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RESEARCH ARTICLE

Solar exposure, the melanocyte and melanoma: Survival pathways and molecular mechanisms.

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ABSTRACT

The keratinocyte and the melanocyte, the main cellular constituents of the epidermis, are two very different cell types. Despite their different origins and functionality, they come together in the skin, synergistically, to function as a unit to control the adverse effects of solar exposure. The most significant element in this protective process is the ability of the melanocyte to produce melanin. This pigmented polymer is responsible for constitutive skin colour that plays a part in our identity as human individuals but more importantly, provides a tanning response. A change in pigmentation that provides both an immediate and prolonged protective effect from the damaging components of solar radiation.

The melanocortin 1 receptor, a cell surface receptor on the melanocyte, receives paracrine stimulation in the form of hormonal communication from the keratinocyte, initiating a series of intracellular molecular interactions in the melanocyte, eventually involving transcription factors in the nucleus, most notably the microphthalmia-associated transcription factor, resulting in upregulation of enzymatic production of melanin and finally, its transfer back to the keratinocyte.

The melanocortin 1 receptor is highly polymorphic and unfortunately this results in the Caucasians' having constitutionally fairer skin combined with an incomplete tanning response, resulting in a higher susceptibility to skin cancer.

The melanocyte is a relatively long-lived cell and over its extended life span can accumulate a series of mutational events. With malignant transition to melanoma this oncogenic baggage, when combined with antiapoptotic machinery that helps melanocyte survival, resulting in relatively rapid progression of the malignant process and contributing to its resistance to therapeutics.

Introduction

One of the enduring anomalies in skin development and function is the disparity of the embryologic origin of the two predominant skin cell types, keratinocytes and melanocytes. Keratocytes are of ectodermal origin and melanocytes of neural crest origin, migrating to, and colonising the basal layer within the skin and its appendages, yet these two vastly different cellular types form a close structural and functional relationship for mutual benefit. This is particularly relevant to protecting the organism from potential adverse effects of solar radiation. The concept of the keratinocyte-melanocyte unit was proposed early and is still highly relevant but there is an important relationship between all cell types in the epidermis, dermis and surrounding supporting cells and tissues with interlinking pathways and cross-talk to protect the organism as a whole and to maintain individual cellular homeostasis.

Melanoma is a malignant tumour arising from the melanocyte. Post-migratory melanocytes are fully differentiated and securely attached to the basement membrane and their morphology, growth, adhesion and migration are under control of the keratinocytes. During melanocyte transformation and melanoma progression, melanocytes loose interaction with their keratinocyte partners, resulting in uncontrolled proliferation and invasion. Melanoma cells at advanced stages often lack melanocyte features and resemble their more primitive multipotent progenitors.

The MAPK kinase pathway is often activated in melanomagenesis with oncogenic BRAF and NRAS driver mutations. Naevi have similar mutations but initial proliferation mostly ending in melanocyte senescence, induced by the oncogenes[1]. However, only 25% of melanomas arise from a pre-existing naevus, with 75% arising *de novo*, from isolated melanocytes[2].

Emerging evidence suggests that melanoma cells are more similar to progenitor cells than fully differentiated melanocytes. In other words, the transformed melanocyte does not represent a different cell of origin but de-differentiation of the melanocyte to a more pluripotent progenitor, reanimating embryonic proliferative and migratory pathways.

The other aspect of disparity is the life cycle of the two cell types. Keratocytes are highly proliferative and short lived, being born of stem cells on the basal level and rapidly moving up through the strata, only becoming fully differentiated towards the epidermal surface where they lose their nuclei and become part of a robust and fairly impermeable physical barrier, the stratum corneum. This process lasting 4-5 weeks before being shed as a loose basket weave layer. On the other hand, the melanocyte has a relatively low proliferative capacity with an extremely long life-span of approximately 50 years, essential to maintaining their sentinel sensory and protective function. The only partially specified melanoblast emerging from the neural crest shares embryologic homology with elements of the peripheral nervous system. Arriving at the skin, fully differentiated, the melanocyte takes its place along the dermo-epidermal junction amongst the keratinocytes to perform its role as a sensor of solar exposure as the most distal component of the peripheral nervous system, reporting back to the CNS but also having

some autonomy to institute more immediate protective responses.

