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Epigenetic Changes in Melanoma and the Development of Epigenetic Therapy for Melanoma

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1. Introduction

Melanoma is responsible for 80% of all skin cancer deaths (Miller & Mihm, 2006), and it is the most common cause of cancer deaths between the age of 20 and 35 years old (Houghton & Polsky, 2002). Melanoma is a highly heterogeneous cancer that is caused by the accumulation of genetic and epigenetic defects allowing the cell to escape normal cellular controls. Genetic changes are caused by irreversible alterations in the DNA sequence, including chromosomal amplification or deletions and gene mutations that culminate in aberrant cellular functions, such as activation of oncogenes and inactivation of tumor suppressors. However, recent progress in cancer research has shown that epigenetic events may play a major role in establishing the correct program of gene expression. Epigenetics is defined as heritable changes in gene expression that are not due to any changes in the DNA sequence. Currently, four epigenetic drugs, vorinostat (Marks & Breslow, 2007), romidepsin (Campas-Moya, 2009), azacitidine (Mani & Herceg, 2010; Wijermans et al., 2005), and decitabine (Mani & Herceg, 2010), have been approved for the treatment of hematologic malignancies in the United States by the Food and Drug Administration (U.S. FDA).

In a human cell, there are approximately two meters of diploid DNA that are packaged inside the nucleus with a volume of about 1000 μm^3 (Kamakaka & Biggins, 2005). This packaging of DNA is facilitated by histones. Histones are a group of highly conserved, basic (positively-charged) proteins that are rich in arginine and lysine residues. This DNA-protein complex is called the chromatin. In chromatin, proteins account for more than half of the weight, from which, histone proteins being the most abundant. There are five distinct families of histones, each with numerous variants or individual genes. DNA is packaged into nucleosomes comprising a histone octamer of two copies of each core histones (H2A, H2B, H3, and H4) (Luger et al., 1997). The core histones interact in pairs. Two H3:H4 dimers interact together forming a tetramer, and two H2A:H2B dimers associate with the H3:H4 tetramer to form a nucleosome. About 146 bp of DNA is wrapped around a histone octamer. One molecule of histone H1 associates at the position where the DNA enters and exits the nucleosome core, thus sealing the two turns of DNA (Luger et al., 1997).

These core histones contain a conserved C-terminal histone fold domain and unique N-terminal tails. The histone N-terminal tails protrude from the nucleosome core and provide sites for posttranslational modifications, including acetylation, methylation, phosphorylation, and ubiquitination (Jenuwein & Allis, 2001). These distinct patterns of posttranslational modifications make up the histone code that is read by multiprotein chromatin remodelling complexes to determine the transcriptional status of the target gene (Strahl & Allis, 2000).

2. Histone acetylation and histone deacetylases

Epigenetic phenomena can be viewed as changes in the packaging and modifications of the DNA. In the case of DNA, it is modified only by methylation. Changes in the packaging of DNA include both histone modifications and chromatin remodeling. Histones can be modified by methylation, acetylation, phosphorylation, biotinylation, ubiquitination, sumoylation, and ADP-ribosylation. Lysine residues in the histone tails can be acetylated or methylated. Arginine residues can be methylated (Howell et al., 2009).

Among all of the posttranslational modifications on histone tails, histone acetylation is among the most extensively studied. In normal cells, acetylation and deacetylation exist in equilibrium. Acetylation is a reaction that is catalyzed by histone acetyltransferases (HATs), and the deacetylation reaction is catalyzed by histone deacetylases (HDACs). These two families of enzymes regulate the delicate balance needed for maintaining the states of chromatin and chromatin dynamics (Figure 1).

Acetylation is a reversible reaction occurring on lysine residues within the N-terminal tails of core histones H3 and H4. For histone acetylation, one of the hydrogens in the free amino group of internal lysine is substituted with an acetyl (CH_3CO) group. The addition of an acetyl group removes the positive charge from the NH_3^+ group on lysine, thus neutralizing the basic charge of the histone tails. This modification is suggested to reduce the affinity between histones and DNA, which, in turn, correlates with active gene expression. Acetylated histone is usually associated with transcriptionally active chromatin (Hebbes et al., 1992; Kouzarides, 2007; Turner, 1993). In addition, it is involved in many processes, such as replication, nucleosome assembly, higher-order chromatin packing and interactions of nonhistone proteins (Grant & Berger, 1999). Lysine at amino acid positions 9, 14, 18, and 23 for histone H3 and at amino acid positions 5, 8, 12, 16 for histone H4 are frequent targets for acetylation. These histone modifications facilitate access and binding of transcription factors.

