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Epigenetics: A Possible Link Between Stress and Melanocyte Malignant Transformation

Fernanda Molognoni and Miriam Galvonas Jasiulionis
*Pharmacology Department, Universidade Federal de São Paulo, São Paulo
 Brazil*

1. Introduction

Melanoma incidence has been growing fast, however the only efficient available treatment is the surgical excision of the affected area when the tumor is detected early. Once diagnosed with metastatic melanoma, most patients have an overall surviving time of 2 years (Howell et al., 2009). Melanoma aggressive nature has encouraged many researchers to study possible molecular alterations behind disease development and progression. During many years the focus of studies on melanoma field was genetic alterations. Despite their importance in familial cases, mutation accumulation does not well explain sporadic tumor cases that can take many years to develop. In the past decades, growing attention has been given to the participation of epigenetic alterations, together with mutations, in the aetiology of cancer. Epigenetic marks control gene expression without altering the primary DNA sequence and are potentially reversible by epigenetic drugs. In a different way of mutations, epigenetic marks are plastic and can be influenced by environmental changes. Therefore, aberrant epigenetic patterns could explain the relationship between cancer and environment injury, since chronic injury is one of the causes for increased cancer risk (Bjornsson et al., 2004). In melanoma specifically, UV radiation and inflammation are considered as risk factors and epigenetic mechanisms could be the link between environmental insult and tumor formation and progression (Autier et al., 2011; Gallagner et al., 2010). The epigenetic mechanisms include DNA methylation, histone modifications, nucleosome remodeling and micro-RNAs (miRNAs). Collectively these mechanisms regulate the genetic information accessibility, promoting in this way the cellular diversity. In the next sections, the importance of epigenetics in melanoma will be discussed, as well their possible relation with environmental injuries.

2. Epigenetics and cancer

Cancer disease is complex and involves many factors including aberrant epigenetic alterations. Epigenetic is the study of heritable patterns of gene expression that do not involve modifications in the primary DNA sequence. These heritable marks are established during embryonic development and stably maintained through cellular division (Reik, 2007). While the genome is the same in each cell type of an individual, the epigenome differs from tissue to tissue and is essential to maintain cellular identity (Mikkelsen et al., 2007). Therefore, its disruption could lead to inappropriate gene expression contributing to diseases such as

cancer (Egger et al., 2004). Epigenetic mechanisms comprise DNA methylation, histone modifications, chromatin remodeling and RNA associated silencing by micro-RNAs (miRNAs). These mechanisms work together to regulate the functioning of the genome.

2.1 DNA methylation in cancer

DNA methylation is the most studied epigenetic mechanism, is generally linked to stable gene expression inactivation and normally occurs in mammals by the covalent modification of the CpG dinucleotide (cytosine to 5-methylcytosine). CpG distribution is not random in mammal genome. There are regions with high CpG frequency called CpG islands. Generally, these islands are located at 5' end of about 60% of human genes. Although some of these islands (about 6%) become methylated in a tissue-specific manner during development or in differentiated tissues, they are commonly unmethylated in normal cells (Straussman et al., 2009). One of the hallmarks of cancer cells is the presence of an aberrant DNA methylation pattern, which is characterized by specific DNA hypermethylation of tumor suppressor gene promoters and global DNA hypomethylation compared to normal cells. The hypermethylation of tumor suppressor promoters is associated with loss of their expression. Global DNA hypomethylation can contribute to genomic instability because it is largely a consequence of DNA methylation loss in non-coding DNA (like repetitive DNA sequences) and transposable elements (Rodriguez et al., 2006). Besides that, DNA hypomethylation can also cause oncogene activation (Jun et al., 2009).

2.2 Histone modifications in cancer

Posttranslational histone modifications, such as acetylation and methylation of lysine residues, have also a crucial role in controlling gene expression (Smith & Shilatifard, 2010.). Unlike DNA methylation, histone modifications can lead to either activation or inactivation. Overall, lysine acetylation is linked to gene activation whereas lysine methylation can be a marker for both, gene activation in the case of H3K4 trimethylation or repression in the case of H3K27 and H3K9 trimethylation. Histone posttranslational modification patterns and enzymes catalyzing the addition or removal of histone marks have been found altered in cancer, as well proteins that are specifically recruited by these modifications, such as polycomb group proteins, DNA methyltransferases (DNMTs) and nucleosome remodeling factors (Sharma et al., 2010). Non-covalent mechanisms, such as nucleosome remodeling, also contribute to regulate the gene activity (Svejstrup, 2010). In addition to their role as a basic organization for DNA packaging, nucleosome positioning regulates gene expression by altering DNA accessibility to transcriptional factors (Jiang & Pugh, 2009). The role of such mechanism in cancer is not well understood; nevertheless, recent data have been shown that nucleosome remodeling machinery seems to work together with histone modifications and DNA methylation in tumor-specific gene silencing (Morey et al., 2008).

2.3 Micro-RNAs in cancer

Another mechanism recently considered as epigenetic is RNA associated silencing by micro-RNAs. Micro-RNAs (miRNAs) are small non-coding RNAs that regulate gene expression through posttranscriptional silencing of target genes (Peter, 2010). Micro-RNAs are expressed in a tissue specific manner and can control many important biological processes including cell proliferation, apoptosis and differentiation. They can function as tumor suppressors or oncogenes, depending on their target genes (Peter, 2010). There is a growing

number of miRNAs found aberrantly expressed in cancer cells and this abnormal expression seems to be tumor-specific (Lu et al., 2005). Moreover, miRNA expression can be regulated by many processes, including epigenetic mechanisms, such as DNA methylation and histone modifications (Deng et al., 2008).

Besides their individual roles, epigenetic mechanisms interact with each other to determine gene expression status and this interaction is crucial to promote properly chromatin architecture and gene activity during development and to maintain cellular identity after cell commitment process (Cerdeira & Bergman, 2009). Consequently, it has been shown that aberrant changes in epigenetic marks can compromise cell fate and participate in the early phases of cell malignant transformation (Feinberg et al., 2006). Different of mutations, these modifications can be reversible by chemical components and/or by environment and this reversible nature led to the development of a promising field: "The epigenetic therapy". In this way, this book chapter proposes to discuss what is known about the epigenome of melanoma, the emerging relation among stress, epigenetics and melanoma and the perspectives regarding epigenetic therapies to treat this metastatic disease.

3. Epigenetics and melanoma

The importance of epigenetic mechanisms in cancer formation and progression has been growing in the past decades. Despite of this, there are less published studies about abnormal epigenetic marks in melanoma than in any other cancer type. Additionally, most of the studies in literature refer to tumor suppressor genes silenced by DNA hypermethylation and few of them focus on posttranslational histone modifications, nucleosome remodeling and miRNAs. In the next sections, data concerning the epigenetic marks mentioned before will be discussed in melanoma.

3.1 The methylome of melanoma

3.1.1 Tumor suppressor genes silenced by DNA hypermethylation in melanoma

Melanoma development, as other tumors, is accompanied by disruption of cellular DNA methylation homeostasis, resulting in both hypermethylation of tumor suppressor promoters and genome wide hypomethylation (Molognoni et al., 2011; Soengas et al., 2001; Tanemura et al., 2009; Van Doorn et al., 2005).