The melanocyte is also a cell specialised in the synthesis of the pigment melanin, this useful polymer providing the skin, hair and eyes with distinctive colouration[3] but, more importantly, having a protective effect on surrounding cells from adverse effects of solar radiation. The melanin produced in the melanocyte is transferred to the keratinocytes in the form of melanosomes. This shields the nuclei of these cells from impinging solar radiation and also scavenges reactive oxygen species (ROS) that can damage DNA, proteins and lipids[4]. Melanocyte homeostasis is regulated by many genes, including those that code for growth factor receptors, transcription factors and their targets[5] and the influence of signalling pathways, including G protein-coupled and tyrosine kinase pathways[6,7,8]. These pathways and their crosstalk regulate the melanocyte constitutively as well as in response to environmental stressors, such as solar radiation.

Melanocytes exist in diverse body tissues but the basic function is to scavenge and quell excessive ROS. However, my focus will be on the epidermal melanocyte for its role in the skin and it being a precursor of cutaneous melanoma. How is it regulated and the signalling pathways that modulate its survival, proliferation and function?

On exposure to ultraviolet radiation (UVR) paracrine messages from the keratinocytes to the melanocytes stimulate a system of immediate pigmentation, oxidising intermediates and releasing tyrosinase and also acting through a melanocyte receptor, the MC1R, upregulating all the melanogenic enzymes through the master melanocyte regulator, the transcription factor, MITF, providing a delayed but stronger and more persistent tanning response.

Melanocytes produce two types of melanin, eumelanin, the black/brown pigment and pheomelanin, a red/yellow pigment. The ratio of these two affecting colouration and having significance in the degree of protection provided to the human as a whole.

Melanin in photoprotection

Melanin, produced by melanocytes is the main photoprotective effector against solar-induced photodamage, the underlying cause of melanoma[9,10]. Fairer skinned individuals having lower constitutive pigmentation and poorer tanning ability are at greater risk than darker skinned individuals[11]. Human melanocytes synthesis both eumelanin and pheomelanin. The ratio of one with the other determines skin colour and correlates directly with total melanin content[12]. Eumelanin is more photoprotective than pheomelanin due to its resistance to photo-degradation and ability to scavenge ROS[13]. Eumelanin content has been shown to correlate inversely with the induction of DNA photoproducts in skin *in situ*[14]. Pheomelanin is photolabile and can be a pro-oxidant[15]. It has even been reported that pheomelanin promotes melanomagenesis via the induction of oxidative DNA damage in mice harbouring an activating BRAF mutation, without exposure to any carcinogen, such as UVR[16]. Suggesting that pheomelanin can be oncogenic.

Melanocortin 1 receptor and Endothelin B receptors

Two particular membrane bound receptors on melanocytes, the melanocortin 1 (MC1R) and

endothelin B receptor (ENDBR), both G-protein coupled (G_s and G_q respectfully) play extremely important roles in regulation of pigmentation and DNA repair in the melanocyte's response to UVR, the main aetiological factor for melanoma. Activation of MC1R by its agonists, α melanocyte stimulating (αMSH), and adrenocorticotrophic (ACTH) hormones stimulate eumelanin synthesis and reduce oxidative stress. The synergistic action of endothelin-1 (ET-1) on ENDBR, and αMSH on MC1R results in stimulation of melanocyte proliferation, melanogenesis and resistance to UVR-induced apoptosis.

MC1R in humans is highly polymorphic and individuals with loss-of-function variants in receptor expression are at increased risk of melanoma, through compromised DNA repair and reduced antioxidative activity, independent of pigmentation. These allelic variants can be present in darker-skinned individuals but the homozygotic red-haired phenotype is considered to be at highest risk[17]. These two receptors and their agonists reduce the risk of melanoma by modifying the DNA damage and antioxidant response to solar exposure, ensuring genomic stability and homeostasis within the melanocyte. MC1R mainly signals through activation of the cAMP pathway[18], stimulating tyrosinase and melanin synthesis. Figure 1.