Histone deacetylation is associated with an inactive (closed) state of chromatin and transcriptional repression (Kouzarides, 2007; Strahl & Allis, 2000). Deacetylation is catalyzed by histone deacetylases (HDAC). HDACs catalyze the removal of acetyl groups from lysine residues. HDACs and HATs are either part of a multiprotein transcriptional complex or interact with DNA binding proteins (Haberland et al., 2009; Jenuwein & Allis, 2001). Deregulation in the activity of HDACs and HATs may lead to alterations in gene expression and has been linked to diseases, particularly cancers. Fraga et al (2005) found that the loss of acetylation of histone H4 at K16 and K20 is a common hallmark of human cancer. Recently, Kondo et al. (2008) found, 5% of the genes are silenced by trimethylation of H3K27 independent of DNA methylation.

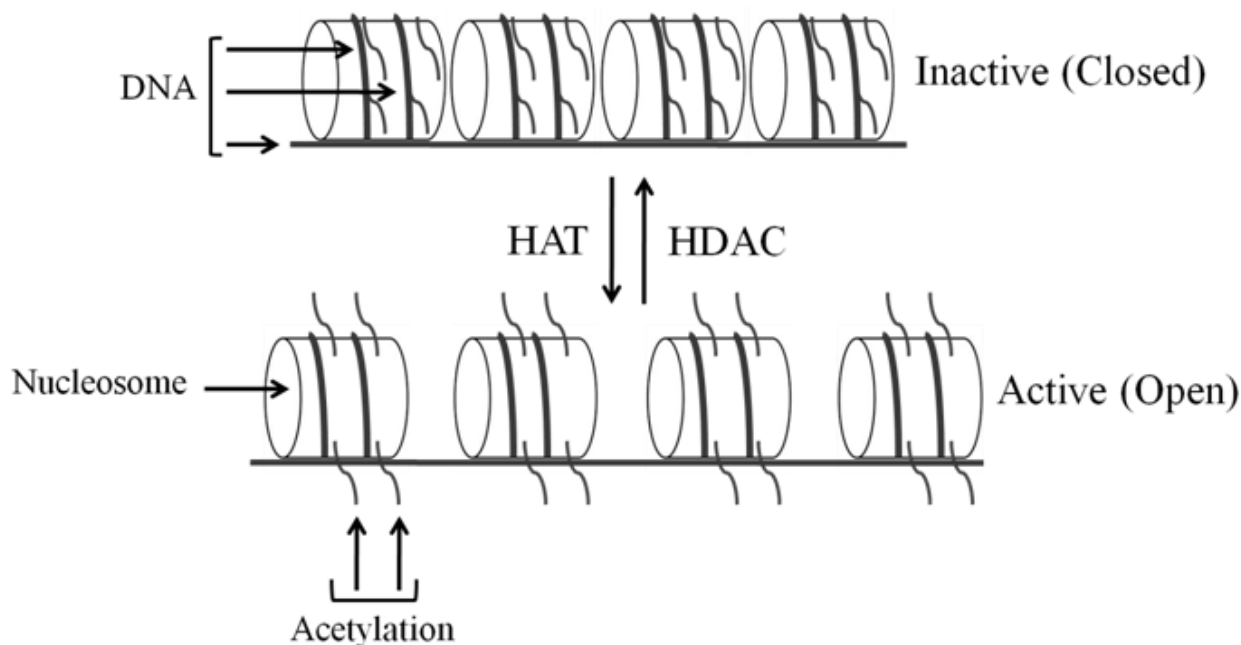


Fig. 1. The states of chromatin and regulation of gene expression. HAT: Histone acetyltransferase; HDAC: Histone deacetylase.