Aberrant CpG island hypermethylation is a common event in melanoma and an important mechanism to shut off tumor suppressor genes (TSGs) involved in all key pathways of tumor development and progression, including cell cycle regulation, cell signaling, differentiation, DNA repair, apoptosis, invasion and immune system recognition (Sigalloti et al., 2010). Hypermethylation patterns are tumor-specific and it is still unclear why some DNA regions become hypermethylated, whereas others remain unmethylated. Most of the studies in the field of melanoma epigenetics describe hypermethylation of tumor suppressor genes. The great interest in this topic has an explanation: the considerable prognostic, diagnostic and therapeutic value of these studies. Because of that, some authors have been described the CpG island methylator phenotype (CIMP), which refers to the coordinated inactivation of tumor suppressor and tumor-related genes in a determined type of cancer (Toyota et al., 1999). In addition, these epigenetic changes would create a distinct CIMP pattern that could be associated to the disease stage, recurrence and patient survival (Tanemura et al., 2009). At least 60 tumor suppressor genes have been identified to date as silenced by DNA hypermethylation in melanoma (Table 1). Some of them will be discussed

in more details. A well-studied example of DNA hypermethylation in melanoma is *CDKN2A* locus. This locus encodes two proteins which are cell cycle regulators through pRB and p53 pathways (p16^{INK4A} and p14^{ARF}, respectively). Aberrant DNA hypermethylation at *CDKN2A* locus can independently affect p16^{INK4A} and p14^{ARF}, which are methylated in 27% and 57% of metastatic melanoma samples, respectively (Freedberg et al., 2008). In addition, *CDKN2A* locus is one of the well-known cases in which genetic alterations can cooperate with DNA methylation to promote gene inactivation (Freedberg et al., 2008; Gonzalgo et al., 1997). In this way, gene deletion can eliminate one allele and DNA hypermethylation silence the remaining one. This cooperation might be responsible for the concomitant inactivation of p16^{INK4A} and p14^{ARF} in a significant percentage of metastatic melanoma. Another important tumor suppressor which expression is lost by DNA hypermethylation in melanomas is *APAF-1*, a cell death effector that mediates p53-dependent apoptosis (Soengas et al., 2001). Then, the successfully shut off of *CDKN2A* locus and *APAF-1* by DNA hypermethylation and/or mutations could be a way utilized by melanoma cells to evade the growth arrest triggered by p53, once p53 is rarely mutated in melanomas (Soussi & Beroud, 2001). *PTEN* is another important gene which activity loss by DNA hypermethylation has been reported to contribute to the melanoma development (Mirmohammadsadegh et al., 2006). *PTEN* gene encodes a phosphatase that degrades PI3K products and its function loss can cause accumulation of PI3K messenger lipids, which in turn increase AKT phosphorylation and activity, leading to apoptosis decrease (Lian et al., 2005). Mirmohammadsadegh and co-workers (2006) observed an increase in *PTEN* CpG island methylation in primary, metastatic melanoma and serum from melanoma patients. Moreover, metastatic disease showed the higher DNA methylation percentage compared to primary tumor.

Besides the classical examples, there are other genes that have been found hypermethylated in melanomas such as *RAR-β2*, *SOCS1* and *SOCS2*. *RAR-β2*, which mediates growth arrest, apoptosis and differentiation triggered by retinoic acid (RA), has been found hypermethylated in 70% of melanoma lesions (Hoon et al., 2004). Interestingly, *RAR-β2* promoter hypermethylation is found with similar frequency in primary and metastatic melanoma lesions, suggesting that this hypermethylation process might be an early event in melanoma disease (Hoon et al., 2004). *SOCS*'s family genes have been implicated in the regulation of signal transduction by a variety of cytokines (Fujimoto & Naka, 2003). Moreover, *SOCS1* restoration suppressed both growth rate and anchorage independent growth of cells in which *SOCS1* was silenced by promoter methylation (Yoshikawa et al., 2001). One study using 20 melanoma cell lines and 40 freshly isolated advanced stage melanoma tumors showed around 90% and 80% of DNA methylation in *SOCS1* and *SOCS2* promoter, respectively (Liu et al., 2008). This methylation percentage was similar in melanoma cell lines and freshly isolated tumors. In addition, at the same work, *RAR-β2* was found with 60% of methylation both in cell lines and freshly isolated advanced stage melanoma tumors. Summarizing there are many tumor suppressor genes silenced by promoter hypermethylation in melanoma and it will be necessary to continue looking for other key genes to provide novel targets for diagnosis and therapy.

3.1.2 Aberrant DNA hypomethylation in melanoma

Global DNA hypomethylation found in cancer cells is largely a consequence of DNA methylation loss in repetitive elements, which in turn, as mentioned before, could contribute to genomic instability and transposon elements activation (Portela & Esteller, 2010). A clear case of repetitive element hypomethylation in cancer is the LINE family member LINE-1,

