elusive, hypomethylation of the HORMAD1 promoter region correlates with its increased expression in breast cancer and small cell lung cancer [163, 164], suggesting at least partial involvement of epigenetic pathways.

Chromosome regulation in meiosis and in mitosis is dependent upon the cohesin complex. In mitotically dividing cells, this complex serves to hold sister chromatids until they settle in metaphase plate, becoming separated in anaphase while in conventional meiosis, sisters stay together through the whole meiosis I to ensure sister centromeres orientate to the same pole to drive the reductional segregation of bi-chromatid homologs. Although the structure of cohesin complexes involved in mitosis and meiosis is similar, the difference lies in subunit composition. In meiosis, specific paralogues of some of the cohesin proteins replace their mitotic counterparts [165]. One of the more prominent cohesin subunits that appears to be restricted to meiosis is REC8 (paralogous counterparts to the RAD21 mitotic cohesin) [165]. The upregulated expression of Rec8 protein was demonstrated in melanoma [37, 166] as well as in CTCL [139, 167], irradiated TP53-mutant lymphoma cell lines, HeLa, and breast and colon cancer cell lines [31, 168]. Recently it has been shown that REC8 imposed monopolarity of sister centromeres in mitotically dividing cells could result in uniparent disomy (UPD) at least in the model organism *S. pombe* (fission yeast) [169] possessing a facultative sex. REC8 in cooperation with *Mos*-kinase forms a monopolar spindle of octoploid lymphoma cells (after ionizing irradiation) which undergo recombination of DNA DSBs by meiotic recombinase DMC1 [62]. Interestingly, Rec8 does not appear to be incorporated into mitotic cohesin complex in HEK293 cells unless another meiosis-specific cohesin subunit, STAG3, is activated [170]. In melanoma, STAG3 as well as STAG2 (mitosis specific cohesin subunit) levels have been linked to the resistance of B-RAF inhibitors [171]. STAG cohesins also participate with CTCF in the topological suppression of transcription and it is the the reduced level of STAG3 that is associated with resistance to B-RAF inhibitors.

The cohesin-related regulators, SGO1/2 are also the meiosis-specific proteins that protect cohesin complex, in particular Rec8, from the protease separase-mediated cleavage at the centromeres of sister chromatids in meiosis I and retained Rec8 around the centromere until the start of anaphase II [172–174]. Upregulation of SGO2 expression has been demonstrated in melanoma [37] alongside with upregulation also in CTCL [139, 167] and SGO 1/2, along with REC8, in irradiated lymphoma cells [168]. However, the role of meiotic cohesins in cancer has not been extensively investigated.

Another meiosis-specific cohesin subunit, which has gene expression tightly restricted to the testis in healthy humans, is RAD21L (also RAD21/REC8 paralogue) [165]. However, it is also important for the maintenance of female fertility during natural aging [175].

While the majority of somatic cells are deficient in active telomerase, cancer cells not only can reactivate telomerase, but can also initiate a mechanism of the alternative telomere maintenance (ALT) in the absence of telomerase activity [176] or undergo transient ALT [177]. Some meiosis genes were found associated with supposed homology search in ALT [178, 179]. ALT requires a recombination-like mechanism to recognize the telomere end as DSBs and mediate the strand invasion of the end into a nonhomologous chromosome end. This strand invasion permits the initiation of a break-induced DNA replication process where the invaded non-homolog telomeric DNA serves as a replicative template for the invading telomere to elongate [180]. In summary, the review of the classic meiotic genes demonstrates their involvement in cancer, and melanoma in particular, although their function in cancer is ill defined.

