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Melanoma Cell Signalling: Looking Beyond RAS-RAF-MEK

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1. Introduction

Melanoma is an invasive and malignant form of skin cancer (Besaratinia and Pfeifer, 2008). It originates from melanocytes, which reside in the epidermal layer of the skin. Besides the skin, melanoma's rapidly proliferative and aggressive nature leads to its manifestation in internal organs such as brain, lung and liver (Franco-Lie et al., 2011; Lejeune et al., 1992). Ultraviolet (UV) radiation (sunlight or tanning beds) is the main carcinogen involved in melanoma development. However, the type (UVA versus UVB) and duration of UV radiation (intermittent versus chronic and childhood sun exposure) necessary for melanoma initiation remains ambiguous (Algazi et al., 2010; Besaratinia and Pfeifer, 2008; Lazovich et al., 2010; Walker, 2008). In addition, the presence of melanocytic nevi and hereditary genetic mutations predisposes individuals to melanoma (Navarini et al., 2010; Pho and Leachman, 2010; Whiteman et al., 2003). As a result of these factors, it is estimated that 132,000 melanoma skin cancers occur annually (World Health Organization [WHO], 2011). This value is set to rise by 4,500 incidences for every 10% decrease in the UV-protective ozone levels (WHO, 2011).

Prevention strategies designed to curtail the onset of melanoma and improved treatment for this evolving anomaly require urgent action. Current treatments and adjuvant therapies for melanoma includes, surgical excision, radio-, chemo- and immunotherapy (Dummer et al., 2010; Petrescu et al., 2010). However, with the recurrence of these melanomas, the spotlight is on molecular targeted therapy. Such therapies require an in depth knowledge of melanoma signalling to treat this cancer. Molecular targeted therapy has focused predominantly on the RAS-RAF-MEK [mitogen activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) kinase] and phosphoinositide-3-kinase (PI3K)/AKT pathways (Algazi et al., 2010; Friedlander and Hodi, 2010; Held et al., 2011; Sullivan and Atkins, 2010). However, due to the complex network of signalling pathways, it has become evident that targeting single pathways to eradicate melanoma is insufficient (Table 1) (Jiang et al., 2011; Johannessen et al., 2010; Nazarian et al., 2010; Shields et al., 2007). Shields *et al.* (2007) found a distinct subset of melanoma cell lines that did not exhibit high ERK and AKT activation but had increased expression of epithelial markers like P-cadherin, E-cadherin and CD24. These epithelial-like melanoma also had a loss of p53 function, decreased microphthalmia-associated transcription factor (MITF) levels and its targeted gene expression. Recent studies have also shown that many subsets of melanoma cells exhibit resistance to B-RAF inhibitors (Jiang et al., 2011; Nazarian et al., 2010).

Alternative signalling pathways/molecules	Resistant to:	Reference
P-cadherin/E-cadherin/CD24 melanoma subgroup	ERK/AKT inhibition	(Shields et al., 2007)
C-RAF/MEK/ERK signalling	B-RAF inhibition	(Nazarian et al., 2010)
Impaired FOXO3a nuclear localisation result in reduced Bim expression	MEK1/2 inhibition	(Yang et al., 2010)
P13K/AKT signalling	B-RAF inhibition	(Jiang et al., 2011)
Amplified wild-type KIT/CDK4 signalling	B-RAF inhibition	(Smalley et al., 2008)
Platelet-derived growth factor receptor β (PDGFRβ) signalling	B-RAF inhibition	(Nazarian et al., 2010)
COT/MEK/ERK signalling	B-RAF inhibition	(Johannessen et al., 2010)
Melanoma subgroups with constitutive B-RAF and MEK activity	N-RAS inhibition	(Inamdar et al., 2010)

Table 1. Signalling pathways/molecules rendering melanoma resistance.

Melanoma resistance to chemotherapy can and has been attributed to changes in cell signalling events (Grossman and Altieri, 2001). Photodynamic therapy (PDT) and cytotoxic agents were found to enhance survivin (member of the inhibitor of apoptotic protein family) expression which desensitised these cells to apoptosis (Ferrario et al., 2007; Qiu et al., 2005). Other anti-apoptotic factors (e.g. Bcl-2, and Bcl-X_L) are also found to be highly expressed in melanoma resulting in a chemo-resistant phenotype (Grossman and Altieri, 2001; Rass and Hassel, 2009). Multi-drug resistance transporters and DNA repair mechanisms that prevent cytotoxicity induced by alkylating agents have also been implicated in chemo-resistance (Grossman and Altieri, 2001; Rass and Hassel, 2009). As such, it is imperative to address possibilities of other mutations and compensatory/alternative signalling pathways involved in melanoma development and persistence. Therefore, this review presents an overview of melanoma cell signal transduction and highlights the recent advances made in this field as well as identifying molecular targets with therapeutic potential.

2. Melanoma signalling and therapeutical targets

2.1 Common therapeutical targets

Common oncogenic mutations in melanoma have been selected for targeted therapy. Inhibitors to these mutant proteins or their downstream effectors are currently undergoing clinical evaluation. However, it has been reported that melanoma cells are able to acquire resistance to some of these drugs (Jiang et al., 2011; Nazarian et al., 2010; Paraiso et al., 2011).