Pathway	Gene	Common Name	References
Apoptosis	<i>DAPK1</i>	Death- associated protein 1	Hoon et al., 2004
	<i>HSPB6</i>	Heat shock protein, alpha crystallin related, B6	Koga et al., 2009
	<i>HSPB8</i>	Heath shock 22 kDa protein 8	Sharma et al., 2006
	<i>HSP11</i>	Heat shock protein H11	Sharma et al., 2006
	<i>RASSF1A</i>	Ras association domain family protein 1A	Spugnardi et al., 2003
	<i>TNFRSF10C</i>	Tumor necrosis factor receptor superfamily member 10C	Liu et al., 2008
	<i>TNFRSF10D</i>	Tumor necrosis factor receptor superfamily member 10D	Liu et al., 2008
	<i>APAF-1</i>	Apoptotic protease activating factor 1	Soengas et al., 2001
Cell cycle	<i>CDKN1C</i>	Cyclin-dependent kinase inhibitor 1C	Muthusamy et al., 2006
	<i>CDKN2A</i>	Cyclin-dependent kinase inhibitor 2A	Freedberg et al., 2008
	<i>TSPY</i>	Testis specific protein, Y linked	Gallagher et al., 2005
Cell fate determination	<i>MIB2</i>	mindbomb homolog 2	Takeuchi et al., 2006
	<i>APC</i>	Adenomatous polyposis coli gene	Worm et al., 2004
	<i>WIF1</i>	Wnt inhibitory factor 1	Tenemura et al., 2009
Chromatin remodeling	<i>NPM2</i>	Nucleophosmin/nucleoplasmin 2	Koga et al., 2009
Degradation of misfold proteins	<i>DERL3</i>	Der1 like domain family member 3	Furuta et al., 2006
Differentiation	<i>GDF15</i>	Growth differentiation factor 15	Muthusamy et al., 2006
	<i>HOXB13</i>	homeobox B13	Muthusamy et al., 2006
DNA repair	<i>MGMT</i>	O-6-methylguanine-DNA methyltransferase	Hoon et al., 2004
Drug metabolism	<i>CYP1B1</i>	Cytochrome P450, family 1, subfamily B, polypeptide 1	Muthusamy et al., 2006
	<i>DNAJC15</i>	DnaJ (Hsp40) homolog, subfamily C, member 15	Muthusamy et al., 2006
Extracellular matrix	<i>COL1A2</i>	Collagen, type I, alpha 2	Koga et al., 2009
	<i>MFAP2</i>	Microfibrillar-associated protein 2	Muthusamy et al., 2006
inflammation	<i>PTGS2</i>	Prostaglandin-endoperoxide synthase 2	Muthusamy et al., 2006
metastasis	<i>CDH1</i>	E-cadherin	Tellez et al., 2009
	<i>CDH8</i>	Cadherin 8, type 2	Muthusamy et al., 2006
	<i>CDH13</i>	Cadherin 13, H-cadherin	Tellez et al., 2009
	<i>SERPINB5</i>	Serpin peptidase inhibitor, clade B, member 5	Denk et al., 2007
	<i>LOX</i>	Lysyl oxidase	Liu et al., 2008
	<i>THBD</i>	Thrombomodulin	Liu et al., 2008
Proliferation	<i>WFDC1</i>	WAP four-disulfide core domain 1	Liu et al., 2008
Signaling	<i>ERα</i>	Estrogen receptor α	Mori et al., 2006
	<i>PGRβ</i>	Progesterone receptor β	Tellez et al., 2009
	<i>PTEN</i>	Phosphatase and tensin homolog	Mirmohammadsadegh et al., 2006
	<i>3-OST-2</i>	Heparan sulfate (glucosamine) 3-O-sulfotransferase 2	Furuta et al., 2006
	<i>RARRES1</i>	Retinoic acid receptor responder 1	Bonazzi et al., 2009
	<i>RARβ2</i>	Retinoic acid receptor β2	Hoon et al., 2004
	<i>RIL</i>	Reversion-induced LIM	Tellez et al., 2009
	<i>SOCS1</i>	Supressor of cytokin signaling 1	Liu et al., 2008
	<i>SOCS2</i>	Supressor of cytokine signaling 2	Liu et al., 2008
Transcription	<i>SOCS3</i>	Supressor of cytokine signaling 3	Tokita et al., 2007
	<i>HAND1</i>	Heart and neural crest derivatives expressed 1	Furuta et al., 2004
	<i>OLIG2</i>	Oligodendrocyte lineage transcription factor 2	Tellez et al., 2009
	<i>NKX2-3</i>	Homeobox protein Nkx-2.3	Tellez et al., 2009
	<i>PAX2</i>	Paired box 2	Tellez et al., 2009
	<i>PAX7</i>	Paired box 7	Tellez et al., 2009
	<i>GATA4</i>	GATA binding protein 4	Atsushi et al., 2009
To be determined	<i>BST2</i>	Bone marrow stromal cell antigen 2	Muthusamy et al., 2006
	<i>LXN</i>	Latexin	Muthusamy et al., 2006
	<i>QPCT</i>	GlutaminyI-peptide cyclotransferase	Muthusamy et al., 2006

Table 1. Genes found hypermethylated in melanoma

which has been shown hypomethylated in a wide range of cancers (Portela & Esteller, 2010). Tellez and co-workers (2009) showed 75% of hypomethylation in LINE-1 repetitive sequence when they analyzed 16 melanoma cell lines by pyrosequencing. Additionally, DNA hypomethylation at specific promoters can activate expression of oncogenes and induce loss of imprinting (Herman & Baylin, 2003). In melanoma, a group of cancer-testis antigens and other genes considered as oncogenes have been shown to be hypomethylated (Howell et al., 2009). Melanoma antigen (*MAGE*) genes, for example, are normally only expressed by male germline cells. In somatic cells, their expression is silenced by promoter hypermethylation. Nevertheless, in malignant melanoma, aberrant expression of *MAGE* genes occurs and is associated with DNA hypomethylation (De Smet et al., 1996; Sigalotti et al., 2002). Recent data suggest that re-expression of *MAGE* genes in melanoma might contribute to malignant phenotype and interfere with therapy response (Simpson et al., 2005). Other genes found hypomethylated in melanoma were *MASPIN*, a serine protease inhibitor (Wada et al., 2005) and *TIMP1*, a metalloprotease inhibitor (Ricca et al., 2009). While the significance of *MASPIN* expression in melanoma formation and progression requires further investigation, *TIMP1* expression in melanoma cells seems to be an early event and promotes *anoikis* resistance (Ricca et al., 2009).

Comparatively to tumor suppressor epigenetic silencing little is known about the role of hypomethylation in melanoma development. More studies are necessary to find new target genes and repetitive sequences regulated by hypomethylation and their possible role in melanocyte malignant transformation.

3.2 Histone modifications in melanoma

The study of histone modifications is more complex than DNA methylation, since there are many possible combinations of histone marks. Additionally, there is the requirement of chromatin immunoprecipitation approaches with specific antibodies for each histone modification and the need of large amounts of starting DNA, which is difficult to obtain from patients' tumor samples. Summarizing, these factors restrict the number of studies about histone modifications in melanoma. Nevertheless, these problems might be solved by the new generation of high-throughput technologies and whole genome amplification protocols. Besides the limited data about histone modifications in melanoma, some studies have revealed changes in the expression of histone modifying enzymes, as well as aberrant changes in the level of global histone modifications in this type of cancer (Richards & Medrano, 2008; Molognoni et al., 2011).

3.2.1 Histone acetylation in melanoma

Generally, available studies have shown a global reduction of monoacetylated H4K16 in many types of cancer (Portela & Esteller, 2010). Loss of acetylation is mediated by histone deacetylases (HDACs), which have been found to be over-expressed or mutated in different types of tumors (Portela & Esteller 2010). It is important to remember that histone deacetylation is linked to inhibition of transcription and histone acetylation with transcription activation. In melanoma, until now there are non-specific studies addressing the global status of histone acetylation. On the other hand, there are some works showing that histone deacetylase inhibitors can re-activate genes that are silenced in melanoma (Sigalotti et al., 2010). These genes are involved in important processes, such as apoptosis (i.e. *BAX*, *BCL-X*), cell cycle (i.e. *CDKN1A*, *CDKN2A*), and DNA repair (*RAD 50*) (Munshi et

al., 2006; Valentini et al., 2007; Zhang et al., 2004). Therefore, HDAC inhibitors are currently being studied as treatment against the development of malignant melanoma. Apart the global loss of histone acetylation and HDACs overexpression, histone acetyltransferases (HATs) have been shown altered in cancer cells as well by translocation, mutations, deletions and overexpression and have been implicated in the development of various tumors (Lafon-Hughes et al., 2008). Moreover, HATs and HDACs are commonly found in multi-subunit complexes where their activities and substrate specificities may be altered by cofactors and vice versa (Sadoul et al., 2007). The HATs Tip60 and HBO1, for example, are present in a complex with the melanoma tumor suppressors ING3 and ING4, respectively. Such complexes, important to regulate cell cycle, apoptosis and DNA repair, as well important p53 cofactors, are diminished in melanoma (Li et al., 2008, Wang et al., 2007). Besides their role in control tumor growth, Tip60 and other HATs (GCN5 and PCAF) can stabilize the transcription factor c-Myc, considered as a melanoma oncoprotein (Frank et al., 2003; Patel et al., 2004, Schlagbauer-Wadl et al., 1999). Furthermore, the HATs CBP and p300 have been shown associated with microphthalmia-associated transcription factor (MITF), a melanocyte lineage survival oncogene that has been related as overexpressed in melanoma and associated with decreased survival in patients with metastatic melanoma (Garraway et al., 2005; Price et al., 1998; Sato et al., 1997).