To date, 18 HDACs have been identified in humans. They are divided into four classes based on their homology to yeast HDACs (Table 1). Class I enzymes, which included HDACs 1, 2, 3, and 8, are related to the yeast RPD3 (de Ruijter et al., 2003; Paris et al., 2008). Class I HDACs 1, 2, and 3 are ubiquitously expressed and are almost exclusively found in the nuclei of cells in various cell lines and tissues (de Ruijter et al., 2003; Paris et al., 2008). Unlike HDACs 1-3, HDAC 8 is found only in cells with smooth muscle/myoepithelial differentiation. HDAC8 expression was found in smooth muscle cells where its expression is suggested to play a role in regulating the dynamics of smooth muscle cytoskeleton (Waltregny et al., 2004). These class I HDACs are involved in the regulation of proliferation, apoptosis, cardiac morphogenesis, and interferon (INF) expression through regulating gene expressions (Bernstein et al., 2000; Foglietti et al., 2006; Zupkovitz et al., 2006). Class II proteins, which included HDACs 4, 5, 6, 7, 9, and 10, share domains with the yeast HDAC-1 (de Ruijter et al., 2003; Paris et al., 2008). Class II HDACs can shuttle between the nucleus and the cytoplasm (Paris et al., 2008). Class II HDAC 6 is not seen in lymphocytes, stromal cells, and vascular endothelial cells (Yoshida et al., 2004; Zhang et al., 2004). It is localized mainly in the cytoplasm. This HDAC6 enzyme is also found on the perinuclear and leading-edge subcellular regions of cells. It is a microtubule-associated deacetylase (Hubbert et al., 2002). HDAC 7 inhibits the expression of Nur77, which is involved in the regulation of apoptosis and negative selection during developing thymocytes (Dequiedt et al., 2005). Unlike class I HDACs, class II HDACs are found only in some tissues. The recently described class IV, comprised solely of HDAC 11 enzyme, shares features of classes I and II HDACs, such as the dependence on zinc for their enzymatic activity. Classes I, II and IV are zinc dependent proteases (de Ruijter et al., 2003; Gao et al., 2002; Glozak & Seto, 2007). Class III HDACs (sirtuins) have been identified based on sequence homology with the yeast transcription repressor Sir2. To date, seven different sirtuins have been identified, and all of the enzymes of class III require NAD^+ for their activity. This class of enzymes is localized in the nucleus (de Ruijter et al., 2003; Glozak & Seto, 2007). HDACs can deacetylate non-

histone proteins, such as tumor suppressors (e.g., p53), and signaling molecules (e.g., STAT1 and STAT3) (Minucci & Pelicci, 2006).

HDAC		Example of Biological Functions	Tissue Distribution	Localization	Reference
Class I	HDAC1	essential in cell survival and proliferation	ubiquitous	nucleus	(Bernstein et al., 2000; Paris et al., 2008; Sun & Hampsey, 1999)
	HDAC2				(Foglietti et al., 2006; Paris et al., 2008)
	HDAC3				(Lagger et al., 2002; Paris et al., 2008; Zupkovitz et al., 2006)
	HDAC8				(Montgomery et al., 2007; Paris et al., 2008)
Class IIa	HDAC4	mediator of neuronal death	heart; brain; skeletal muscle	nucleus/ cytoplasm	(Paris et al., 2008; Waltregny et al., 2004; Waltregny et al., 2005)
	HDAC5	cardiac development	heart; brain; skeletal muscle		(Bolger & Yao, 2005; Paris et al., 2008)
	HDAC7	regulation of apoptosis in developing thymocytes	heart; skeletal muscle; pancreas; spleen		(Paris et al., 2008; Vega et al., 2004)
	HDAC9	cardiac development	brain; skeletal muscle		(Bolger & Yao, 2005; Paris et al., 2008)
Class IIb	HDAC6	regulation of tubulin and Hsp90 acetylation	heart; liver; kidney; pancreas	mainly cytoplasm	(Chang et al., 2004; Dequiedt et al., 2003; Paris et al., 2008; Zhang et al., 2002)
	HDAC10	regulation of thioredoxin-interacting protein expression	spleen; liver; kidney		(Lee et al., 2010)
Class V	HDAC11	regulation of immune function	heart; brain; skeletal muscle; kidney	nucleus/ cytoplasm	(Villagra et al., 2009)

Table 1. Histone deacetylases.