6. Brainstorming session

> *"Nothing in biology makes sense except in the light of evolution"—Dobzhansky 1973 [181].*

B-RAF-mutant melanoma activates MEK-ERK proliferative pathway but cancer can be explained neither only by enhanced proliferation nor it can be reduced to somatic mutation theory, which has been shaken by cancer genome sequencing projects. Cancer is more complex than that [182]. B-RAF-and N-RAS-mutant nevi remaining quiescent and benign just support this notion. A very important role of OIS-induced cellular senescence for initiation of malignant tumors discovered by Serrano et al. [19] and the role of its epigenetic landscape have been revealed in recent years. Melanoma is interesting therefore as RAS, B-RAF mutations just produce this senescent background, which can undergo reverse by reprogramming resulting in drug resistance [25], but senescence can be again restored in invasive B-RAF-mutant melanoma by structurally unrelated silencing with H3K9 demethylases [26]. Thus, OIS senescence in cancer has a dynamic nature with the epigenetic component of the general character [183]. But melanoma is also interesting for the high overexpression of meiosis-related CT genes. Overexpression of CT antigens is prognostic for poor outcome of invasive melanoma; in addition, classic meiotic genes are known to be expressed in cancers [30, 31, 168] and also in melanoma [37]. Some authors reason that overlaying of meiotic protein aberrant activities over the normal mitotic cycle (termed "meiomitosis"), first of all of the stable cohesion of sister chromatids needed for meiosis I, is interfering with normal mitotic separation of chromatids, leading to aneuploidy, genome instability, and tumor progression [36, 37, 184, 185]. The questions arise: (1) whether the mitotic cycle in tumors is normal? (2) If the meiotic features found in tumors belong to conventional gametic meiosis? (3) If an aneuploidy can perpetuate the tumor growth? Let us begin with the latter. This problem is well known as "Aneuploidy Paradox" [186], which means that incorrect segregations of genetic material should hinder and prevent cell division; however, aneuploidy paradoxically is well known as correlating with tumor growth and aggression, which may be due to selection of the fittest aneuploid clones. This conundrum cannot be explained satisfactorily with clonal selection of rare positive mutations because the "Muller's Ratchet" [187] will inevitably accumulate deleterious mutation leading ultimately to extinction of the asexual cell line. The problem, of the "Muller Rachet", however is still explored by population evolutionists [188]. Aneuploidy in cancer arises from the inherent chromosome instability of polyploidy cells. So, we arrive here to the polyploidy which in different proportions is a very characteristic feature of all malignant tumors (comparing with their normal tissue origins), progresses with cancer aggression, and which up to now is often ignored by cancer researchers [189]. However, it is just a reversible polyploidy, which provides the extraordinary resistance of cancers to therapy [56, 190–192] and likely a cancer line immortality as such. Moreover, our studies brought us to the notion of a cancer life cycle, composed of a cell cycle (lasting 17-23 h) and ploidy cycle (reversible polyploidization which takes 1–2 weeks or more), both cycles are reciprocally linked [32, 193]. This reciprocal cancer life cycle is an analogue of the "neosis" of cancer cells, related to polyploidy and senescence with rejuvenation of reduced offsprings described by Rajaraman [194, 195] and was confirmed in tumors by multiple authors [190–192], also in melanoma [59]. Thus, the answer to the first question is that the cell cycle in cancers including melanoma is not conventional and at least, in the tumor subpopulation, it is composed of two reciprocally joined different cycles, conventional mitotic and a ploidy cycle, one being quick and another being slow. The latter is often overlooked [189] as being hidden due to the low proportion in relation to the mitotic cycles. The ploidy cycle of giant cells associated with senescence reprogramming becomes clearly manifested in resistant tumors after high dosage DNA damage with anticancer drugs and ionizing irradiation [177, 196–198]. Therefore, cancer research needs prolong follow up of