3.2.2 Histone methylation in melanoma

In addition to acetylation status, studies have demonstrated a possible role of aberrant histone methylation in melanoma. Melanoma cells were found to express elevated levels of the H3K27 histone methyltransferase EZH2 (McHugh et al., 2007). Moreover, in highly metastatic human melanoma cell line A375, there is a decrease in JARID1b histone demethylase (known by KDM5B as well) expression. The ectopic expression of JARID1b also resulted in cell cycle arrest in G1/S phase, accompanied by decreased cellular proliferation and DNA replication (Roesch et al., 2006). These are preliminary data that need confirmation in large series of melanoma tissues to define the role of histone methylation in melanoma biology. We are far from a clear comprehension of the melanoma histone code profile and further investigations will certainly open new avenues in the understanding of melanoma formation.

3.3 MicroRNAs in melanoma

Like mentioned before, microRNAs (miRNAs) regulate gene expression and are involved in the modulation of important cellular processes related with cancer, like apoptosis and cell proliferation (Peter, 2010). In this way, alterations in their expression might promote tumorigenesis. The study of miRNAs in tumor cells comprises a new scientific field and little is known about their roles in melanoma formation and development. The approach used at most available works is the hybridization of small RNA fractions isolated from cultured cells or tissue samples to specialized miRNA microarrays (Mueller & Bosserhoff, 2010). Many examples of miRNAs found de-regulated in melanoma cells were identified by comparing normal human melanocytes and/or benign nevi with melanoma cell lines or tumor tissue samples (Mueller & Bosserhoff, 2010). In this way, two important miRNAs found de-regulated in melanoma were described, miR-137 and miR-182, both of them regulating *MITF*, an important gene in melanoma genesis. MiR-137 was found down-regulated in melanoma cell lines, which resulted in *MITF* over-expression (Bemis et al.,

2008). In opposite way, miR-182 was shown to be over-expressed in melanoma, which contributed to metastatic potential by repressing *MITF* and *FOXO3* (Segura et al., 2009). MiR-182 seems to be involved in melanoma progression since it has been found over-expressed with the evolution of the disease, from primary to metastatic stages. These conflicted alterations might be related to the complex regulation of *MITF* in melanoma, which has been found up-regulated at the beginning phases of tumorigenesis and down-regulated in cells that acquired invasive and metastatic characteristics (Levy et al., 2006). Additionally, Muller and co-workers (2008) showed down-regulation of miRNA let-7 in melanomas. Let-7 regulates β 3-integrin and according to these authors its down-regulation might be responsible for the over-expression of β 3-integrin in melanomas.

The use of specialized miRNA microarrays approach limited the analysis to already known miRNAs, restraining the discovery of new miRNAs important in melanocyte transformation. To over cross this limitation, Stark and co-workers (2010) employed next-generation sequencing technology together with microarray profile for studying miRNAs in melanoblasts, melanocytes and melanomas. They identified, with this huge study, 279 novel miRNAs candidates to be important at the progression of the disease. With this work they showed that less-differentiated cell type (melanoblasts) expressed the highest number of miRNAs, whereas the most differentiated cell type, the melanocytes, expressed the fewest miRNAs species. Melanoma cell lines presented an intermediated number of expressed miRNAs. This data is in contrast with what has been shown for other types of cancer. Generally, miRNA global expression is up-regulated during differentiation process and down-regulated when partial de-differentiation occurs during malignant transformation (Lu et al., 2005; Wienholds & Plasterk, 2005). Therefore, the control of miRNA expression during melanocytic lineage commitment might be different from the other types of cells. The miRNAs studies in cancer are attracting many researchers nowadays, nevertheless more studies are necessary to define “melanoma-miRNAs”, as well their importance in disease establishment and progression.

4. Microenvironment and melanoma progression

In the human skin, melanocytes reside in the epidermis and interact both with keratinocytes (cell-cell interaction) and the basement membrane (cell-extracellular matrix interaction). The growth and differentiation of melanocytes are tightly regulated by these interactions, which are mediated by adhesion molecules, such as cadherins (Tang et al., 1994) and integrins (Haass et al., 2005), and by soluble factors (Imokawa, 2004). Cell adhesion complexes, the cytoskeleton and the nucleus are linked and changes in the extracellular environment may affect the gene expression. In this way, it is now known that changes in this microenvironment can result in the disruption of melanocyte homeostasis and melanoma development (Haass & Herlyn, 2005; Li et al., 2001; van Kempen et al, 2005), although the molecular mechanisms involved are not completely elucidated.

Epigenetics has provided new insights about the interaction between genome and cellular environment. Since alterations in the skin microenvironment (i.e. ultraviolet radiation, inflammation, cutaneous wounding) seem to be critical factors for malignant transformation (Edwards et al, 1989; Tucker & Goldstein, 2003; van Kempen et al, 2007; von Thaler et al, 2010) and epigenetic abnormalities may substantially contribute to stress-induced pathologies (Johnstone & Baylin, 2010), a better understanding of epigenetic mechanisms underlying melanoma genesis may reveal the causal relationship between stress and cancer.

In addition, the comprehension of the epigenetics of melanoma could lead to the identification of epigenetic marks resulting in aberrant gene expression patterns related to initiation and progression of this tumor type and also contribute to the development of new therapeutic approaches, the epigenetic drugs, for this malignant tumor.

5. Experimental models of melanoma genesis

Experimental models both of murine and human cancers have contributed to a better comprehension of tumor biology and provided tools to develop new cancer therapies. In the case of melanoma, a variety of *in vitro* and *in vivo* models has been utilized, but is important to consider the advantages and drawbacks of each model (for review, see Becker et al, 2010; Santiago-Walker et al, 2009). Some models may be more suitable for answering a specific scientific question than others. Several human melanoma cell lines, mainly from metastatic tumors, have provided important information about gene expression profile, genetic abnormalities and biological phenotype of melanoma. However, many of these cell lines are maintained in culture for long time and, consequently, may accumulate additional alterations, not necessarily involved in the acquisition of malignant or metastatic phenotype. These cells have been utilized in xeno-transplantation models to analyze the aggressive behavior of melanoma, but are not suitable, for example, to study the role of immunological components in tumor progression. In the other way, murine syngeneic transplantation models have shown as a good option to study melanoma immunology and test new immunotherapeutic approaches. Genetically modified animals, in which oncogenes are super-expressed or tumor suppressor genes are silenced, have been used to study the role of specific genes in the genesis of melanoma (Larue & Beermann, 2007).

As mentioned before, cellular microenvironment is crucial for maintaining the normal function of melanocytes. In this way, some models were established in order to recapitulate, as closely as possible, the microenvironment context of the skin (Khavari, 2006). Two-dimensional melanocyte cultures (with or without keratinocytes), multicellular tumor spheroids and, specially, three-dimensional skin reconstructions (although without vascular and lymphatic components) have shown excellent ways to mimic skin environment in patient' lesions and can complement the data coming from murine melanoma models.

Even considering their limitations, mainly regarding the localization of melanocytes in the skin (Khavari, 2006), it has been proved that mouse melanoma models may substantially contribute to better understand the molecular mechanisms underlying the melanoma genesis and also to the evaluation of new drugs and therapies (Becker et al., 2010).