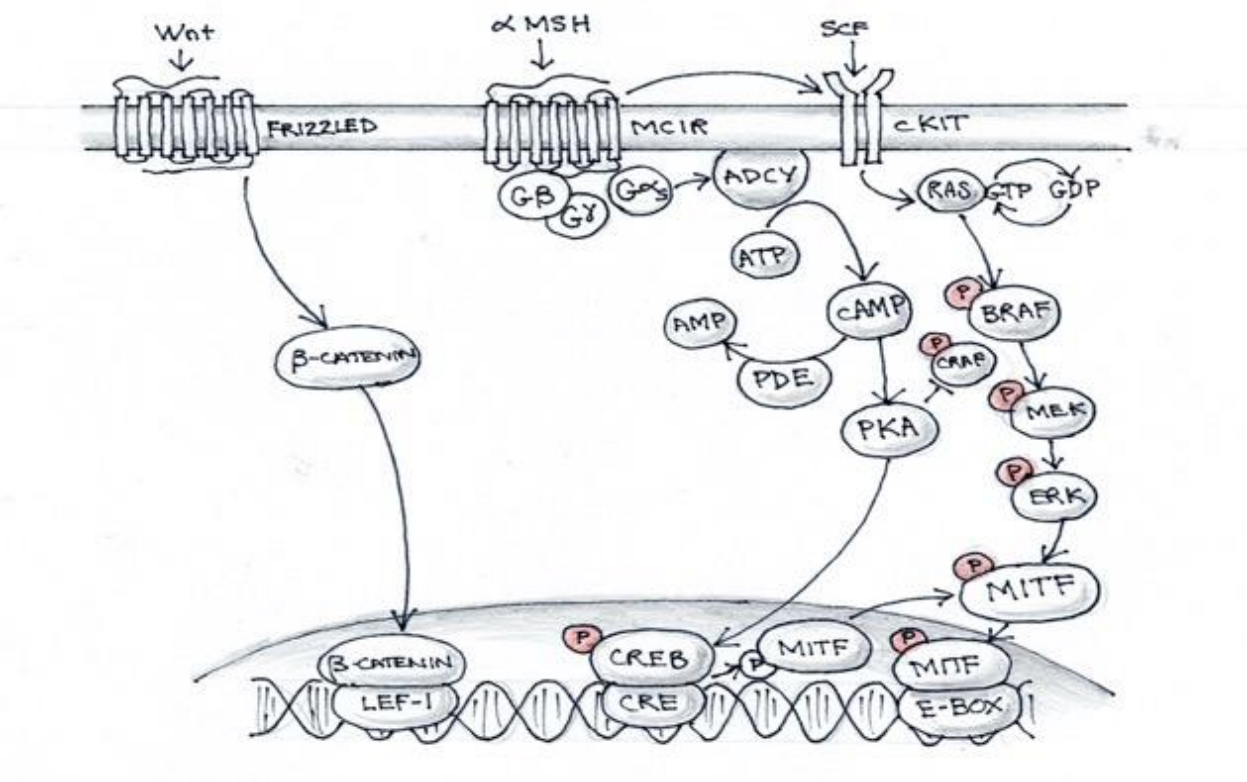

Figure 1. cAMP signalling showing cross-talk between cAMP and MAPK signalling. MITF regulation by 3 pathways – Frizzled-Wnt signalling (melanocyte development); MC1R-cAMP signalling; and cKIT-MAPK signalling (differentiation and proliferation). αMSH/ MC1R signalling can activate the MAPK pathway in a cAMP-independent manner. G-proteins a, b, ɣ; ADCY, adenylate cyclase; cAMP, cyclic AMP; PDE, phosphodiesterase; CREB, cAMP responsive element binding protein; CRE, cAMP responsive element; MITF, microphthalmia associated transcription factor; Wnt, wingless-type ligand; SCF, stem cell factor. (Adapted from Rodrıguez & Setaluri 2014).