individual cells and ploidy measurements [177, 191, 199, 200]. Tumor cells enter this ploidy cycle when they senesce by OIS or get the DNA damage in any other way (e.g., by ionizing irradiation or oxidative stress). If the treatment is harsh, the majority of induced giant cells will die in the time course, during mitotic catastrophe or in unsuccessful attempts of multipolar or aberrant bipolar bridged mitoses, but a minor minority of resistant cancer cells repair the DNA damage and repopulate tumors through depolyploidization by budding or other type of ploidy reduction [33, 56, 189, 191, 201, 202]. So, in our brainstorming session, we arrived to ploidy cycles and DNA damage. Here is a right link to the origin of meiosis and sex. The whole genome duplications (WGD) is a well-known driver of gene and species evolution [203] and appeared already in prokaryotes as the first evolutionary steps toward eukaryotic sex [204]. The most immediate reasons of the meiosis origin were the necessity to repair DNA damage [205]. Another reason, coupled to the first, was the relief of mutational load of aneuploidy resulting from polyploidy when it was advantageous to have more than one copy of the genome per cell [206]. Thus, the aneuploidy paradox in cancer might be resolved by asexual (somatic) meiosis (including recombination and reduction) and this meiosis is very likely ancestral. Briefly, the evolution of meiosis in eukaryotes could start from polyploid endomitosis (insect-type, without actual karyotomy), (enriched in MOS-kinase as found in tumor cells) [207], followed by zygotic meiosis, and ending in gametic meiosis in most extant vertebrates [149, 208–210]. Meiosis originated in evolution several times; there is also a view that individual blocks of genetic program of meiotic regulation could evolve independently [211]. Considering the expression of CT genes not only in testis but also in ovaria, early embryo and placenta, Loyd Old [212] associated their expression with the female gametogenesis-like program in tumor cells by formulating the title of his article "Cancer is a somatic cell pregnancy." Some researchers consider a possible parthenogenetic variant of the embryological in essence theory of cancer which is known from the nineteenth century [29, 213] while ontogenetic variant of this theory for the origin of tumors termed "a life-code" has been recently suggested by Jinsong Liu [214]. An interesting asexual parthenogenetic variant for triploid tumors, which are typical for resistant cancers may be achieved by digyny (69, XXY, in case of male cancers) [215]. Some observations suggest that triploidy may exchange with diploid subline on the basis of multinucleated giant cells in the same tumor [216]. The cycle of cancer stem cells likely can start with the relic uniparental disomy. The latter is described in facultative sex of the fission yeast [169], in plants, stressed and spontaneously [217] and in senescing human cells [218]. All these parasexual mechanisms may include aberrant meiotic elements and genes activity [62] and may exist in parallel or as a complex chain of one process of the survival support and escape of resistant tumors. In fact, their studies are only started. So, the answer to the second question if we should reckon exclusively with the mechanisms of conventional gametic meiosis in somatic tumors is also negative. SC in tumors was never found although the relevant genes and proteins ectopically expressed [62, 160], including melanoma [37]. We should rather reckon with evolutionary forms of meiosis in asexual life cycles. This turn of reasoning is becoming particularly context-updated if we also consider the recent gene expression phylostratigraphic analysis showing that ancestral regulatory networks drive cancer [219]. The latter in turn is associated with polyploidy [220]. Moreover, in recent time, the ancient inverted meiosis (IM) appeared on the stage [221]. IM does not require the cohesion of sister chromatids (thus, SC is not needed): the homologs are joined by their ends, recombine by sub-telomeric sequences, segregate sisters in the first meiosis and homologs in the second. Thus, IM can repair the damaged telomeres, provide some degree of genetic diversity,