2.1.1 KIT

KIT, a receptor tyrosine kinase (RTK), is involved in normal melanocyte signalling (Easty et al., 2011). It is necessary for the migration of melanocytic precursors from the neural crest and regulates the survival, development and homeostasis of melanocytes (Hou et al., 2000; Wehrle-Haller, 2003). KIT undergoes genetic alterations in chronically sun damaged, acral and mucosal melanoma subgroups (Curtin et al., 2006; Friedlander and Hodi, 2010). Some melanomas also possess amplified wild type (WT) KIT due to high copy number (Curtin et al., 2006). Its increased expression has also been observed in melanoma cells without

aberrant gene amplification (Curtin et al., 2006). A gain-of-function mutation or increased kinase activity of KIT causes constitutive activity of the MAPK and PI3K pathways which may lead to a hyper-proliferative and invasive melanoma subgroup (Woodman and Davies, 2010). Therefore, it has been postulated that targeting the KIT receptor may reduce the incidence of melanoma.

Imatinib (RTK inhibitor) prevents autophosphorylation of KIT which leads to the inactivation of MAPK, JAK-STAT, PI3K/AKT and anti-apoptotic pathways (Heinrich et al., 2000; Jiang et al., 2008). Imatinib was shown to reduce proliferation in KIT mutant mucosal melanoma cell cultures (Jiang et al., 2008). Although, this inhibitor was ineffective in unamplified WT KIT melanoma, it is unclear if it can eradicate those tumours which overexpress this receptor. Smalley *et al.* (2008) found that imatinib treatment was only effective in those melanomas which had elevated levels of phosphorylated (phospho) KIT. This suggests that irrespective of its overexpression, the efficacy of imatinib in treating melanoma requires the presence of active KIT. This inhibitor has specificity towards certain KIT mutation. While it is effective against mutant KIT in the juxtamembrane domain, it is ineffective against mutations occurring in the kinase domain of these receptors. In support, V559A (juxtamembrane domain) mutated KIT in a metastatic lung melanoma patient responded to imatinib therapy (Terheyden et al., 2010). However, imatinib had no effect in D820Y (kinase domain) mutated KIT in SM3 melanoma cells but another RTK inhibitor, sunitinib, inhibited the proliferation of these cells (Ashida et al., 2009).

Some tumours have evolved imatinib resistance by creating secondary genetic mutations in KIT but their occurrence in melanoma is unknown (Lim et al., 2008). A genetic comparison between imatinib-naïve and resistant melanoma cells will be useful to identify secondary mutations generated in resistant cell lines. Mutations can occur in the extracellular, juxtamembane and kinase domains of the KIT receptor (Woodman and Davies, 2010). Double KIT mutations have been reported in those melanomas which marginally responded to imatinib treatment (Curtin et al., 2005; McDonnell et al., 2011; Torres-Cabala et al., 2009). Three indolinone compounds were found to inhibit proliferation, and induce cell cycle arrest and apoptosis in mast cells harbouring KIT juxtamembrane and kinase domain mutations (Liao et al., 2002). Other RTK inhibitors, like nilotinib and dasatinib are effective against certain multi-exon KIT mutations except for those occurring at exon 14 (T670I) (Garrido and Bastian, 2010; Schittenhelm et al., 2006). Collectively, little is known about the effectiveness of different inhibitors on patients with specific KIT mutations. Since these inhibitors do not target all mutants, a matrix of various inhibitors and their efficacy against different KIT aberrations will aid in patient selection. The weight of evidence also suggests that patient selection for KIT inhibition therapy should not solely rely on the overexpression and mutational status of this receptor (Hofmann et al., 2009; Smalley et al., 2008). It is also necessary to identify constitutive KIT activation (phosphorylated form) and their involvement in melanoma progression before administration of RTK inhibitor therapy. This information is necessary, before an evaluation of KIT as a viable therapeutic target in melanoma patients is possible.

2.1.2 N-RAS

N-RAS, a GTPase of the RAS family activates RAF proteins in the MAPK signalling cascade and is involved in regulating cellular homeostasis and stress response (Held et al., 2011; Whitwam et al., 2007). Of the RAS isoforms (K-RAS and H-RAS), N-RAS is frequently mutated at codon 61 in 15-20% of melanomas (Held et al., 2011; Karnoub and Weinberg, 2008; Platz et al., 2008; Whitwam et al., 2007). N-RAS mutations increased as the cancer progressed from

radial to vertical growth phase suggesting that these mutations are involved in both melanoma development and progression (Demunter et al., 2001; Omholt et al., 2003; Rosso et al., 2009). The mutant N-RAS exists in a GTP-bound conformation due to its defective GTPase activity which prevents the hydrolysis of GTP to GDP (Karnoub and Weinberg, 2008). This constitutive activity induces persistent activation of the MAPK and PI3K pathways resulting in melanoma cell survival and proliferation (Jiang et al., 2011; Sullivan and Atkins, 2010). Eskandarpour *et al.* (2009) found that mutant N-RAS is also necessary for the invasive and migratory phenotypes of melanoma cells. Also the overexpression of RAS has been implicated in melanoma chemoresistance to cytotoxic agents (Fujita et al., 1999).

RAS undergoes post-translational modifications to facilitate its association to the plasma membrane which is necessary for its bioactivity (Nammi and Lodagala, 2000; Sebti and Hamilton, 1997). A crucial modification is the farnesylation at its carboxy-terminus catalysed by farnesyl tranferase (Nammi and Lodagala, 2000; Reiss et al., 1990; Sebti and Hamilton, 1997). N-RAS is deactivated by farnesyl transferase inhibitors (FTI) which reduce its oncogenic potential making it a viable target for melanoma therapy (Johnston, 2001; Smalley and Eisen, 2003). However, early studies found that BZA-5B (FTI) increased resistance to cisplatin (cytotoxic drug) treatment in 224 melanoma cells (Fokstuen et al., 1997). In contrast, Niessner *et al.* (2011) found that SCH66336 (Lonafarnib; FTI) together with sorafenib showed efficacy in inducing growth inhibition and apoptosis of melanoma cells through mammalian target of rapamycin (mTOR) signalling however, no changes to the upstream effector, AKT was observed. They found that the FTI did not affect RAS activity but inhibited another GTPase, RHEB, which affected the mTOR signalling pathway.