2.1 Clinical applications of histone modifications

Given the association between HDAC enzymes and cancers, there is growing interest in using HDAC inhibitors (HDACI) as antitumor agents. Inhibition of HDAC activity should lead to chromatin decondensation and an increase in gene transcription (Figure 1) (Karagiannis & El-Osta, 2006). HDACIs have been shown to have pleiotropic effects, including cell cycle arrest, growth inhibition and chromatin decondensation. They interfere directly with the mitotic spindle checkpoint, differentiation, and apoptosis in cancer cell types (Choi et al., 2007; Marchion & Munster, 2007; Stearns et al., 2007; Xu et al., 2005). Imre et al. (2006) showed that HDACIs reduce the responsiveness of tumor cells to the tumor necrosis factor- α (TNF- α) mediated activation of the nuclear factor-kappa B (NF-kappa B). All HDACIs upregulate p21, an important mediator of growth arrest (Richon et al., 2000). Studies in clinical trials have attempted to use HDACIs in combination therapy with some successes (Johnstone, 2002). This combined strategy has shown promise in some malignancies (Bishton et al., 2007).

To date, more than 18 HDACIs have been tested in clinical trials for cancer therapy (Carew et al., 2008; Paris et al., 2008). In the United States, two histone deacetylase inhibitors, namely vorinostat (Zolinza) and romidepsin (Istodax), have been approved for the treatment of cutaneous T-cell lymphoma. HDACIs are usually classified into various groups based on their structures, including hydroxamic acids, cyclic peptides, short chain fatty acids, and benzamides. Hydroxamic acid derived compounds (trichostatin A, oxamflatin) have been used in clinical trials for treating both hematologic malignancies and solid tumors. These compounds contain an acid moiety that can fit into the catalytic site and bind to the zinc atom, thus inhibiting the HDAC enzyme (Marchion & Munster, 2007; Marks et al., 2000). For cyclic peptide group (depsipeptide, trapoxin), HDACIs are effective in nanomolar range. On the other hand, short chain fatty acid compounds (butyrate, trybutyrin) require relatively high concentrations for their action. A member of this group, valproic acid has been used in antiepileptic treatment. The use of valproic acid as an anti-epileptic underlines the wide functional distribution of HDACs, contributing to problems targeting the cancer treatments using histone deacetylase inhibitors. The benzamide group molecules (MS-275, CI-994) exert their action at micromolar concentrations. Since the enzymatic pocket is highly conserved in nature, most HDACIs do not selectively inhibit individual HDAC enzymes. Rather, HDACIs inhibit several HDAC enzymes simultaneously. They target mainly classes I and II HDACs (Marks & Xu, 2009; Paris et al., 2008). Table 2 shows the histone deacetylase inhibitors.

Histone deacetylase inhibitors have been investigated in clinical trials for melanoma (Table 3). A multicenter, phase II clinical trial was conducted to evaluate the efficacy, safety, and pharmacokinetics of the histone deacetylase inhibitor, pyridylmethyl-N-{4-[(2-aminophenyl)-carbamoyl]-benzyl}-carbamate (MS-275) in 28 patients with pretreated metastatic melanoma. MS-275 is an oral benzamide HDACI. In the study, patients with unresectable American Joint Committee on Cancer (AJCC) stage IV melanoma, refractory to at least one earlier systemic therapy, were randomized to receive MS-275 3 mg bi-weekly or 7 mg weekly on a 28-day cycle. The primary endpoint of the study was objective tumor response, and the secondary study endpoints were safety and time-to-progression. No objective responses were observed in pretreated metastatic melanoma patients. The median time-to-progression was comparable in both arms of the study. MS-275 was well tolerated, with nausea, diarrhea, and hypophosphatemia as the most frequently reported adverse events (Hauschild et al., 2008).

