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Review Article

Invasive Melanoma: The Treatment-Resistant Skin Cancer with the Deadly Reputation

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Abstract

Although melanoma accounts for less than a tenth of all skin cancers, it is responsible for three quarters of skin cancer deaths. It has a more aggressive nature, tendency to metastasise and is more resistant to anti-cancer therapies than non-melanoma skin cancer. The more common skin malignancies arise from the epidermal keratinocytes but the melanoma arises from the melanocyte, sitting on the dermo-epidermal junction. The difference is the neural crest origin of the melanocyte. Cells of neural crest origin are characterised by being heterogeneous, multipotent, mobile, having a high degree of plasticity and, in development and disease able to demonstrate epidermal to mesenchymal transition. The evolutionary deployment of the neural crest cells allowed early chordate species to transform from thin sessile filter feeders into the more mobile, active, and predatory vertebrates, demonstrating adaptation to a wider range of environmental niches. Mature cells of neural crest origin can also, in certain circumstances, be induced to revert to a precursor, stem cell-like state to access plasticity and immune-modulation. These characteristics can be manipulated to the advantage of the melanoma cell mass to increase tumour invasiveness and progression.

Keywords: Melanoma, Multipotent cells, Neural crest, Ocellus

The Neural Crest

Neural crest cells (NCC) are transient, multipotent, migratory cells of ectodermal origin. They are of relatively recent evolutionary origin, found only in vertebrate embryos and represent a highly multipotent population of embryonic stem cells. These cells were essential for the construction of the vertebral body plan. The particular features of tissues derived from neural crest cells allowed sessile filter-feeding ancestors to evolve into an active, mobile predator, rapidly ascending to the top of the food chain. In particular, the evolution of an animal with a head, containing an osseous jaw with dentition combined with a concentration of advanced sensory systems. This was supported by an improved endocrine system and fast neural transmission from peripheral sensors, allowing reliable regulation of function by the central nervous system (CNS). An understanding of the evolution of the neural crest and the dissemination of its multipotent cells goes some way to explain the novel characteristics and the differences in response and behaviour of this heterogenous group of cells. Adameyko proposed that the neural crest originates from neuroepithelial progenitors of pigmented ocelli in Amphioxus-like animals.[1] With changes in photoreceptive needs these photoreceptors evolved into neural, glial and pigmentary progeny that gained the ability to migrate out of the central nervous system, providing a more useful role at the periphery. The neural crest represents a model for addressing the mechanisms behind evolutionary innovation.

Neural crest in embryological development

Development of the neural crest begins in the dorsal neural tube where neuroepithelial progenitors undergo an epithelial to mesenchymal transition and delaminate into the sub-epithelial space Figure 1.

Inductive and specification events combine with navigational clues to guide the cells along various routes to their final, more peripheral destinations. The majorities of neural crest-derived cells remain multipotent at the beginning of migration but gradually become more restricted in their differentiation potential on their journey to their destination. Recent studies suggest that some populations of NCC may become specified within the neural tube.[2]

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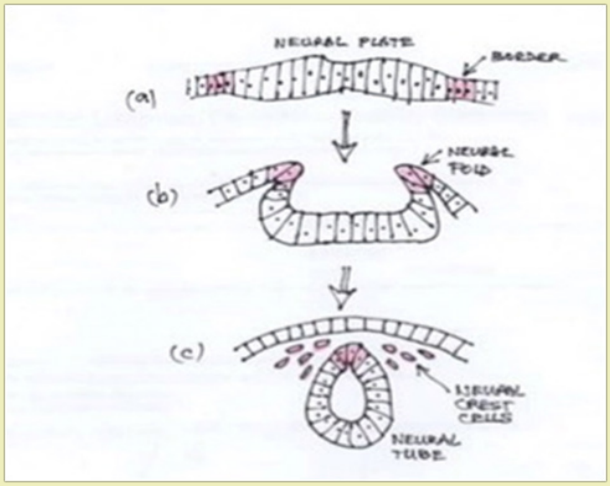

Figure 1: Neural crest formation. Diagram showing transverse section through the ectoderm layer. (A) Neural crest cells arising at the neural plate border. (B) As neurulation proceeds they are incorporated into dorsal neural folds. (C) Epithelial to mesenchymal transition in a rostro-caudal wave preceding migration to the periphery..