Smalley *et al.* (2003) found that SCH66336 increased melanoma chemosensitivity to cisplatin-mediated cytotoxicity through G2/M-phase cell cycle arrest. Interestingly, this was not coordinated by typical RAS-driven ERK or P13K pathways. SCH66336 alone caused G1-phase cell cycle arrest and retinoblastoma inactivation in human (Colo 853) and mouse (B16) melanoma cells resulting in low proliferation and high apoptosis levels (Smalley and Eisen, 2003). In this study, RAS activity post-FTI treatment was not observed. Therefore, it is not clear if SCH66336-induced cytotoxicity is a result of RAS inactivity or the inhibition of other farnesylated proteins. It has also been reported that the RAS mutational status did not correlate with their sensitivity to FTI which suggests that other signalling molecules are affected by these inhibitors (Niessner et al., 2011; Sebti and Hamilton, 1997; Sepp-Lorenzino et al., 1995). Although, FTI are beneficial in joint therapies to overcome drug resistance, its non-specificity to N-RAS needs to be addressed (Flaherty, 2006; Held et al., 2011; McCubrey et al., 2009). Furthermore, FTI may also be ineffective if RAS downstream targets acquire oncogenic mutations.

2.1.3 B-RAF

B-RAF is a serine threonine kinase and together with C-RAF and A-RAF belong to the RAF kinase family. In the MAPK cascade, B-RAF phosphorylates MEK which results in the activation of the ERK pathway. B-RAF mutations are prevalent in 50-60% of melanomas with the most common mutation occurring at the 600th amino acid (valine to glutamate) (Held et al., 2011; Inamdar et al., 2010). It predominantly occurs in cutaneous melanomas at sites damaged by intermittent UV exposure (Bauer et al., 2011; Puzanov and Flaherty, 2010). Mutant B-RAF is constitutively active and independent of RAS activation (Inamdar et al., 2010). Persistent B-RAF activation leads to ERK-induced melanoma survival, proliferation, angiogenesis and invasion (Inamdar et al., 2010). Therefore, the B-RAF protein has become a promising candidate for molecular targeted therapy.

The general inhibitor, Sorafenib binds to the inactive forms of B-RAF and thus, is more effective in blocking WT B-RAF then constitutively active mutant B-RAF (McCubrey et al., 2009). In contrast, PLX4720 binds to both the inactive and active forms while SB590885 only associates with active B-RAF (McCubrey et al., 2009). PLX 4720 specifically inhibits B-RAF (V600E) mutant in melanoma cells and enhances Bim_s (pro-apoptotic protein) levels to induce apoptosis (Jiang et al., 2010). Another mutant B-RAF specific inhibitor, PLX4032 sensitised melanoma cells to ionizing radiation which induced cell cycle arrest, inhibited colony formation and invasion (Sambade et al., 2011). Although, RAF inhibitors seem promising in combating melanoma growth, this therapy has met with 'roadblocks' due to the emergence of alternative signalling pathways in these cells. PLX4032 reduced tumours in melanoma patients but drug resistance occurred after the initial anti-tumour response (Nazarian et al., 2010). This was due to reactivation of C-RAF/MEK/ERK by N-RAS mutations and upregulation of the PDGFRβ-dependent survival pathways. Jiang *et al.* (2011) found that melanoma cells resistant to PLX4720 maintained high ERK levels but low MEK activity. MEK inhibition itself was shown to be ineffective in overcoming PLX4720 resistance but serum starvation, PI3K/AKT and ERK inactivation reduced melanoma cell viability. Another route of resistance evident in melanoma patients relapsing from RAF or MEK inhibition therapy was that of COT-mediated ERK activation which was independent of RAS/RAF signalling (Johannessen et al., 2010).

ATP-competitive RAF inhibitors were found to inhibit ERK activation in B-RAF mutant cells but increased the proliferation of cells in RAS/RAF WT tumours (Hatzivassiliou et al., 2010). This could be due to the induction of WT B-RAF/C-RAF homo- or heterodimers after inhibitor treatment which allows signalling to continue via the uninhibited subunit of the dimer (Hatzivassiliou et al., 2010; Poulikakos et al., 2010). It is suggested that by increasing RAF inhibitor concentrations, both subunits of the dimer can be inactivated negating downstream signalling (Poulikakos et al., 2010). In addition, protein kinase D3 blockade in conjunction with RAF or MEK inhibition can prevent the reactivation of the MAPK pathway and thereby decrease the survival of resistant melanoma cell lines (Chen et al., 2011). On the whole, further research is needed to determine other modes of overcoming RAF inhibitor resistance. This also highlights the necessity to target downstream effectors of B-RAF/N-RAS and other compensatory survival pathways in melanoma.

2.1.4 Phosphoinositide-3-kinase/AKT

The PI3K/AKT pathway is activated by N-RAS and/or RTK which directs cell growth, proliferation, differentiation and survival (Held et al., 2011; Sullivan and Atkins, 2010). There are three classes of P13K and this dictates their substrate specificity (Aziz et al., 2009). P13K has several downstream targets such as AKT, mTOR, FOXO and nuclear factor-κB (NFκB) (Held et al., 2011). Phosphatase and tensin homolog (PTEN) dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PIP_3) thus preventing AKT activation and blocking PI3K signalling. As a result of mutant N-RAS, PTEN depletion/inactivation and/or constitutive activation of receptors, the PI3K pathway is permanently activated leading to malignant transformation of melanocytes (Held et al., 2011). Constitutive PI3K activity was associated with radiation resistant melanoma cells as treatment with LY294002 (PI3K inhibitor) sensitised melanoma cells to radiation and apoptosis (Krasilnikov et al., 1999). PI3K-dependent matrix metalloproteinase expression has also been implicated in vasculogenic mimicry in highly aggressive melanomas (Hess et al., 2003).