It has been demonstrated that activation of the cAMP pathway is critical for stimulation of melanogenesis in human melanocytes exposed to UVR[19] and that loss-of-function MC1R allelic variants have increased sensitivity to UVR, as shown by increased melanocyte apoptosis on exposure to UVR[20]. More recently it has been found that the activation of MC1R by αMSH as well as increasing melanogenesis also enhances repair of UVR-induced DNA photoproducts[21,22]. These photoproducts are formed by direct absorption of UVR by pyrimidine bases in DNA, predominately sites containing a thymine residue. This creates a bulky lesion that distorts the helix, halting transcription and replication. If not repaired, sustained DNA damage results in mutations, establishing a role for MC1R in regulating DNA repair in melanocytes.

Irradiation of melanocytes with UVR also results in oxidative DNA damage[23]. Treatment of melanocytes with αMSH reduced UVR-induced generation of ROS, increased levels and activity of antioxidants catalase and ferritin, reducing the generation of 8-oxyodeoxyguanosine (8-oxodG), a major form of oxidative DNA damage. αMSH also activates Nrf2, a transcription factor that regulates expression of genes that code for phase II detoxifying enzymes, such as heme oxygenase-1 and glutathione transferase by binding to antioxidant response elements in their promoters[24]. Treatment with αMSH contributes to the accumulation of p53 in melanocytes, another transcription factor influential in reducing oxidative DNA damage in melanocytes[25].

Melanocortin 1 receptor has transcriptional effects on genes involved in the cell cycle, DNA repair, antioxidant defences, apoptosis and pigmentation[26]. Treatment with αMSH reversed the effects of UVR on the expression of genes involved in these processes. Loss-of-function MC1R allelic variants have reduced DNA repair and antioxidant capacity resulting in vulnerability to malignant transformation of their melanocytes into melanoma.

DNA Damage Response

DNA damage response to UVR results in a signal transduction pathway that coordinates cell cycle transition, DNA repair, and apoptosis to preserve genomic stability[27]. MC1R has a critical role in efficient operation of the repair process. Activation of MC1R by αMSH binding results in phosphorylation and hence activation of the DNA damage sensors ataxia telangiectasia mutated (ATM) and Rad 3 related (ATR), and DNA-PK[25,28]. Chk1&2, as well as the transcription factors p53 and γ-H2AX, the phosphorylated form of histone 2AX, are immediate downstream targets of ATM and ATR. γ-H2AX is crucial for recruitment of DNA repair proteins to DNA damage sites[29]. Activation by αMSH increased levels of XPC, the enzyme involved in recognition of DNA damage, the first step in nucleotide excision repair (NER), the main repair pathway for DNA photoproducts[30].

Activation of MC1R increases cAMP levels and activation of cAMP dependent PKA, inducing phosphorylation of ATR, required for association of ATR with the DNA repair protein XPA[31].

The other significant receptor on melanocytes, ENDBR, can increase intracellular Ca^{2+} mobilisation and PKC activation. Its ligand ET-1 is synthesised by keratinocytes and is increased upon UVR exposure[32]. Figure 2.