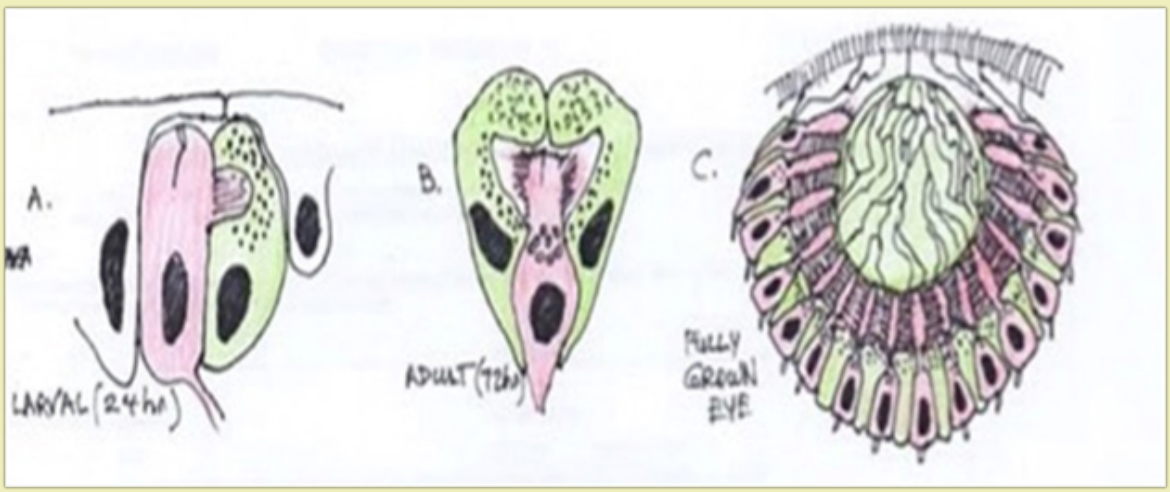

Figure 2: Two-celled larval eye and prototype pigment-cup eye with rhabdomeric photoreceptors in Playnereisdumerilli. Note the nuclei of the photoreceptor cells positioned behind the shielding pigment granules.
Red-Rhabdomeric photoreceptor cell; Green-pigment cells. (Adapted from Arendt 1917).

The proto-eye

Gehring and Ikeo have suggested a two-cell proto-eye, made of one photoreceptor cell and one pigment cell,[3] resembling the two-celled eye represented in primary ciliary larvae such as *polychaete trochophore*[4] Figure 2.

This point is to a very early evolutionary relationship between photoreception and pigmentation-A relationship that has persisted into modern mammalian anatomy. The proto-eye is represented in many invertebrate groups as the simple pigment cup eye-photoreceptors embedded in a cup-shaped layer of shaded pigment. It appears that the animal eye relies on the basic principle of a photoreceptor in the vicinity of dark shielding pigment. The receptor converts light (Photon stream) into intracellular signaling. The dark pigment (melanin in vertebrates) reduces photon scatter and orients the direction optimally sensitive to light. Not only can melanin absorb photons, but also electrons and free radicals such as reactive oxygen species, and so acting as a chemical filter for sensitive cells such as the light sensing organs found in primitive chordates.

Evolutionary origins of the neural crest

I support Adameyko's hypothesis that multipotent progenitors of the ocellus could be an evolutionary origin of the neural crest.1 but would state it a little more broadly and say that the evolution of the neural crest started with the exit of pigment cells from the central nervous system (CNS) to give rise to a pigmented integument but I am not prepared to hypothesise which organism first expressed a neural crest. The final elaboration of the total neural crest cell (NCC) lineage probably occurred incrementally through different vertebrate taxa. At the level of the cyclostomes, in the Cambrian period approximately 500 million years ago, there were already an evolutionarily conserved neural crest-gene network (NC-GN) involving specifiers, migration controllers and effectors. And in the early Chordata phylum, represented by sessile marine tunicates (Urochordata) there was an expression of a component of the NC-GN with migrating pigment producing cells. The origin