In melanoma therapy, besides PI3K, AKT and mTOR are also potential targets because of their involvement in tumorigenesis (Ko and Fisher, 2011; Sullivan and Atkins, 2010).

Govindarajan *et al.* (2007) showed that AKT overexpressing WM35 melanoma cells had high levels of vascular endothelial growth factor (VEGF; pro-angiogenic) and reactive oxygen species (ROS) *in vitro* and when implanted into nude mice, generated highly invasive and angiogenic tumours *in vivo*. Although, AKT overexpression and mutations have been reported, it is the activity of phospho-AKT that drives melanoma development (Stahl et al., 2004; Sullivan and Atkins, 2010). Approximately, 43-60% of those melanomas examined, had deregulated AKT signalling (Stahl et al., 2004). In a phase two study, using everolimus (mTOR inhibitor) and bevacizumab (angiogenic inhibitor), 53% of the melanoma patients had reduced tumour measurements, 12% of which were significant (Hainsworth et al., 2010). However, it was found that the RAD001 (mTOR inhibitor) induced a PI3K-dependent feedback loop activating the ERK pathway in some human cancers (Carracedo et al., 2008). Therefore, it is critical that the dual inhibition of the MAPK and PI3K pathways be used in treating these melanomas.

PI-103, a dual PI3K/mTOR inhibitor promoted *in vivo* tumour growth via inhibiting apoptosis and immunosurveillance in FVB/N WT mice transplanted with 37-31E-F3 melanoma cells (Lopez-Fauqued et al., 2010). In these mice, the combination of sorafenib (B-RAF inhibitor) and PI-103 increased the tumour volume compared to that seen for sorafenib alone (Lopez-Fauqued et al., 2010). Unlike the immunocompetent FVB/N WT mice, PI-103 was effective in reducing tumour growth in immunocompromised BALB/c nude mice. This data suggests that the immune status of the mouse models can also affect efficacy of PI-103 treatment. Although, the outcomes of this study could be specific to the type of melanoma cells, mouse models and PI3K inhibitor that were used, there is the possibility of risks associated with treating patients with different immune profiles or melanoma patients under immunotherapy in combination with signal transduction inhibition [for more information see Shada *et al.* (2010)]. Some of these PI3K/AKT/mTOR inhibitors are still undergoing clinical trials (Ko and Fisher, 2011; Sullivan and Atkins, 2010).

2.2 New therapeutical targets

In this section, potential signalling molecules and lesser known therapeutical targets undergoing clinical trials are discussed (Figure 1). The inhibition of these targets may help overcome drug resistance in melanoma (Hatzivassiliou et al., 2010; Jiang et al., 2011; Nazarian et al., 2010; Paraiso et al., 2011).

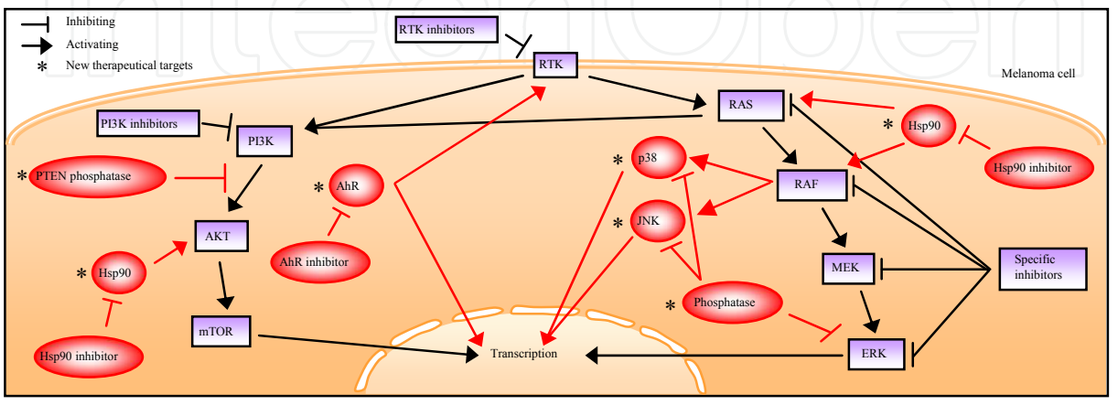

Fig. 1. A schematic diagram depicting common and new therapeutical targets in melanoma.

2.2.1 Aryl hydrocarbon receptor

Aryl hydrocarbon receptors (AhR) are cytosolic transcription factors which are triggered in response to environmental toxicants (e.g. dioxins and polychlorinated biphenyls) (Schmidt and Bradfield, 1996). After ligand binding, the AhR complex translocates into the nucleus where it dimerises with the AhR nuclear translocator while its co-factors [e.g. heat shock protein 90 (Hsp90)] dissociate to initiate transcription of target genes. It can also be activated independent of ligand binding but the mode of action is not clear (Schmidt and Bradfield, 1996). In the skin, UV radiation produces 6-formylindolo[3,2-*b*]carbazole (FICZ), an AhR ligand derived from tryptophan which can stimulate this pathway in response to stress (Fritsche et al., 2007). Fritsche *et al.* (2007) found that AhR-knockdown HaCaT keratinocytes do not possess phosoho-ERK1/2 activity due to inhibition of EGFR internalisation, which suggested that AhR is also involved in EGFR activation in these cells. It is unclear if the same occurs in melanocytes but the high levels of phospho-ERK in melanoma cells suggest a role for Ah receptors.