and not the least, it can count homologous chromosome pairs, to get rid of aneuploidy. Strikingly, IM was revealed in the proportion of normal human oocytes sorting out the aneuploid embryos in a polar body [222]. Although SC is not needed, however the telomere clustering at the spindle pole body for the chromosome homology search by spinning the chromosomes, for DNA recombination between homologs, is needed. Although currently the study of IM in human cancer is in infancy [62], the IM related to telomere DSBs well fits several peculiarities found in tumors: cellular senescence linked to telomere attrition, polyploidy associated with cellular senescence, mitotic slippage, reprogramming, and alternative telomere lengthening characteristic for some cancers [62]. We proposed a hypothesis that ALT-associated PML bodies in mitotic slippage of tumor cells may serve as a site for IM recombination repair [177]. Interestingly, the meiotic genes involved in the homology search and recombination RAD21L (Rec8 paralog) and Hop2-Mnd1 heterodimer (RAD51-dependent) were found associated with ALT [178, 179]. The expression of the proteins, which may be involved in IM-related ALT (SPO11, MOS, TRF2-colocalised with PML-bodies), and mitotic slippage were also observed in polyploidy cells of B-RAF V600E mutant melanoma SkMel28 cell line treated with doxorubicin and vemurafenib (mutated B-RAF-inhibitor) (**Figure 3**). The question how much the meiotic features in tumors are stochastic and how much program-directed is central for addressing the problem. The most prominent feature of cancer is adaptation to extinction by the mechanisms acquired in the evolution of life on earth. The naturally occurring tumors are found already in *Hydra* [223]. When the organisms were challenged by extinction, they have adapted to it by transient polyploidy, epigenetic plasticity, including pluripotent stemness with its bivalency of genes, intrinsically disordered proteins, and rearrangement of the nuclear architecture domains by phase transitions—these epigenetic adaptations are by two orders faster than the gene mutation-selection-based process would allow [224]. In accord, the expression of stemness genes, early stress response genes, epigenetic master activator CTCFL/BORIS and in particular, CT antigens genes as universal adaptors for reconstruction of the genome functional network—all these epigenetic evolutionary adaptations are found in melanoma, which are highly mortal-risky and treatment resistant in patients. At the same time, the tumor pathways are rare evolutionary attractors of the genome multi-dimensional network [225], entrapping cancer cells by the therapy resistance—only a small number of cells, but inevitably survive and repopulate the tumors [56, 177]. These rare genome space states can be only chosen by the mechanisms of nonequilibrium thermodynamics, which is by coherating fluctuations, through the method of trial and error [224, 226]. Those are inevitably accompanied by a lot of cell death and a lot of aberrant phenotypes, which may persist as transient or axillary to reproductive cancer cell line. The fidelity of the genome achieved through the evolutionary meiosis and ploidy life cycles can counteract the aneuploidy; otherwise, tumor cells may balance between both options. The snap-shot studies, not considering this factor (e.g., the productive expression of meiotic genes in only sub-population of tumor cells) can thus bring to misleading interpretations [227]. Moreover, both forward and reverse mutations occurring by gene conversion were recently found in the oldest (from 1951) human cancer cell line cervical carcinoma HeLa [228], which is also known serving a positive control for the meiotic proteins antibodies and expresses them in reversible polyploidy cycles [31]. As suggested by Maciver in 2016 [229], gene conversion in asexual polyploid species can compensate the "Muller's Ratchet." Gene conversion is the process by which one DNA sequence replaces a homologous sequence such that the sequences become identical after the conversion event. In this case, the nonreciprocal "copy-paste" recombination is occurring which is stimulated by

DNA strand breaks in hot spots [230]. This type of the genetic reconstruction seems also to be compatible with tumor cell senescence, mitotic slippage, and ALT.

7. Conclusion

The CT antigens and meiotic genes enhanced expression in tumors, including B-RAF-mutant melanoma, is associated with poor prognosis for the patient survival and treatment outcomes. The review shows that the functions of CTA and meiotic genes in cancer are multilayered: they involve genetic, whole-genomic, cytogenetic, epigenomic, and posttranslational levels of regulation, which are evolutionarily evolved. That means that the expression of CT antigens and meiotic genes is in general adaptive, explaining the correlation of this expression with poor melanoma prognosis. The matter concerns some recently acknowledged biological processes, whose mechanisms and thermodynamics are not fully understood. These are reversible polyploidy and reversible senescence, transient ALT, gene conversion, and likely also several forms of evolutionary, nonconventional, asexual meiosis and parthenogenesis. The fidelity of the genome aimed through the evolutionary meiosis and ploidy life cycles can potentially compensate the aneuploidy, or the tumor cells may balance between the advantages and disadvantages of both options [150]. All these questions still remain open for future studies.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A