of these cells remains controversial. Other deuterostomes, eg. Sea urchins, acquire pigment cells of mesodermal origin. There are several lines of research, however, that support a CNS origin. Bronner-Fraser and Baker proposed that melanin containing cells in Ascidian CNS might be precursors of melanocytes[5] and Abitua and Devine demonstrated that a particular tunicate possesses a cephalic melanocyte lineage that can be reprogrammed into a migratory multipotent population producing cells of mesodermal origin.[6] These cells have components of the NC-GN and give rise to melanocytes of the light-detecting ocellus and otolith.[7] Signalling pathways governing specification of the Ascidian ocellus are conserved in vertebrate neural crest lineage such as Wnt signalling and Fox D-mediated repression of MITF. However, the MITF/Fox D relationship may relate back to the most primitive photo-sensory structures with no relationship to future NCCs. Another interesting feature of early chordate biology is the adult Ascidian ganglion, derived from the embryonic neural tube but capable of regeneration after damage.[8–10] So, derived from the CNS but acquiring a regenerative potential, a characteristic of neural crest derived cells but not expressed by CNS cells.

Early photoreceptors, like the ocellus, use a rhabdomeric photo-sensory cell in conjunction with a pigmented cup cell for light sensing. Vertebrates use ciliary photo-receptors with an alternative signal transduction cascade, in the retina for vision. Melanocytes include a rhabdomeric photo-sensory pigment, melanopsin. Rhabdomeric systems are used more widely in non-vertebrate visual apparatus. Ademeyko likens the melanocyte to a tiny ocellus, but in vertebrates there have been a reversal of roles. Ciliary receptors being used exclusively in the eye for visualisation. The light sensitive protein melanopsin now used in melanocytes to balance response to circadian rhythms and melanin used for pigmentation. In the most basic chordates, melanopsins are found in rhabdomeric photoreceptors (Hesse organs), consisting of a photosensitive cell and a melanin containing cell.[11,12] These two components are conserved together in the melanocyte, suggesting an evolutionary connection. New environmental circumstances, however, have required a change of function of the photo-sensitivity/melanin combination from photoreception to light-controlled pigmentation for camouflage and protection against ultraviolet radiation. Melanocytes have to survive considerable genotoxic stress and pigmentation plays a critical role in survival and reproduction for the emerging homo genus, a less hirsute and naked human predecessor, fully exposed to the sun. Melanin protects against DNA and folate damage and formation of free radicals. Pigmentation has also been hypothesised to affect adaptation to ambient temperature and sexual selection.

Heterogeneity

NCCs are embryonic progenitors that generate a bewildering array of cell types in vertebrates Figure 3.