Compound	Chemical Group	[Range]	HDAC Specificity	<i>In Vitro</i> Effect	Reference
Sodium butyrate	Short-chain fatty acid	mM	Class I, IIa	Apoptosis Cell-cycle arrest	(Bhalla, 2005; Bolden et al., 2006; Johnstone, 2002; Schwabe & Lubbert, 2007)
Valproic acid (VPA)	Short-chain fatty acid	mM	Class I, IIa	Apoptosis Differentiation	(Bhalla, 2005; Bolden et al., 2006; Johnstone, 2002; Schwabe & Lubbert, 2007)
Trichostatin A (TSA)	Hydroxamic acid	nM	Class I, IIa	Apoptosis Cell-cycle arrest Differentiation	(Bhalla, 2005; Bolden et al., 2006; Johnstone, 2002; Schwabe & Lubbert, 2007)
Suberoylanilide hydroxamic acid (SAHA) or vorinostat	Hydroxamic acid	μ M	Class I, II	Apoptosis Cell-cycle arrest	(Bhalla, 2005; Bolden et al., 2006; Johnstone, 2002; Schwabe & Lubbert, 2007)
Depsipeptide (FK 228)	Cyclic tetrapeptide	nM	Class I	Apoptosis Cell-cycle arrest	(Bhalla, 2005; Bolden et al., 2006; Johnstone, 2002; Schwabe & Lubbert, 2007)
Apicidin	Cyclic tetrapeptide	nM	HDACs 1 and 3	Apoptosis Cell-cycle arrest	(Bolden et al., 2006; Johnstone, 2002; Schwabe & Lubbert, 2007; Vannini et al., 2004)
MS-275	Benzamide	μ M	Class I	Cell-cycle arrest	(Bolden et al., 2006; Hu et al., 2003; Johnstone, 2002; Schwabe & Lubbert, 2007)

Table 2. Histone deacetylase inhibitors

Due to the low response rates of HDACIs as single-agent therapies, HDACIs have also been investigated in combination with other therapeutic agents (Table 3). In a phase I/II clinical trial for patients with stage IV melanoma, the combination of valproic acid and the topoisomerase I inhibitor karenitecin associated with disease stabilization in 47% of patients. The median overall survival and time-to-progression were 32.8 and 10.2 weeks, respectively. In addition, histone hyperacetylation was observed in peripheral blood mononuclear cells (Daud et al., 2009).

HDACIs have also been investigated in combination with other treatment modalities. A phase I/II study of HDACI valproic acid with standard chemoimmunotherapy in patients with advanced melanoma was conducted to evaluate its clinical activity and to assess toxicity. In the study, patients were treated initially with valproic acid alone for 6 weeks. After the treatment with valproic acid alone, dacarbazine plus interferon- α therapy was started in combination with the valproic acid. However, the results showed that the combination of valproic acid and chemoimmunotherapy did not produce superior results as compared to standard therapy (Rocca et al., 2009).

Epigenetic Agent	Combination	Malignancy	Phase	Reference
Histone Deacetylase Inhibitors (HDACIs)				
Valproic acid	Karenitecin (topoisomerase I inhibitor)	Melanoma	I, II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
Vorinostat (Zolinza)	NPI-0052 (proteasome inhibitor)	Melanoma	I	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
Vorinostat (Zolinza)		Unresectable Metastatic Melanoma (Stage IV)	II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
MS-275		Melanoma	II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
Romidepsin		Nonresectable Intraocular Melanoma or Unresectable Stage III or Stage IV Melanoma	II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
DNA Methyltransferase Inhibitors (DNA Hypomethylating Agents) (DNMTIs)				
5-azacytidine (Vidaza)	Recombinant Interferon α -2b	Melanoma	I	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
5-aza-2-deoxycytidine (Dacogen)	Temozolomide	Melanoma	I, II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
	Pegylated Interferon α -2b	Melanoma	I, II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)
	Panobinostat, Temozolomide	Melanoma	I, II	(Cang et al., 2009; Howell et al., 2009; Sigalotti et al., 2010)