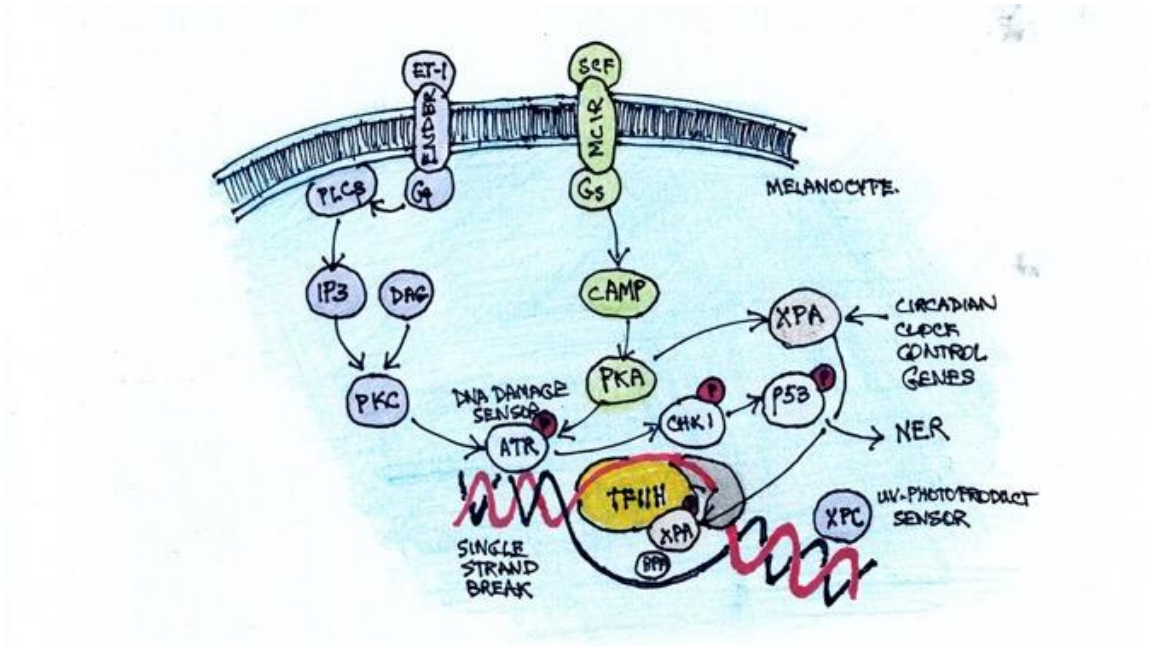

Figure 2. Regulators of NER in melanocytes. NER is the major DNA repair pathway in mammals for removing UVR-induced photoproducts. NER is a completely self-driven process upon detection by XPC-sensor protein in melanocytes. However, it takes input from other cellular processes and exogenous factors like αMSH and ET-1. These factors influence the DNA sensor protein ATR, which, in turn influences NER, either directly through a p53-mediated pathway or by stabilisation of XPA, an important rate-limiting intermediary which is however, also regulated by the circadian clock genes to anticipate daily and seasonal changes in the requirements of NER.

Transcription factors

The human genome is regulated at multiple levels allowing the establishment of phenotypically distinct cell types and providing individual cells with the ability to respond to intra- and extracellular stimuli. Transcription factors represent a broad family of proteins that interact with chromatin to control gene transcription. Although plasticity allows cells to react to their environment to maintain homeostasis and viability, unfortunately, it also allows for cellular reprograming and phenotypic changes in disease states e.g. cancer that can have major adverse effects on the organism.

MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR

The microphthalmia-associated transcription factor (Mitf) is considered to be the master regulator of melanocytes[33]. It has the ability to regulate expression of many target genes involved in melanin synthesis, proliferation and survival of melanocytes[34]. It directly targets the genes for the melanogenic enzymes *tyrosinase, TYRP1, DCT*. Melanosomal genes *PMel17, OA1* and melanosomal transfer gene *Rab27A,* and of critical importance genes regulating melanocyte survival, anti-apoptotic *Bcl2, BIRCT* (encoding a member of the inhibitor of apoptosis protein family) and *DICER* (reduces expression of the pro-apoptotic BIM). As well as genes that encode for melanocyte growth and survival factor receptors and their respective ligands, *SCF:KIT; NGF:NGFR; ET-I:ENTBR,* and of probably most significance, α-MSH:MC1R which interacts synergistically with factors that stimulate PKC, tyrosine kinase or intracellular calcium mobilisation to act on these MAP kinases and their down-stream targets,

leading to increased melanocyte proliferation and melanogenesis[35]. Also *APE/Ref1* than regulates redox state, and *HIFIα* induced by hypoxia. Other targets are the cell cycle regulatory genes *TBX2, CDK2, CDKN1A* (p21) and *CDKN2A.*

Mitf is regulated by the ERK1/2 pathway. Treatment of melanoma cells with SCF activates ERK1/2 resulting in phosphorylation of Mitf, transiently increasing its transcriptional activity, increasing tyrosinase expression[36]. Treatment of cultured human melanocytes by α-MSH and/or ET-1 in the presence of bFGF increased total protein levels of Mitf as well as its phosphorylated form[37]. Mitf was also regulated transcriptionally as shown by melanocytes treated with α-MSH [22,26].