A linear model of melanocyte malignant transformation associated with sustained stress condition was recently established by our group (Oba-Shinjo et al, 2006). In this model, the murine lineage of non-tumorigenic melanocytes, melan-a (Bennett et al, 1987), was submitted to sequential cycles of anchorage impediment (blockade of cell-extracellular matrix interactions), which initially led to evident morphological and gene expression alterations and later to the acquisition of a full malignant phenotype (Molognoni et al, 2011). Melan-a melanocytes subjected to 1, 2, 3 and 4 deadhesion blockades were named respectively 1C, 2C, 3C and 4C cell lines, are non-tumorigenic and correspond to intermediate phases of malignant transformation or pre-malignant melanocytes. Different melanoma cell lines were established after submitting the spheroids obtained after 4C cell line deadhesion to limiting dilution. All clones randomly selected showed to be tumorigenic when subcutaneously transplanted into syngeneic mice. Both non-metastatic (for example,

4C3-, 4C11-, a1, a2, a3) and metastatic (Tm1, Tm4, Tm5) melanoma cell lines were obtained by this process. Some metastatic melanoma lineages (4C3+ and 4C11+) were also established from non-metastatic cell lines (4C3- and 4C11-, respectively) after spontaneously loss of p53 (Figure 1).

Different expression profile of E- and N-cadherin was observed in the transition phases from melan-a to 4C and also from 4C11- to 4C11+ cell lines (unpublished data), suggesting first the onset of epithelial to mesenchymal transition (EMT) and later mesenchymal to epithelial transition (MET). This data is reinforced by high expression of the key EMT regulator, Snail1, in 4C and 4C11- cell lines (unpublished data). Beta-1 integrins, important class of adhesion molecules involved in cell-extracellular matrix interactions, present their expression increased at the cell surface in metastatic melanoma cell lines. Additionally, strong evidences point β 1-integrin as target of aberrant N-glycosylation along melanoma genesis (unpublished data). In our model, even with the limitations of a mouse model and a culture system, sustained stress led to significant alterations both in cell-cell (cadherins) and cell-ECM (β 1-integrin) adhesion molecules, which have already been well described as proteins consistently involved in the loss of human melanocyte homeostasis.

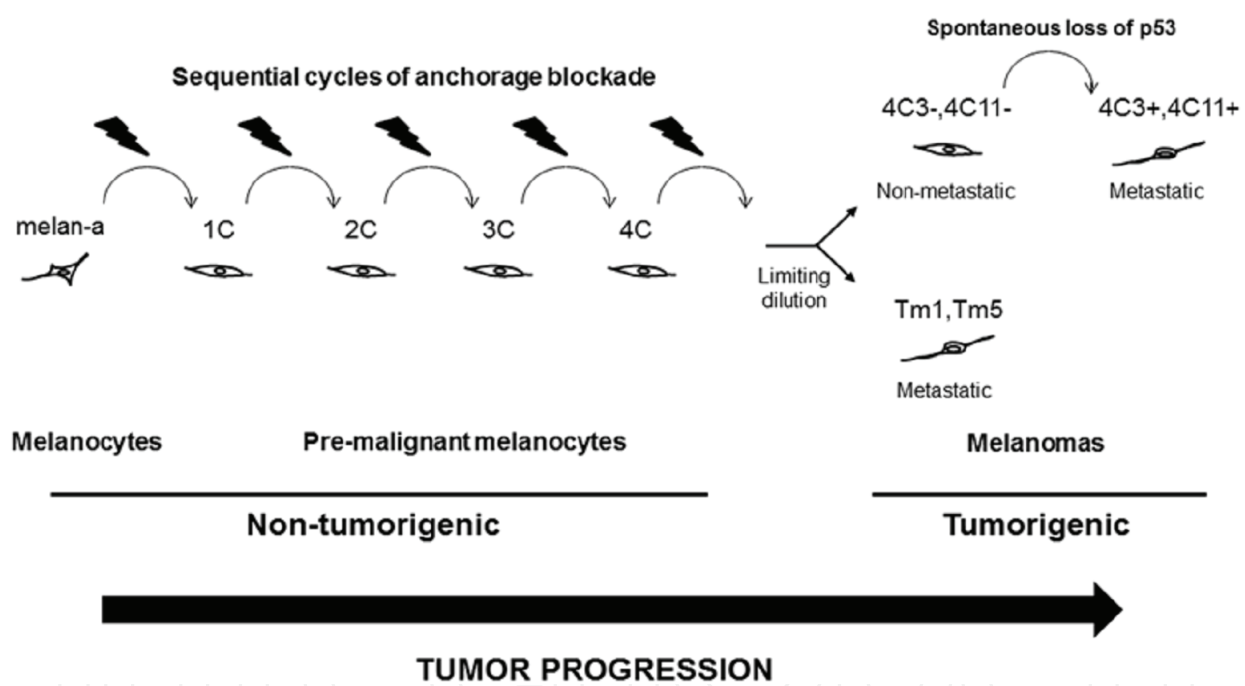


Fig. 1. Model of melanocyte malignant transformation associated with sustained stress condition

No treatment with carcinogenic agent or insertion of oncogene was utilized in our model, the only stimulus applied on non-tumorigenic melan-a melanocytes leading to malignant transformation was a sustained alteration in the microenvironment, the sequential cycles of anchorage blockade (Figure 1). As discussed before, the epigenetics seems to be a crucial link between environment and disease. In fact, alterations in the global level both of DNA methylation and histone marks were detected after few hours of melanocyte anchorage impediment. A global DNA hypermethylation was accompanied by increased mRNA and protein levels of Dnmt1, 3a and 3b (Campos et al., 2007). Regarding histone marks, elevated levels of the activation mark H3K4me3 and silencing mark H3K9me3 was observed in

melan-a melanocytes maintained in suspension for 24 hours. Elevated levels of the histone deacetylase Sirt1 was also noted during melanocyte deadhesion (unpublished data). Recently, Kashiwagi and colleagues (2011) described the association of Sirt1 and Dnmt3b in chromatin regions resistant to nuclease, suggesting that Dnmt3b is preferentially recruited into hypoacetylated and condensed chromatin. Interestingly, co-immunoprecipitation assays revealed Sirt1-Dnmt3b interaction in melan-a melanocytes maintained in suspension, but not in adhered melanocytes (unpublished data). It is important to note that deadhered melanocytes also presented global DNA hypermethylation. These data suggest that the sustained stressful condition of anchorage blockade result in significant changes in the chromatin structure, which may have an important impact in the cell fate.

Comparing some epigenetic marks along melanoma genesis, in our model, an interesting pattern came up in which intermediate phases of malignant transformation, represented by the pre-malignant 4C melanocytes and non-metastatic 4C11- melanoma cell line, showed epigenetic marks characterizing an open chromatin state. Among some of these identified marks are increased levels of the activation histone mark H3K4me3, the histone methyltransferase *MLL1* (responsible for methylating H3K4), the chromatin remodelling factor *Chd1* (that recognizes the H3K4me3 histone mark), and the stress-related protein and histone deacetylase Sirt1 (that deacetylates the H4K16ac histone mark and many other non-histone proteins) (Molognoni et al., 2011). Regarding DNA methylation, a progressive global DNA hypomethylation along melanoma genesis and a drastic reduction in the expression of the methyl-binding protein MeCP2 since pre-malignant 4C melanocytes occurs. These results suggest that a decrease in MeCP2, protein that recognizes methylated CpGs and is implicated in gene repression, takes place before global DNA hypomethylation. Dnmt1 expression is increased since pre-malignant 4C melanocytes to metastatic melanoma cells while only metastatic melanoma cells present elevated levels of Dnmt3a and no significant difference in the expression of Dnmt3b is observed along melanocyte malignant transformation (Molognoni et al., 2011).