Gene	Symbol	Log2FC
Melanoma-associated antigen 3	MAGEA3	7.645235
Melanoma-associated antigen 12	MAGEA12	7.348702
Cancer/testis antigen 2	CTAG2	7.111641
MAGE family member C2	MAGEC2	6.874003
Melanoma-associated antigen 6	MAGEA6	6.828297
Chondrosarcoma-associated Gene 1	CSAG1	6.204377
Preferentially expressed antigen of melanoma	PRAME	5.821726
Melanoma-associated antigen 1	MAGEA1	5.752684
MAGE family member A2B	MAGEA2B	5.738676

Gene	Symbol	Log2FC
Melanoma-associated antigen 4	MAGEA4	5.327805
Prostate-associated gene protein 5	PAGE5	5.246215
Prostate-associated gene protein 2	PAGE2	4.905513
MAGE family member B2	MAGEB2	4.803597
Melanoma-associated antigen 11	MAGEA11	3.985815
PAGE family member 2B	PAGE2B	3.714482
MAGE family member C1	MAGEC1	3.522569
Melanoma-associated antigen 10	MAGEA10	3.168079
Cancer/testis antigen family 25, member 1a	DSCR8	2.770747
Interleukin 13 receptor subunit alpha 2	IL13RA2	2.338307
Transgelin	TAGLN	2.28783
Catenin alpha 2	CTNNA2	2.112868
Mesenteric estrogen-dependent adipogenesis	MEDAG	2.087961
PDZ binding kinase	PBK	2.022606
Homeobox protein BarH-like 1	BARX1	1.99113
Centrosomal protein 55	CEP55	1.86278
Sperm-associated antigen 4	SPAG4	1.521662
T-cell activation RhoGTPase activating protein	TAGAP	1.510325
MAGE family member B17	MAGEB17	1.498956
Homeobox protein ARX	ARX	1.147917
Outer dense fiber of sperm tails 3B	ODF3B	1.144663
ATPase family AAA domain containing 2	ATAD2	1.116308
MAGE family member D1	MAGED1	0.941916
GATA zinc finger domain containing 2A	GATAD2A	0.892566
ADAM metallopeptidase domain 28	ADAM28	0.838868
Phosphotyrosine picked threonine-protein kinase	TTK	0.78873
Opa-interacting protein 5	OIP5	0.775664
Acrosin binding protein	ACRBP	0.518623
Nucleolar protein 4 like	NOL4L	0.487608
GATA zinc finger domain containing 2B	GATAD2B	0.484958
Outer dense fiber of sperm tails 2	ODF2	0.40552
MAGE family member F1	MAGEF1	0.334573
Cancer/testis antigen 101	KIAA0100	0.315249
Transgelin 2	TAGLN2	0.241303
DDB1- and CUL4-associated factor 12	DCAF12	0.228037

Appendix Table 1.
The list of genes with significantly upregulated expression of CT antigenes in the cohort of 51 primary melanomas compared to 27 B-RAF V600E-mutant nevi from the NCBI's Gene Expression Omnibus GSE98394 dataset (described in detail in [80]). EdgeR [127] was used to perform differential expression analysis through the generalized linear model approach. The differentially upregulated in melanoma genes (log2FC > 0, $p < 0.01$) were filtered for CT antigenes. The whole CT antigenes list comprising of 220 genes was acquired from the CT database [70]. Expression is presented as log_2 FC units.