Table 3. Current epigenetic agents used in clinical trials for melanoma patients

3. DNA methylation

DNA methylation is carried out by different DNA methyltransferases (DNMT). DNMT1 involves in the maintenance of established methylation patterns. DNMT3a and DNMT3b are implicated in *de novo* DNA methylation (Bestor, 2000; Okano et al., 1999; Rothhammer & Bosserhoff, 2007). This epigenetic event takes place at the C5 position of cytosine on the CpG dinucleotide rich regions (CpG islands) that are distributed throughout the genome. Proper DNA methylation patterns are essential for human development and normal functioning. In normal cells, CpG islands located in the promoter regions are mainly unmethylated; however, in melanoma cancer cells, aberrant hypermethylation occur. In addition, genome-wide hypomethylation occurs in melanoma cancer cells (Jones & Baylin, 2007). This epigenetic modification results in silencing the transcription of selected tumor suppressor genes (Robertson, 2005; Rothhammer & Bosserhoff, 2007). Aberrant DNA hypermethylation of promoter regions has been shown to result in the silencing of at least 50 genes (Fulda et al., 2001; Gallagher et al., 2005; Mori et al., 2005; Muthusamy et al., 2006; Paz et al., 2003; Rothhammer & Bosserhoff, 2007; Soengas et al., 2001; van der Velden et al., 2003). Table 4 shows some genes affected by promoter DNA hypermethylation in melanoma. For example, *CDKN2A* is a major gene involved in the pathogenesis of melanoma. It is the most frequently mutated gene inherited in familial cutaneous melanoma (Palmieri et al., 2009; Sigalotti et al., 2010). Freedberg et al (2008) showed that aberrant promoter DNA hypermethylation at *CDKN2A* locus independently affects the tumor suppressors p16^{INK4A} and p14^{ARF}, which function in the pRB and p53 pathways, respectively. In human melanoma, p16^{INK4A} and p14^{ARF} are methylated.

Gene	Pathway	Reference
APAF1(apoptotic protease activating factor 1)	Apoptosis	(Soengas et al., 2001)
MT2A (methallothionein 2A)	Apoptosis	(Gallagher et al., 2005)
HSPB1 (heat shock 27 kDa protein)	Apoptosis	(Gallagher et al., 2005)
MAGE-A1(melanoma antigen, family A1)	Immune recognition	(De Smet et al., 1996; Karpf et al., 2004; Sigalotti et al., 2010)
ER- α (estrogen receptor alpha)	Signaling	(Mori et al., 2006)
WFDC1 (wap 4-disulfide core domain 1)	Proliferation	(Muthusamy et al., 2006)
CDKN1B (cyclin-dependent kinase inhibitor 1B)	Cell cycle	(Worm et al., 2000)
CDKN1C (cyclin-dependent kinase inhibitor 1C)	Cell cycle	(Shen et al., 2007)
APC (adenomatous polyposis coli gene)	Cell fate determination	(Worm et al., 2004)
GDF15 (growth/ differentiation factor 15)	Differentiation	(Muthusamy et al., 2006)
TPM1 (tropomyosin 1)	Anchorage-independent growth	(Liu et al., 2008)
MIB2 (skeletrophin)	Cell fate determination	(Takeuchi et al., 2006)
MGMT (O ⁶ -methylguanine-DNA-methyltransferase)	DNA repair	(Hoon et al., 2004)
CDH1 (E-cadherin)	Invasion/metastasis	(Liu et al., 2008)
CDH8 (cadherin 8)	Invasion/metastasis	(Muthusamy et al., 2006)

Table 4. Genes with an altered DNA methylation status in melanoma

3.1 Clinical applications of DNA methylation

DNA methylation is a reversible epigenetic event and can be nullified by specific DNA demethylating agents (DNA methyltransferase inhibitors). Several ongoing clinical trials are conducted to investigate their clinical effectiveness and safety in melanoma patients (Table 3). In these studies, DNA demethylating agents 5-azacytidine (Vidaza) and 5-aza-2-deoxycytidine (decitabine, Dacogen) are the most intensively studied. Azacytidine is a pyrimidine nucleoside analog of cytidine, and decitabine is a cytosine nucleoside (cytidine) analog. These epigenetic agents were approved by the FDA for the treatment of myelodysplastic syndromes and acute myeloid leukemia. Agents that inhibit DNA methyltransferases can reactivate silenced genes and induce apoptosis of cancerous cells (Howell et al., 2009). Since epigenetic modifications affect cellular pathways, epigenetic agents also display pleiotropic activities (Howell et al., 2009). In a phase I trial, Gollob et al. (2006) found that a low dose of 5-aza-2'-deoxycytidine (decitabine) can be safely administered with high-dose interleukin to cancer patients and has antitumor activity in melanoma. The inclusion of decitabine resulted in DNA hypomethylation. In addition, Appleton et al. (2007) showed that decitabine reduces DNA methylation and can be combined safely with carboplatin for the treatment of melanoma.