An open and highly accessible chromatin is a hallmark of stem cells and essential for their ability to give rise to any cell type (pluripotency). *Chd1* expression was showed to be required to maintain the open chromatin state of pluripotent mouse embryonic stem cells and also for somatic cell reprogramming to the pluripotent state (Gaspar-Maia et al., 2009). *Chd1* seems to promote the disassembly of nucleosomes at promoter regions, resulting in active transcription and open chromatin (Persson & Erkwall, 2010). Another molecular alteration that corroborates with the hypothesis that a less differentiated phenotype is acquired in the beginning of melan-a melanocyte malignant transformation is the increase in Sirt1 expression, which is related with pluripotent state. Recently, Calvanese and coworkers (2010) demonstrated that Sirt1 down-regulation is necessary for human embryonic stem cell differentiation. Low levels of Sirt1 allow the expression of key developmental genes, which are epigenetically silenced in first phases of embryogenesis. In this way, Sirt1 has been considered a regulator of stem cell pluripotency and differentiation. The elevated expression of Snail1, a major transcription factor regulating EMT (Barrallo-Gimeno & Nieto, 2005), also reinforces the acquisition of a less differentiated state by pre-malignant 4C melanocytes and non-metastatic 4C11- melanoma cells, which present a mesenchymal phenotype, different to melan-a melanocytes and metastatic 4C11+ melanoma cells that express low levels of Snail1 and a epithelial phenotype (unpublished result). Finally, the acquisition of tumorigenic properties (transition 4C to 4C11- cell lines) was characterized by the augment of silencing histone marks H3K9me3 and H3K27me3, whereas the acquisition of metastatic properties

was accompanied by elevated expression of Dnmt3a, the highest grade of global DNA hypomethylation, and loss of Sirt1, Mll1, H3K4me3 mark, Chd1 and Snail1 (Molognoni et al., 2011). Besides that, a higher number of coding genes and miRNAs has their expression up-regulated in the tumorigenic cell lines 4C11- and 4C11+ after treatment with epigenetic drugs than in non-tumorigenic melan-a and 4C melanocytes (Molognoni et al., 2011), suggesting a higher number of genes and miRNAs aberrantly silenced by abnormal epigenetic marks.

In our model, it is possible that sustained stress condition (cycles of anchorage blockade) have led melan-a melanocytes to acquire early epigenetic marks conferring an open chromatin state and a less differentiated state in order to adapt the cells to the injury conditions and permit, later, the epigenetic reprogramming resulting in an incorrect differentiated state characterized by a full malignant phenotype (Figure 2).

A great number of genes were identified as having their expression abnormally regulated by aberrant epigenetic marks in our melanoma genesis model (unpublished data). Among them, Tissue Inhibitor of Metalloprotease-1 (Timp1) was described as presenting its promoter progressively demethylated along melanoma genesis and its expression increased since the early steps of melanocyte malignant transformation (Ricca et al., 2009). Apart its well-known function as a metalloprotease inhibitor, this protein regulates many other processes, such as cell proliferation and apoptosis (Chirco et al., 2006; Li et al., 1999). Our group showed that the expression of Timp1 confers *anoikis* resistance along melanocyte malignant transformation and also favors metastatic process (Ricca et al., 2009). Other examples of genes, which aberrant expression along melanoma genesis seems to be regulated by epigenetic alterations, are *Snail1*, *Chd1*, *p14^{ARF}*, *p16^{INK4A}*, *Cdkn2b*, *Cbs*, *Itga4*, *Xist*, *Vav1*, *Serpine1*, among others (unpublished data). Although these data came from a murine melanoma model, according to Melanoma Molecular Map Project (available online at <http://www.mmmp.org/MMMP/>) consistent parallel was observed in the expression of these genes in human melanoma samples. This analysis might provide novel epigenetic markers related to prognosis, diagnosis and response to treatment.

6. Oxidative stress and epigenetic reprogramming

As mentioned before, stress conditions (i.e., inflammation, UV radiation) have been implicated in the genesis of different pathologies, including cancer. Recently, Johnstone and Baylin (2010) pointed the emergent link between chronic stress and epigenetic alterations and its association with abnormal cell expansion, cellular dysfunction, changes in cell fate in cell renewal systems. They proposed that heritable epigenetic changes caused by stress could result in the evolution of abnormal cell states that contribute to disease.

In our model, in which the malignant phenotype was achieved after submitting non-tumorigenic melanocytes to a sustained stress condition, significant alterations were identified in the global DNA methylation level, histone marks and expression of different components of the epigenetic machinery (for example, Dnmts, HDACs, HATs, EZh2, MeCP2, Chd1, Sirt1). Abnormal epigenetic marks seems to profoundly impact in the expression of both coding genes and microRNAs, since different number of coding genes and microRNAs was re-expressed along melanoma genesis after treatment with the epigenetic drugs (Molognoni et al., 2011). These data strongly suggest a role of aberrant epigenetic marks in the initiation and progression of melanoma.