Environmental toxins can initiate melanogenesis by triggering the AhR signalling pathway in melanocytes (Jux et al., 2011; Luecke et al., 2010). Luecke *et al.* (2010) showed that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), activated the AhR signalling pathway and induced tyrosinase activity, which correlated with an increase in melanin content in melanocytes. They also found that UVB radiation induced AhR-dependent pigmentation albeit weaker than that stimulated by TCDD. Since AhR-deficient mice displayed pigmented skin and fur, this transcription factor was not necessary for constitutive melanogenesis but is involved in eliciting responses initiated by exogenous stimuli (Luecke et al., 2010). In accordance, Jux *et al.* (2011) found that AhR expressed in normal murine melanocytes were involved in both cell proliferation and UV-induced skin pigmentation. Moreover, AhR-deficient melanocytes expressed low levels of c-KIT (overexpressed in some melanoma tumours) than WT melanocytes. On the whole, there is evidence to suggest that melanocytes express functional AhR which can be activated by UV radiation (Jux et al., 2011; Luecke et al., 2010).

Melanoma cells express AhR mRNA which corresponds to its intracellular protein content (Villano et al., 2006). Interestingly, these levels corresponded to increasing invasiveness of melanoma cells but were lower than that seen in melanocytes. In the highly invasive A2058 melanoma cells, the expression of AhR target genes, CYP1A1 and CYP1B1 was increased by TCDD which is a known stimulator of this signalling pathway (Villano et al., 2006). The use of AhR antagonist abrogated CYP1 expression in A2058 cells which suggests that this signalling pathway is functional in these tumour cells. Furthermore, TCDD-dependent increase in matrix metalloproteinase expression was found to aid in the metastasis of A2058 melanoma cells (Villano et al., 2006). In addition, Roman *et al.* (2009) found that both tumour volume and vasculature were decreased when B16F10 melanoma cells were transplanted onto $AhR^{-/-}$ mice, compared to $AhR^{+/+}$ mice. This decrease in angiogenesis was mediated by the downregulation of hypoxia-inducible factor-1α (HIF-1α)-dependent VEGF expression. As UV radiation can activate the AhR pathway in melanoma, it is conceivable that hyperactivation of this pathway can direct angiogenesis and metastasis of these cells (Jux et al., 2011; Kramer et al., 2005; Villano et al., 2006). Currently, further investigation is required to further our understanding of the AhR signalling pathway in melanoma.

2.2.2 Heat shock protein 90

B-RAF, N-RAS, C-RAF and p53 are some of the client proteins of Hsp90 (Heath et al., 2011; Mehta et al., 2011). Hsp90 is involved in maintaining the conformation, stability and cellular

localisation of its client proteins (Powers and Workman, 2006). It also acts as a molecular chaperone for proteins involved in invasion/metastasis, angiogenesis and survival (Powers and Workman, 2006). Conjunctival melanoma tissues expressed higher levels of Hsp90 than did nevi (Westekemper et al., 2011). More importantly, those tumours which recurred locally had increased Hsp90 levels compared to recurrence-free conjunctival melanoma tumours. This suggests that Hsp90 plays a role in the metastatic progression of melanoma. Hsp90 inhibition correlated with modulations to the phospholipid metabolism and growth arrest induced by 17-AAG (Hsp90 inhibitor) in SKMEL28 and CHL-1 melanoma cells (Beloueche-Babari et al., 2010). In hypoxic melanoma tumours, Hsp90 was implicated in Bcl-2-dependent stabilisation of HIF-1α, which was found to regulate VEGF and promote tumour angiogenesis. Thus, the inhibition of Hsp90 will destabilise HIF-1α and may reduce the vascularisation of melanoma tumours. Since Hsp90 interacts with several oncognenic proteins involved in melanoma, disrupting their interaction may reduce the stability of these pro-tumour proteins (Powers and Workman, 2006).

In melanoma and breast cancer cells, survivin induced PDT resistance (Ferrario et al., 2007). PDT increased survivin expression and phosphorylation both *in vitro* (BA mouse breast cancer cells) and *in vivo* (C3H mice transplanted with BA cells). Treatment with 17-AAG and PDT reduced both phospho-survivin and –AKT levels. Additionally, there was an increase in poly (ADP-ribose) polymerase cleavage and Bcl-2 protein degradation which resulted in BT-474 (human breast cancer) cell death post-17-AAG/PD therapy. Likewise, in YUSAC2/T34A-C4 melanoma cells, forced expression of phospho-survivin led to reduced apoptosis after PDT treatment, while the reverse occurred when dominant-negative survivin was expressed. Qiu *et al.* (2005) also found that survivin desensitised melanoma cells to betulinic acid-induced cytotoxicity. Betulinic acid caused an increase in EGFR activation, phospho-ERK, phospho-AKT and survivin levels in melanoma cells. The blockade of EGFR caused a decrease in both AKT and survivin expression which resulted in cell death. Therefore, high ERK/AKT activity in combination with increased survivin levels lead to melanoma cell survival (Ferrario et al., 2007; Qiu et al., 2005). Since, both survivin and AKT are Hsp90 client proteins and have been implicated in PDT- and chemo-resistant melanoma cells, targeting Hsp90 may have beneficial effects (Qiu et al., 2005).