TRANSCRIPTION FACTOR P53

The transcription factor p53 is considered a universal sensor of genomic stress[37]. It accumulates following UV exposure inducing growth arrest to allow DNA repair, as shown in human melanocytes[38]. P53 was also found to upregulate expression of POMC, the precursor for melanocortin in keratocytes, that stimulate melanogenesis, implicating p53 in regulation of important paracrine factors known to have a significant impact on melanocytes.

TRANSCRIPTION FACTOR P38

Exposure to UVR activates MAP kinase p38 and JNK/SAPK, which regulate the activity of downstream transcription factors that mediate the stress response[39]. Increase in pigmentation, the tanning response, is part of this stress response, which is mediated by the paracrine /autocrine network that is activated by UVR.

The transcription factor, Upstream Stimulating Factor-1 (USF-1) was activated by p38 and was shown to be an important regulator of *MC1R* and *POMC* expression in melanocytes exposed to UVR[40]. Additionally, USF-1 up-regulated the expression of *Tyrosinase*, *TYRP-1* and *DCT*. Phosphorylation of USF-1 resulted in its activation and enhanced ability to bind DNA[41].

ACTIVATING TRANSCRIPTION FACTOR-2

Activating transcription factor-2 (ATF-2), also known as cAMP response element (CRE) binding protein2 (CREB2) is a member of activating protein -1 (AP-1) transcription factor family that regulate expression of genes through homo- and hetero-dimerisation with other AP-1 family members, such as the CREB, Fos, Maf, or Jen family transcription factors. Itself being regulated at multiple levels, transcriptionally, post-transcriptionally and post-translationally, that influence ATF-2 function, and therefore the transcriptional programs coordinated by ATF-2. This gives a glimpse of the complexity of these regulatory mechanisms. ATF-2 is an important mediator of mammalian cell responses to various stimuli, including stress. It is known to regulate genes involved in DNA repair, such as XPC and ERCC1; apoptosis, such as Bcl2; and the cell cycle, such as CDK4. It was also activated by p38, as well as by JNK[42], and thus, plays an important role in the DNA damage response in melanocytes to solar radiation. Gene analysis of human melanocytes irradiated with UVR or treated with α-MSH revealed that ATF-2 and its target genes Bcl2, CDK4 and ERCC1 were reduced in expression by UV but up-regulated in expression by α-MSH[26]. It has been reported that exposure of human melanocytes to UV induced phosphorylation of ATF-2 and pre-treatment with ET-1 augmented this effect[43]. Induced phosphorylation of ET-1 even without any UV

exposure, suggesting that this paracrine factor primes melanocytes to respond immediately in order to avoid genotoxic effects of UV.

In melanoma, dual oncogenic and tumour suppressor roles have been demonstrated[44,45]. PCK-dependent ATF phosphorylation (PKCε drives nuclear accumulation and transcriptional activity while blocking its tumour suppressive function at the mitochondria. In melanomas with low PKCε expression levels, where phosphorylation is attenuated following therapeutic stress, ATF-2 can execute its pro-apoptotic function at the mitochondria. However, up-regulation of PKCε in progressive melanoma blocks the tumour suppressive effect by driving nuclear ATF-2 function, transcriptionally promoting mobility, invasiveness, and resistance to therapeutics. Increased PKCεlevels and increased nuclear ATF-2 both correlate with clinical staging[44].

Apoptosis

Apoptosis is a genetically regulated form of cell death which is responsible for the programmed culling of cells during the process of homeostasis in eukaryotes. It is an important biological response to cellular stress and damage as well as in the maintenance of normal development. There are two major apoptotic pathways, the exogenous or death receptor pathway which is activated by pro-apoptotic stimuli from outside the cell, stimulating the caspase cascade. Whereas, the endogenous or mitochondrial pathway is activated by intrinsic mechanisms within the cell itself. Cytochrome C is released from the mitochondria activating Caspase 9. Evasion of apoptosis plays a central role in the development of malignant clones and is fundamental to melanoma pathogenesis. Members of the BCL-2 protein family have pro- and anti-apoptotic activities and are classified into three subgroups, the anti-apoptotic and pro-survival BCL-2 and BCL-XL, the pro-apoptotic BAX and Bak, and the pro-apoptotic BH3-only protein. These pro- and anti-apoptotic regulators are held in fine balance in healthy cells. Oncogenic activity is usually associated with an abnormal expression of these family members.