In addition to therapeutic applications, modifications of DNA methylation may serve as biomarkers in clinical use for melanoma (Howell et al., 2009). Mori et al. (2006) showed that methylated ER- α can be detected in paraffin-embedded primary and metastatic melanoma tumors. In addition, methylated ER- α DNA was detected in the serum of melanoma patients with AJCC stage I to IV disease. Methylated ER- α was detected in 42% of stage III and 86% of stage IV metastatic melanomas. Serum methylated ER- α is an unfavorable prognostic factor. Liu et al (2008) found that SOCS1, SOCS2, RAR β 2, DcR1, and DcR2 genes were the most frequently methylated genes in melanoma. The investigators also found that RECK, IRF7, PAWR, DR5, and Rb were not methylated in melanoma although these genes were found to be highly methylated in other cancers (Howell et al., 2009; Liu et al., 2008), suggesting that different cancers have distinct methylated genes. This is important since biomarkers must be specific and be able to differentiate between different forms of malignancies.

4. Conclusions and future perspectives

Melanoma is a complex disease that is caused by aberrant genetic and epigenetic events. Epigenetic modifications play a significant role in the biology of melanoma, and epigenetic therapy emerges as a promising treatment modality for melanoma as well as for diagnostic developments for the malignancy. A major difference between the two events is that epigenetic changes can be reversed by chemical and/or environmental modalities. Histone modifications and DNA methylation are extensively studied epigenetic events that affect the expression of genes. Currently, four epigenetic agents have been approved by the U.S. FDA for hematologic malignancies and many HDACIs and DNMTIs are being investigated in clinical trials for solid tumors, such as melanoma. However, there have not been any FDA-approved epigenetic agents for solid tumors. Consequently, further investigations are required to find successful treatment strategies or protocols involving epigenetic agents. Future developments would address the issues of systemic toxicities, nonspecific epigenetic effect, and low bioavailability. In addition, a promising strategy is combination therapy. In tumors, DNA methylation and histone acetylation can act synergistically to silence tumor

suppressor genes. This approach could potentially enhance the reversal of epigenetic silencing. Although in its infancy, epigenetic therapy has been shown to be an effective treatment modality for cancers, as evident by the approval of 4 epigenetic drugs by the U.S. FDA. Encouraging results from preclinical and clinical trials prompts further investigations into designing new drugs or strategy that are more suitable for epigenetic therapies for melanoma patients, with the goal of improving patient outcomes.

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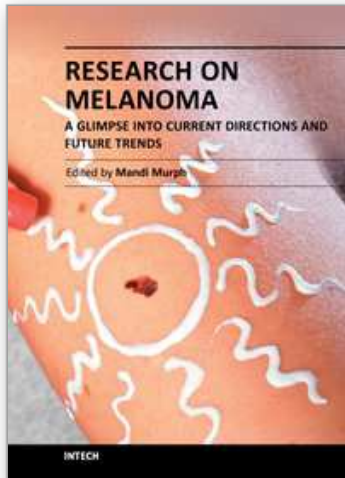
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Research on Melanoma - A Glimpse into Current Directions and Future Trends

Edited by Prof. Mandi Murph

ISBN 978-953-307-293-7

Hard cover, 414 pages

Publisher InTech

Published online 12, September, 2011

Published in print edition September, 2011

The book *Research on Melanoma: A Glimpse into Current Directions and Future Trends*, is divided into sections to represent the most cutting-edge topics in melanoma from around the world. The emerging epigenetics of disease, novel therapeutics under development and the molecular signaling aberrations are explained in detail. Since there are a number of areas in which unknowns exist surrounding the complex development of melanoma and its response to therapy, this book illuminates and comprehensively discusses such aspects. It is relevant for teaching the novice researcher who wants to initiate projects in melanoma and the more senior researcher seeking to polish their existing knowledge in this area. Many chapters include visuals and illustrations designed to easily guide the reader through the ideas presented.

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Duc P. Do and Syed A.A. Rizvi (2011). Epigenetic Changes in Melanoma and the Development of Epigenetic Therapy for Melanoma, *Research on Melanoma - A Glimpse into Current Directions and Future Trends*, Prof. Mandi Murph (Ed.), ISBN: 978-953-307-293-7, InTech, Available from:

<http://www.intechopen.com/books/research-on-melanoma-a-glimpse-into-current-directions-and-future-trends/epigenetic-changes-in-melanoma-and-the-development-of-epigenetic-therapy-for-melanoma>

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