Gene	Symbol	Log2FC
SPANX family member A2	SPANXA2	4.748924
SPANX family member B1	SPANXB1	4.617090
Sperm protein associated with the nucleus, X-linked, family member A1	SPANXA1	4.501381
Transgelin 3	TAGLN3	4.426952
SPANX family member D	SPANXD	3.947176
Transmembrane protein with EGF-like and two follistatin-like domains 2	TMEFF2	3.767568
SPANX family member C	SPANXC	3.684016
Interleukin 13 receptor subunit alpha 2	IL13RA2	2.558249
Coiled-coil domain containing 33	CCDC33	2.399770
PAGE family member 4	PAGE4	2.248496
Nucleolar protein 4	NOL4	2.078128
Tudor domain containing 15	TDRD15	1.896378
VENT homeobox pseudogene 1	VENTXP1	1.859120
DDB1 and CUL4 associated factor 12 like 2	DCAF12L2	1.816185
SPANXA2 overlapping transcript 1	SPANXA2-OT1	1.793161
RNA binding motif protein 46	RBM46	1.765131
F-box protein 39	FBXO39	1.599419
ADAM metallopeptidase domain 28	ADAM28	1.545184
T cell activation RhoGTPase activating protein	TAGAP	1.530934
Tektin 5	TEKT5	1.443142
Maelstrom spermatogenic transposon silencer	MAEL	1.415596
Actin-like 8	ACTL8	1.358688
MAGE family member A1	MAGEA1	1.315031
ADAM metallopeptidase domain 21	ADAM21	1.210916
PRAME N-terminal-like, pseudogene	PRAMENP	1.202568
MAGE family member A10	MAGEA10	1.163532
MAGEA10-MAGEA5 readthrough	MAGEA10-MAGEA5	1.163181
NLR family pyrin domain containing 4	NLRP4	1.053507
ADAM metallopeptidase domain 22	ADAM22	0.922948
Acrosin binding protein	ACRBP	0.854224
Transmembrane protein 108	TMEM108	0.793037
Ankyrin repeat domain 45	ANKRD45	0.779239
BAGE family member 2	BAGE2	0.733106
Mesenteric estrogen dependent adipogenesis	MEDAG	0.72858
Sperm associated antigen 4	SPAG4	0.70602

Gene	Symbol	Log2FC
Placenta enriched 1	PLAC1	0.669653
Fetal and adult testis expressed 1	FATE1	0.61294
Transmembrane protein with EGF-like and two follistatin-like domains 1	TMEFF1	0.603075
Piwi-like RNA-mediated gene silencing 4	PIWIL4	0.601545
Piwi-like RNA-mediated gene silencing 2	PIWIL2	0.566213
Centrosomal protein 290	CEP290	0.489041
Stromal antigen 2	STAG2	0.470227
Cutaneous T cell lymphoma-associated antigen 1	CTAGE1	0.457364
SSX family member 2 interacting protein	SSX2IP	0.426617
Transgelin	TAGLN	0.425961
MSANTD3-TMEFF1 readthrough	MSANTD3-TMEFF1	0.423834
Tudor domain containing	TDRD6	0.344416
ATPase family AAA domain containing 2	ATAD2	0.322527
TTK protein kinase	TTK	0.316241
ATPase family AAA domain containing 2B	ATAD2B	0.30301
Stromal antigen 1	STAG1	0.277385
OIP5 antisense RNA 1	OIP5-AS1	0.26571
M-phase phosphoprotein 10	MPHOSPH10	0.235959
DDB1- and CUL4-associated factor 12	DCAF12	0.158102

Appendix Table 2.
Significantly upregulated expression of CT antigenes in the cohort of 368 melanoma metastases compared to 103 primary melanomas from the TCGA-SKCM dataset (https://www.cancer.gov/tcga). The data was extracted from the TCGA database using the TCGA Biolinks Bioconductor package [124]. EdgeR [127] was used to perform differential expression analysis through the generalized linear model approach and the differentially expressed genes (DEGs) which were upregulated in metastatic melanoma (log2FC > 0, p < 0.01) were filtered for CT antigens. The CT antigenes list comprising of 220 genes was acquired from the CT database [70]. Expression is presented as log_2FC units.

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