B-CELL LEUKAEMIA/LYMPHOMA 2 (BCL2)

Melanocytes, over their long life-span, are constantly exposed to exogenous genotoxic UVR and endogenous oxidative stress by quinone toxicity from melanin synthesis. They have to be more efficient at scavenging ROS than other cell types but they are also more poorly susceptible to pro-apoptotic signals, such as UVB. Survival pathways operate in melanocytes which are unique for the requirement to survive UV exposure to ensure melanin synthesis. Firstly, Lerner et al showed that some *Mitf* alleles which exhibit normal pigmentation at birth followed by greying due to melanocyte loss, suggesting that Mitf plays an active role in modulating post developmental melanocyte survival. Later, McGill et al found that *Mitf* and *Bcl2,* that encodes for the antiapoptotic factor Bcl2, genetically interact *in vivo* as demonstrated by profound melanocyte loss in compound heterozygous mice. They showed that Mitf occupies the Bcl2 promoter, regulating levels of Bcl2 in melanocytes and that modulation of *Bcl2* expression is critical for melanocyte survival. *Bcl2* is a target gene of the melanocyte master regulator *Mitf,* modulating melanocyte lineage survival and thus, also melanoma cell viability. *Mitf,* being a central

transcriptional regulator of pigmentation, it, therefore, seems reasonable to link *Bcl2* expression to the pigmentation response. *Bcl2*'s protective effect may also be directed against the stress of pigmentation itself. Unfortunately, one of the consequences of this *Mitf-Bcl2* linkage is the extreme treatment resistance of melanoma.

Upstream of *Mitf*, SCF signalling, through is cognate receptor KIT, has a major impact on the transcriptional repertoire of melanocytes, affecting diverse gene functional categories, such as survival, proliferation, signalling, redox, DNA repair, motility and membrane trafficking.

Apoptosis plays an important role in tissue homeostasis. Impaired cell death is a ubiquitous characteristic of cancer cells, determining their resistance to apoptotic signals. Melanoma cellular integrity is maintained by pro-survival members of the Bcl2 family; Bcl-2, Mel-1, Bcl-X_1, livin, survivin and inhibitors of apoptosis (IAPs). Melanoma is characterised by a labile and stage-dependent phenotype where their cells rarely undergo spontaneous apoptosis, as compared to other cell types, through pre-existing enrichment of survival advantages bestowed on them by their progenitor cell, the melanocyte.

SURVIVIN

The anti-apoptotic protein survivin is a dual mediator of apoptosis resistance and cell cycle progress. Melanocyte expression levels predispose mice to UV-induce melanoma and metastasis. Genetic alterations are common in melanoma, usually involving repression of tumour suppressors or activation or amplification of oncogenes, leading to aberrant signalling. Raj et al had previously shown that survivin is up-regulated and highly expressed in melanoma as compared to normal human melanocytes and is required for melanoma cell viability[1]. More recently, they showed that p53 and retinoblastoma (Rb) are both required to repress *survivin* transcription in normal human melanocytes. P53 and RB (Via E2Fs) regulate survivin expression by directly binding to the *survivin* promoter. P53 also affects survivin by activating p21. They also identified a survivin E2F-binding site in the survivin promoter. Mutations in either binding site is sufficient to increase promoter activity. Compromise of either pathway leads to up-regulation of survivin expression in transformation of melanocytes to melanoma[2].

Melanocyte microenvironment

Melanocytes, after cell division, separate and migrate along the basement membrane, extend their dendrites and establish contact with multiple keratinocytes. Once adhesion is established, keratinocytes control melanocyte proliferation and differentiation through expression of cell surface receptors. Their homeostasis is then controlled by paracrine and endocrine communication through soluble factors such as growth factors and cytokines. There is also intercellular communication, either cell-cell, cell-matrix adhesion or through gap junctions[50].