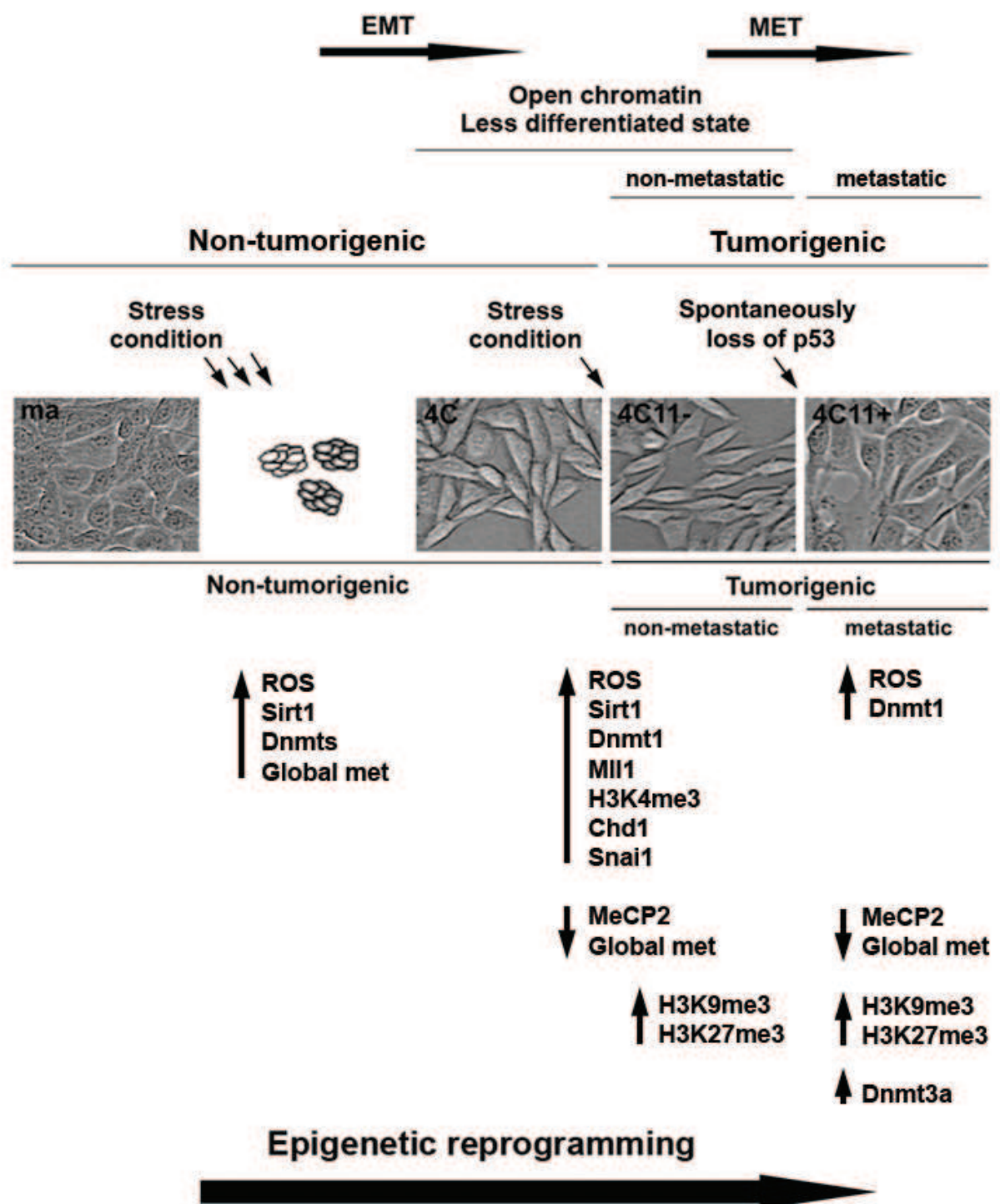


Fig. 2. Epigenetic reprogramming along murine melanocyte malignant transformation associated with sustained stress

The anchorage impediment, the driving force for malignant transformation in our model, was accompanied by global DNA hypermethylation and increased levels of DNA methyltransferases (Dnmts) (Campos et al., 2007) (Figure 2). In addition, elevated production of reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide, and nitric oxide characterized oxidative stress in this condition (Campos et al., 2007; Melo et al., 2011). Reinforcing the association between epigenetic and stress hypothesized by Johnstone

and Baylin (2010) and Hitchler and Domann (2007), inhibiting oxidative stress by scavenging superoxide anion abrogated epigenetic alterations observed during the anchorage blockade (Campos et al., 2007). Moreover, melan-a melanocytes treated with the demethylating agent 5-aza-2'-deoxycytidine (Molognoni et al., 2011) or with the eNOS inhibitor L-NAME (Melo et al., 2011) before each deadhesion cycles do not transform. ROS-activated signaling pathways regulating Dnmts protein levels are still unknown and are under investigation in our laboratory. These data indicate that abnormal epigenetic patterns seems to be one of the initial events in the melanocyte malignant transformation related to microenvironment changes characterized by sustained oxidative stress. Overall, the mechanisms underlying the regulation of epigenetic marks by oxidative stress still need to be elucidated. An instigating study by O'Hagan and coworkers (2008) showed the recruitment of the stress-related protein SIRT1 to double-strand DNA breaks induced in an exogenous promoter construct of the E-cadherin CpG island, which is frequently aberrantly DNA hypermethylated in epithelial cancers. DNA damage caused by oxidative stress induces the dissociation of Sirt1 from repetitive sequences and a functionally diverse set of genes and its re-localization to DNA breaks to promote repair, resulting in transcriptional changes that parallel with those in the aging (Oberdoerffer et al., 2008).

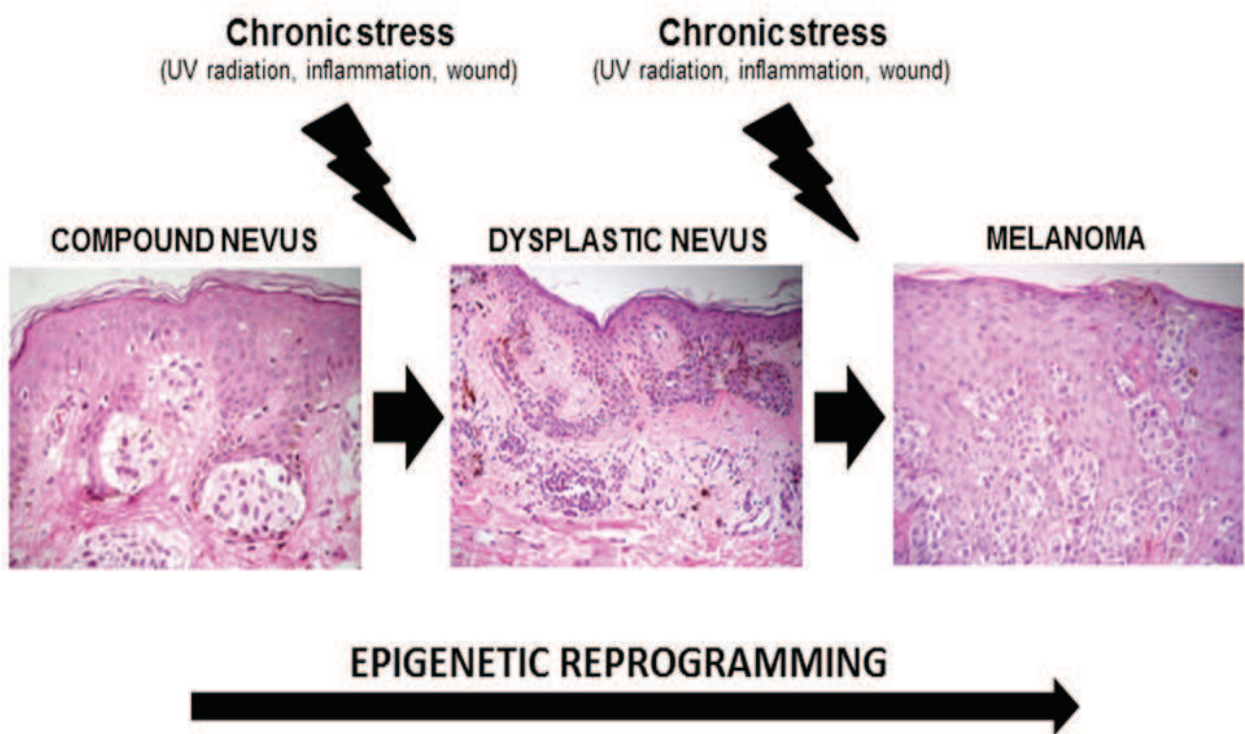


Fig. 3. Epigenetic reprogramming as a key contributor to human melanocyte malignant transformation associated with chronic stress.