Mehta *et al.* (2011) found that Hsp90 inhibitors suppressed proliferation, colony formation and transformation of melanoma cells irrespective of their B-RAF mutational status. However, Hsp90 inhibitors (PF-4470296 and PF-3823863) degraded mutant but not WT B-RAF protein and reduced the activation of MEK/ERK in B-RAF mutant A2058 melanoma cells (Mehta et al., 2011). These inhibitors also induced the degradation of C-RAF, AKT, ErbB2 and cMET (involved in tumour progression) in both mutant (A2058) and WT (MeWo) BRAF melanoma cell lines. In *in vivo* studies, PF-3823863 induced tumour growth inhibition in both A2058 and MeWo melanoma xenografts. Although, PF-4470296 and PF-3823863 are effective in treating both WT and mutant B-RAF melanomas, the mechanism involved seems to be different; unlike mutant B-RAF, WT B-RAF is not depleted but other oncogenic client proteins responsible for tumour survival and growth are affected. However, Banerji *et al.* (2008) found 17-AAG to be ineffective when administered to two melanoma patients with WT N-RAS/B-RAF (1-1.5 months to progression) compared to one with mutant N-RAS (and WT B-RAF; 49 months to progression) and another with mutant B-RAF (and WT N-RAS; 15 months to progression). In the same study, two other patients with mutant B-RAF (and WT N-RAS) only had 1.5-2 months of stabilised disease

before the tumour progressed. This study had a small number of test subjects and only one patient had mutant N-RAS which makes the results inconclusive. Nevertheless, data on a patient's mutational status corresponding to Hsp90 inhibition will assist in the use of such inhibitors similar to the application of B-RAF (section 2.1.3) and KIT inhibitors (section 2.1.1) as discussed earlier.

Montaqut *et al.* (2008) found that AZ628 (B-RAF inhibitor)-resistant melanoma cells had elevated levels of C-RAF that was responsible for the survival of these cells. Treatment with geldanamycin sensitised these cells to apoptosis by inhibiting Hsp90. This suggests that a combined application of RAF and Hsp90 inhibitors may improve treatment outcomes of melanoma patients. In a phase I clinical trial, the combination of sorafenib (B-RAF inhibitor) and tanespimycin (17-AAG) showed clinical efficacy in four out of six melanoma patients (Vaishampayan et al., 2010). When 17-DMAG (Hsp90 inhibitor) was co-treated with imatinib mesylate (RTK inhibitor), a synergistic anti-proliferative effect was seen in uveal melanoma cells (WT B-RAF) (Babchia et al., 2008). Imatinib inhibits specific KIT mutations and secondary mutations have arised in imatinib-resistant tumours (Lim et al., 2008; Terheyden et al., 2010). Since KIT is a client protein of Hsp90, the inhibition of this heat shock protein may destabilise KIT irrespective of different receptor domain mutations thereby improving imatinib's efficacy. On the whole, Hsp90 inhibitors would augment the effectiveness of other oncogenic protein (e.g. B-RAF, KIT) inhibitors in these patients.

Gaspar *et al.* (2009) identified a possible mechanism of resistance which may occur in melanoma treated with 17-AAG. After continuous drug exposure, a 17-AAG-resistant melanoma cell line, WM266.4-RA6 was developed. This resistance was found to occur via downregulation of NAD(P)H/quinone oxidoreductase (NQO1) as ES936 (NQO1 inhibitor) reduced 17-AAG sensitivity in the non-resistant WM266.4 parental line. This suggests that 17-AAG efficacy relies on NQO1 upregulation in these cells (Gaspar et al., 2009; Siegel et al., 2011). Although, the same resistance occurred in glioblastoma cells, other structurally dissimilar Hsp90 inhibitors (VER-49009 and NVP-AUY922) were also shown to be effective (Gaspar et al., 2009). In another study, NVP-AUY922 inhibited proliferation in WM266.4 (mutant B-RAF), SKMEL2 (mutant N-RAS; high NQO1) and SKMEL5 (mutant BRAF; low NQO1) melanoma cells in an NQO1-independent manner (Eccles et al., 2008). Although, the efficacy of its inhibiton in WT/mutant B-RAF or N-RAS is still ambiguous, Hsp90 has a broad spectrum of targets and its inhibition will affect multiple signalling pathways in tumours irrespective of their mutational status. Furthermore, Hsp90's role in both the RAS/RAF/MEK and PI3K/AKT pathways which are common oncogenic pathways in melanoma makes it a promising target. Currently, some of these Hsp90 inhibitors are undergoing clinical trials.

2.2.3 p38 MAPK and JNK

Besides ERK, p38 MAPK and c-Jun NH_2-terminal kinase (JNK) belong to the MAPK family (Muthusamy and Piva, 2010). UV-induced activation of p38 and JNK in normal skin cells were either pro- or anti-apoptotic depending on the cell type, UV type and dose used (Muthusamy and Piva, 2010). Unlike ERK, p38 and JNK pathways have not been frequently linked to melanoma incidences. However, there is evidence to suggest that these pathways may play a role in synergistic or additive effects together with chemotherapeutic agents to elicit cytotoxicity in melanoma cells (Keuling et al., 2010; Selimovic et al., 2008; Shieh et al., 2010).