Malignant transition of melanocytes involves an escape from keratinocyte control through down-regulation of receptors for keratinocyte communication, replaced by upregulation of melanoma cell-cell communication, constitutive activation of signalling cascades resulting in proliferation, and unresponsiveness to

exogenous inhibitory growth factors, such as transforming growth factor-β(TFG-β E cadherin is expressed on the surface of both keratinocytes and melanocytes and is a major adhesion molecule between the two cell types. Melanoma cells have decreased expression of E cadherin and increased N cadherin leading to a switch from keratinocyte control to a preferential association with fibroblasts and endothelial cells. Altered expression of cell-matrix adhesion molecules results in a loss of anchorage to the basement membrane. Escape from keratinocyte control also leads to a shift from paracrine to autocrine growth factors, upregulating melanoma cell-melanoma cell communication. Invasion into the dermis, a progression of melanoma from radial to vertical growth phase, results in recruitment of fibroblasts and endothelial cells for matrix and growth factor production and control[51].

Haas et al tested a variety of growth factors and cytokines and found that basic fibroblast growth factor (bFGF) and stem cell factor (SCF), the c- kit ligand, were the strongest inducers of melanocyte proliferation, demonstrating that dermal cells can stimulate melanocytes at the dermo-epidermal junction[50]. When bFGF was combined with UVB, a lesion with high grade atypia was produced with resemblance to lentiginous melanoma[52] Combination of bFGF, SCF and ET-3 led to nest formation and upward migration of single atypical melanocytes, addition of UVB gave the typical appearance of melanoma in situ[53].

Juvenile skin appeared to be more susceptible to transformation by growth factors and UVB.

ET-1 mediated a variety of responses characteristic of de-differentiation.

Conclusion

The melanocyte is an enigma. On the one hand, in the skin, it plays a vitally important role in photoprotection against sun-induced skin cancer. On the other hand, it is the precursor for melanoma, the deadliest form of skin cancer. How can this situation be reconciled?

Humans have been chronically exposed to solar irradiation for the last two and a half million years, all other aerobic organisms much longer, yet we have all survived and reproduced our individual species. This is without the protection of sun screens, hats and clothing. Although early human species were probably more hirsute, with constitutionally darker skin and a more complete tanning response. The contrast between the indigenous Australians and the later arrival of a population of European origin shows the obvious difference in appearance and resistance to skin cancer. The new Australians, a mainly Celtic race with fair skin and incomplete tanning response, suitably adapted to high latitudes in the northern hemisphere, to allow for adequate vitamin D production. In relation to Vitamin D, at least, mild regular sun exposure is essential to good health.

The pattern of sun exposure causing melanoma or non-melanoma skin cancer is different. Culminative sun exposure over a life time for non-melanoma but more the intermittent nature of the exposure with melanoma. This is demonstrated by a higher incidence of melanoma in those individuals who work indoors as compared to outdoor workers. Also, to the most common site of

incidence of melanoma, the back and the back of the shoulders. The parts of the skin surface most intermittently exposed.

The life-style of modern urban living is a major contributor to the high incidence of melanoma in Caucasian populations. Individuals are awake at night, under artificial light, interfering with melatonin production, which has an influence on DNA repair mechanisms. Late nights also mean that the individual is unlikely to wake with the change of light at dawn, and so not resetting and coordinating their internal circadian clock to the universal circadian pattern, missing the extensive protective effects provided by this system. This is combined with a maladaptive pattern of sun exposure. Recreational sun exposure more often confined to the weekend and extended over the whole day, to make up for lost time. It would be more beneficial to arise at dawn to get early morning sun exposure with the less damaging longer wavelengths of light, which as well as being less dangerous, it also conditions the skin if exposure is continued more into the middle of the day. Midday sun exposure, in summer, in Australia is best totally avoided, but if necessary, accompanied by maximal protective measures.

Conflict of Interest:

None

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None

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