O'Hagan and coworkers (2008) showed that, at the damage site, SIRT1 recruited epigenetic machinery components, such as EZH2 and DNMTs. Most cells had their DNA repaired, but a small number of cells presented the exogenous E-cadherin promoter silenced by heritable epigenetic marks. A similar event may be occurring in our malignant transformation model, since double-strand breaks, revealed by increased levels of γ -H2AX, and elevated levels of Sirt1 (unpublished data) were detected during the melanocyte anchorage blockade.

It is important to reinforce that ultraviolet radiation, a known environment factor predisposing to melanoma development (Autier & Dore, 1998; MacKie, 2006), and even inflammation, observed mainly in the early phases of melanoma genesis (Van Kempen et al., 2005), induces ROS generation. In this way, we can hypothesize that increases in ROS levels, caused for example by chronic inflammation, aging and UV radiation, might be responsible for aberrant epigenetic marks as a result of fails in the repair of primary DNA damage. It is easy to suppose that melanoma development associated with sustained exposition to these conditions may be related to oxidative stress and, possibly, to progressive epigenetic alterations (Figure 3).

7. Clinical applications

Melanoma is one of the most aggressive and radio- and chemo-resistant tumor types. In this way, the understanding of epigenetic mechanisms involved with both initiation and progression of melanoma could provide new avenues to identify diagnosis and prognosis markers and also develop novel therapeutic approaches.

7.1 Epigenetic tumor markers

Aberrant DNA methylation marks have some advantages to be used as tumor markers. One of these advantages is that DNA methylation is a stable and heritable mark. Additionally, DNA is less prone to degradation than RNA and can be easily obtained from patients' samples, such as sputum, serum and urine samples (Herman & Baylin, 2003). Highly sensitive techniques for detecting and quantifying DNA methylation are currently available, as methylation-specific polymerase chain reaction (Cottrell & Laird, 2003) and bisulfite treatment followed by DNA sequencing.

Aberrant epigenetic marks can be used to assess clinical outcomes or response to therapies. Both abnormally hypermethylated and hypomethylated genes can be used as tumor markers in clinical application for early detection of disease, tumor progression, metastatic potential and response to therapeutic agents. Different epigenetic biomarkers have been described as presenting clinical relevance in different tumor types, such as gliomas, neuroblastomas, leukemias, prostate, bladder, lung, and colorectal cancer (Taby & Issa, 2010). However, very few data are available concerning both diagnosis/prognosis markers and the predictive value of markers in response to therapy in melanoma (Howell et al., 2009; Schinke et al., 2010). A promising predictive marker of melanoma progression was that reported by Mori and coworkers (2006), in which estrogen receptor A (*ER-A*) methylation was showed as a poor prognostic factor for melanoma patients. Recently, Shinojima and colleagues (2010) identified zygote arrest 1 (*ZAR1*) gene, responsible for oocyte-to-embryo transition, as frequently aberrant methylated in melanoma surgical specimens and melanoma cell lines, but not in normal human epidermal melanocyte cell lines or melanocytic nevi, suggesting *ZAR1* methylation as an early diagnostic marker for malignant melanoma. The methylation of circulating *RASSF1A* DNA showed to be less frequent in responder melanoma patients compared to non-responders to biochemotherapy (Mori et al., 2005).

7.2 Epigenetic therapy

Since epigenetic marks are potentially reversible by pharmacologic drugs, a better understanding of epigenetic alterations in melanoma may be valuable to establish novel therapeutic regimes in the treatment of patients with advanced melanoma. There are two

classes of drugs approved by the US Food and Drug Administration (FDA) for cancer treatment that affect epigenetic marks: demethylating agents and histone deacetylase inhibitors (HDACi). Demethylating agents, as 5-azacytidine (Fenaux et al, 2009) and decitabine (Kantarjian et al., 2007), are nucleoside analogues that induce passive DNA demethylation through irreversible covalent bond with Dnmts (Issa, 2009). These DNA methylation inhibitors have been shown effective in a variety of non-solid tumors, such as acute myeloid leukemia and myelodysplastic syndrome, but the earlier clinical trials using decitabine as the only drug for solid tumors, including melanoma, have been disappointing (Abele et al., 1987; Schwartamman et al., 2000). Apart the unsuccessful results obtained by the treatment of solid tumors with demethylating agents, a promising use of this drugs relies on combined therapies, for examples with immunotherapy and chemotherapy. For melanoma, decitabine treatment seems to potentiate the effect of IL-2 therapy (Gollob et al., 2006) and overcome the resistance to interferon-induced apoptosis (Reu et al., 2006) in humans.

HDAC inhibitors target the catalytic domain of HDACs, blocking their substrate recognition (Xu et al., 2007). Short-chain fatty acids (such as valproic acid and sodium butyrate), hydroxamic acids (such as trichostatin A and vorinostat), benzamides (such as entinostat) and cyclic peptides (such as romidepsin) are different classes of HDACs. Among them, vorinostat and romidepsin were approved by the US FDA for the treatment of lymphoma (Mann et al., 2007). In melanomas and other tumor types, a number of genes involved in growth and survival have been described as up-regulated after HDAC inhibitors (Boyle et al., 2005; Minucci & Pelicci, 2006). Several HDAC inhibitors are under clinical trials in other cancer types, but the results have also indicated low activity in solid tumors (Prince et al., 2009). Experimental data from combined treatment of the SIRT1/2 inhibitor suramin and the xanthine derivative pentoxifylline showed synergistic inhibition of antitumor and antimetastatic activity in murine B16F10 melanoma cells (Dua et al., 2007). Valproic acid was showed to induce dose-dependent growth arrest, apoptosis, and sensitization to cisplatin and ectoposide in M14 human melanoma cells (Valentini et al., 2007).

An important aspect that needs to be considered about the use of epigenetic drugs in clinical practice is that they lack specificity and then may induce the reactivation of normally silenced sequences, such as imprinted genes, repetitive sequences and even pro-metastatic genes. Although this possibility exists, until now no clinical data support these concerns. Drugs selectively targeting specific genes are been investigated and may provide a promising future in the cancer therapy.

8. Conclusions

Since environmental factors, in special UV radiation, are important risk factors contributing to melanoma formation, and epigenetic changes may vary according to environment alterations, it is imposed to suppose the role of aberrant epigenetic marks induced by stress conditions in the genesis of melanoma. Epigenetics has emerged as a promising field in developing novel and efficient drugs against cancer. In this way, efforts should be done in order to determine not only genes which aberrant expression as a consequence of abnormal epigenetic marks, but also clarify the molecular pathways involved in deregulation of epigenetic machinery in response of stress conditions. This knowledge may bring new insights concerning chronic stress, epigenetic alterations and melanoma genesis, and also may provide novel targets to drug development and epigenetic marks with value in diagnosis, prognosis and response to treatment.

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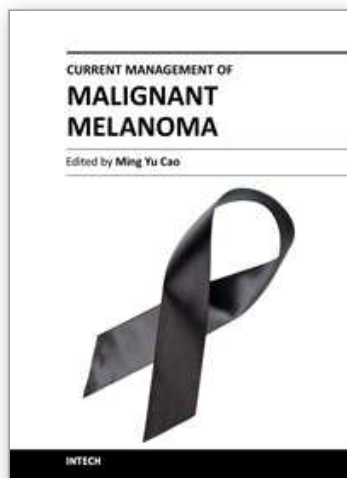
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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