Melanoma cells resistant to ABT-737 die when they are co-treated with the p38 inhibitor, SB202190 (Keuling et al., 2010). The combination of ABT-737 and SB202190, enhanced caspase-dependent apoptosis in four melanoma cell lines harbouring different mutations. In contrast, the use of either SB203580 (p38 inhibitor) or SP600125 (JNK inhibitor) abolished Taxol-mediated apoptosis, ROS generation and decreased uncoupling protein 2 (UCP2) levels in A375 and BLM melanoma cells (Selimovic et al., 2008). Therefore, Taxol affects melanoma cells by upregulating these (p38 and JNK) pathways which in turn regulates the membrane potential, intracellular UCP2 and ROS levels. The JNK pathway was found to mediate doxycycline-induced cell death via ROS generation and apoptosis signal-regulating kinase 1 (ASK1) activation in A2058 melanoma cells (Shieh et al., 2010). Imatinib mesylate, a RTK inhibitor, mediated apoptosis and induced high levels of phospho-JNK and p38 in B16F0 melanoma cells (Chang et al., 2011). In this study, SP600125 was shown to enhance apoptosis in the imatinib mesylate-treated melanoma cells.

p38 was implicated in aiding melanoma transendothelial migration in co-cultures with human vascular endothelial cells (HUVEC) (Khanna et al., 2010). When A2058 melanoma cells were co-cultured with HUVEC, the latter's vascular endothelial (VE)-cadherin junctions were disrupted and gap formations occurred allowing migration of melanoma cells. Neutralisation of soluble factors (IL8, IL1β) released from A2058 melanoma cells abrogated the p38 pathway in HUVEC and prevented VE-cadherin disassembly and gap formation which was also affirmed by the inhibition of p38 in these cells. In contrast, downregulation of Ras association domain family 1, isoform A (RASSF1A)/ASK1/p38 in part, was involved in melanoma development. RASSF1A levels were lower in melanoma tissues compared to benign and normal melanocytes (Yi et al., 2011). Expression of RASSF1A in RASSF1A-deficient A375 melanoma cells induced an anti-proliferative and pro-apoptotic effect which coincided with decreased tumorigenic potential of these cells as well as an increase in ASK1 and p38 levels.

Collectively, the roles of p38 and JNK in melanoma development, apoptosis or chemoresistance needs to be tested on a case by case basis as it seems to vary with different cytotoxic agents and cell types. Forced expression of active p38/JNK or its inhibition may be useful in enhancing the efficacy of chemotherapeutic agents in inducing apoptosis in tumour cells. In order to prevent disruption of normal cellular homeostasis, it is imperative to identify melanoma-specific treatment vehicles.

2.2.4 Phosphatases

Phosphatases regulate cell signal transduction by dephosphorylating phospho-proteins resulting in either their activation or deactivation (Bermudez et al., 2010; Haagenson and Wu, 2010). Protein tyrosine phosphatases (PTP) and serine/threonine phosphatases (S/TP) dephosphorylate tyrosine and serine/threonine residues, respectively (Hamilton and Bernhard, 2009). Phosphatases in the nucleus are involved in controlling cell cycle progression and other nuclear processes (Bollen and Beullens, 2002). The MAPK signalling pathway has several MAPK phosphatases (MKP) regulating the activity of each kinase. The dual specificity phosphatases (DSP) target MAPK at both tyrosine and threonine residues (Bermudez et al., 2010). In some human cancers, these phosphatases are either overexpressed or suppressed leading to deregulated cell signalling (Haagenson and Wu, 2010).

PTEN is a phosphatase that removes phospho-groups in both lipids and proteins (Hamilton and Bernhard, 2009), and is deleted/inactivated in some melanomas (Paraiso et al., 2011). PTEN dephosphorylates AKT and inhibits cell survival and its loss enables melanoma cells to overcome B-RAF inhibition via the AKT survival pathway (Paraiso et al., 2011). In PLX4720 (B-RAF inhibitor)-treated $PTEN^{+/+}$ melanoma cells, AKT signalling was inhibited and Bim-mediated apoptosis was enhanced compared to $PTEN^{-/-}$ cells (Paraiso et al., 2011). Stewart *et al.* (2002) found no mutations in PTEN coding regions but the protein levels were low or undetectable in five melanoma cell lines (WM35, WM134, A375, A375-S2, MeWo). When PTEN adenoviral vectors (Ad-PTEN) were transfected into these cells, there was an increase in AKT dephosphorylation, apoptosis and growth inhibtion. A decrease in cell migration/invasive property and a corresponding increase in E-cadherin levels were also observed. These data emphasise the role PTEN phosphatase plays in melanoma.

Chen *et al.* (2010) found that high levels of phospho-myristoylated alanine-rich C-kinase substrates (MARCKS) and their upstream activator, protein kinase Cα (PKC) were responsible for metastasis of B16F10 melanoma cells. In weakly motile F1 melanoma cells, phospho-MARCKS were undetectable but PKC levels were still high which suggests that an inhibitory mechanism exists to maintain low phospho-MARCKS levels in these cells. When the F1 cells were treated with okadaic acid (protein phosphatase inhibitor; inhibits PP1 and 2A) the phosphorylation of MARCKS increased while the addition of a PKC inhibitor abolished these levels (Chen and Rotenberg, 2010; Clarke et al., 1993). This study suggests that there is a ratio between PKC and protein phosphatase levels which determines the amount of phospho-MARCKS present in these cells and this may affect their motility. Therefore, it is possible that in metatstatic melanoma cells, high levels of protein kinases may override the effect of protein phosphatases or these phosphatases may be either suppressed or lost.

McArdle *et al.* (2003) observed that advanced melanoma had greater phosphotyrosine residues than did early stage lesions. Microarray analysis of metastatic melanoma cell lines (WM9, WM39, WM852) showed a 32% difference in total phosphatase gene expression compared to normal melanocytes. In some of these cells, DSP, PTP, S/TP and acid/alkaline phosphatases were downregulated when compared to naevus and melanocytes (McArdle et al., 2005). Of the DSP identified, DSP10 (MKP5) was lower in all three melanoma cell lines tested while DSP5 expression was decreased. DSP10 is a cytoplasmic and nuclear phosphatase which dephosphorylates p38 and JNK while DSP5 is localised to the nucleus and inactivates ERK (Bermudez et al., 2010). It was speculated that since DSP10 maps to chromosome 10q25, it might be downregulated/deleted as it is in the same region as PTEN (chromosome 10q23.3) which is often lost in some melanomas (McArdle et al., 2005). The low levels of PTP in conjunction with amplified phosphotyrosine levels may prevent inactivation of crucial kinases that drives melanoma metastasis.

In contrast, some melanoma cell lines have higher total PTP activity than do melanocytes. Since, only total PTP was measured irrespective of subcellular localisation, type and function, it is possible that those which were upregulated may be pro-tumorigenic. Sun *et al.* (2011) found that the PP1 catalytic subunit β isoform was significantly overexpressed in human melanoma compared to nevi samples. DSP4 (MKP2) which dephosphorylates MAPK was found to be upregulated in melanoma cell lines (Teutschbein et al., 2010). It is possible that their increase could compensate for the high levels of ERK produced in these cells. Laurent *et al.* (2011) found that overexpression of PTP4A3 in uveal melanoma cell lines correlated to a high degree of cell migration and invasisveness *in vivo*. Another phosphatase, PP2A was involved in tumour cell migration as its inhibition by cytostatin upregulated those cytokines involved in augmenting natural killer cell levels and activity *in vivo* which

resulted in reduced mice B16 melanoma pulmonary metastasis (Kawada et al., 2003). In another study, MKP1 (DSP1) expression was found to be higher in melanoma tissue samples (~six-fold) than in melanocytes (Kundu et al., 2010). Tyrosine phosphatase inhibitor-3 inhibited MKP1 activity and had a synergistic effect with interferon α2b to inhibit WM9 melanoma cell growth (Kundu et al., 2010). MKP1 has been associated with chemoresistance in other human cancers (lung and breast cancer) but it is not known if the same occurs in melanoma (Haagenson and Wu, 2010).

Tang *et al.* (1999) observed a greater expression of cyclin-dependent kinase 2 (CDK), CDK6 and CDC25A in metastatic melanomas than in benign nevi. CDC25A is a tyrosine phosphatase that dephosphorylates/activates CDK, allowing entry into the cell cycle and as such may be involved in melanoma proliferation (Tang et al., 1999). Koma *et al.* (2004) found that deltagamma 1 (Δγ1) (truncated variant of PP2A B65γ regulatory subunit) confers radioresistance to metastatic melanoma cells. When F10 cells were transfected with Δγ1, there was a decrease in radiation-induced p53 protein levels, BAX transactivation and apoptosis *in vivo*. This is due to Δγ1-mediated dephosphorylation of MDM2 which targets p53 for degradation and as a result prevents the production of p53-inducible apoptotic factors. It is conceivable that the transition from benign to metastatic melanoma may also be aided by progressive mutations occurring in these phosphatases.

Although, microarray and global gene expression data is useful to elucidate those phosphatases regulated in melanoma, there seems to be a lack of functional studies conducted in these tumours. Data on the mutational status of phosphatases in melanoma is limited. Nevertheless, the existing data creates a compelling argument that these proteases may prove to be a valuable tool in targeting phospho-proteins that regulate pro-tumour activities in these cells. As phosphatase inhibitors can promote tumour activity, it is necessary to delineate the specific roles played by these phosphatases in melanoma (Fujiki and Suganuma, 2009).

3. Conclusion

On the whole, it has been shown from numerous studies that melanomas cannot be treated using a single agent. This is partly due to the presence of melanoma subgroups harbouring one or more mutations; KIT only, N-RAS only, B-RAF only, KIT and N-RAS, and KIT and B-RAF mutant melanomas (Curtin et al., 2006). In addition, a cocktail of inhibitors and new therapeutical targets are necessary to prevent drug resistance due to activation of alternative/compensatory signalling. Although, joint therapies have recently been suggested, a cocktail of drugs may induce systemic toxicities and other anomalies, and as such requires more pre-clinical studies on effective dosages. In conclusion, the RAS-RAF-MEK pathway still remains a promising target for therapy but the identification of new molecular targets might enhance the efficacy of existing treatments. This would allow for melanoma therapy to 'strike from all angles' in terms of oncogenic mutations, survival pathways, metastasis and angiogenesis.

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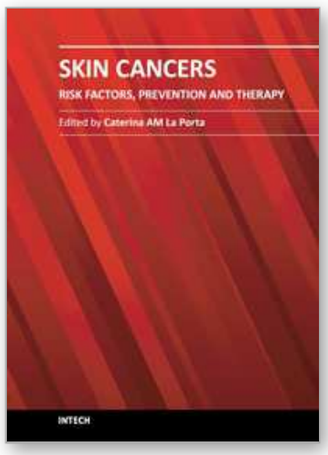

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Skin cancers are the fastest growing type of cancer in the United States and represent the most commonly diagnosed malignancy, surpassing lung, breast, colorectal and prostate cancer. In Europe, the British Isles have been the highest rates of skin cancer in children and adolescents. The overall idea of this book is to provide the reader with up to date information on the possible tools to use for prevention, diagnosis and treatment of skin cancer. Three main issues are discussed: risk factors, new diagnostic tools for prevention and strategies for prevention and treatment of skin cancer using natural compounds or nano-particle drug delivery and photodynamic therapy.

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