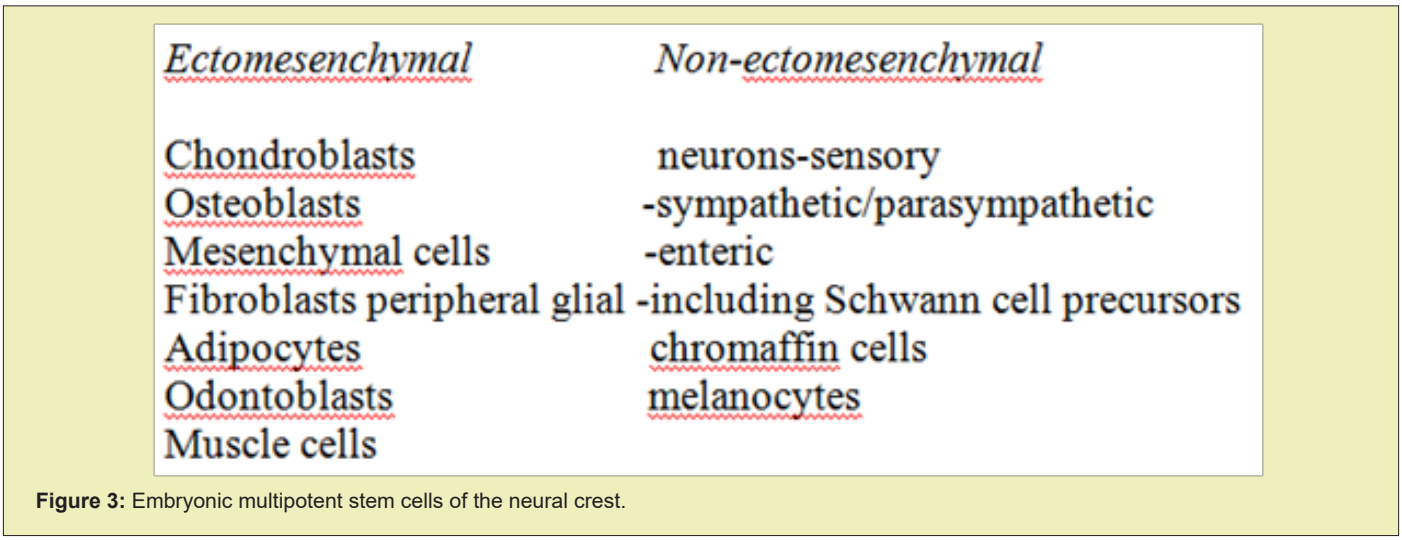

Figure 3: Embryonic multipotent stem cells of the neural crest.

Trunk NCCs produce neuronal, glial and pigment cell progeny, whereascranial NCCs also produce facial bone and cartilage derivatives. Together they build the head, teeth, neuroendocrine tissue, autonomic and sensory nervous systems and provide pigmentation. Up to early migration, NCCs progress through a sequence of common transcriptional states, followed by fate bifurcations during migration, as a series of sequential binary decisions. There is an initial separation of sensory neuron-glial fate, followed by a separation of autonomic from mesenchymal fate. Cell fate commitment culminates with activation of mutually exclusive, fate-specific gene expression programs. Twist 1, normally activated upon delamination, only in the cranial compartment, is sufficient to reverse the trunk neural crest development pattern to mesenchymal routes.

Nerve-melanocyte relationship

In embryonic development, peripheral nervous tissue and melanocytes arise from a common neuro-ectodermal source as part of the neural crest. The progenitors are multipotent and are capable of self-renewal and as adult cells some retain stem cell-like characteristics.

Adameyko et al were able to demonstrate Schwann cell precursor (SCP)-to-melanocyte transition *in vivo* with mouse and chick embryos in normal development. They identified growing nerves projecting throughout the body as a stem cell/progenitor niche containing SCPs from which large numbers of skin melanocytes originate.

They also found that Schwann cell and melanocyte development share signaling molecules with both the glial and melanocyte cell fates linked to nerve contact and regulated in an opposing manner by various growth factors.[13] All melanocytes are specified by microphthalmia-related transcription factor (MITF), that activates many genes required for melanogenesis. They found a peripheral decline in Sox2 in nerves might make SCPs susceptible for an induction of MITF and differentiation into melanocytes.[14] Figure 4.

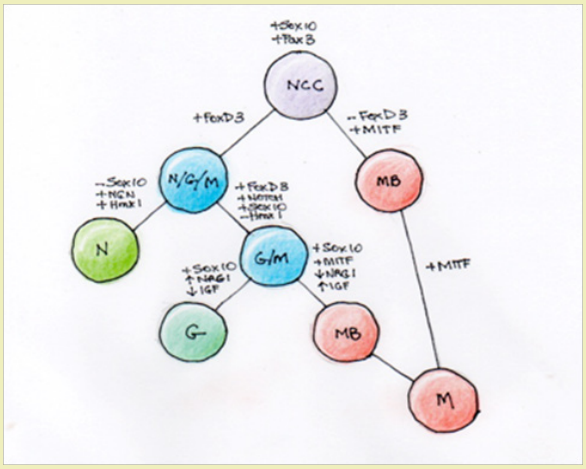

Figure 4: Transcription factors and hierarchical relationships associated with diversification of Neural crest cells in the trunk. NCC, neural crest cells; N/G/M, neuronal/glial/melanoblast progenitors; MB, melanoblast; NRG1, neurogenin 1; IGF, insulin-like growth factor; Hmx 1-homeobox transcription factor; N, neuronal committed cell; G-glial cells; M-melanocyte. (Adapted from Ernfors 2010).

In the development of melanocytes and neurons the two cell types follow similar migration pathways to the periphery and their mature structure, consisting of extended dendritic processes to communicate with surrounding cells is also similar. In both cell types their differentiated function is influenced by neighboring cells. They concluded that a large number of melanocytes in hair follicles and the interfollicular dermis, representing nearly all populations of melanocytes in the trunk skin of adult mice, are of SCP origin. They also showed that myelinating mature Schwann cells retain the capacity to differentiate into melanocytes after injury.[13]

Skin repair

Studies from animals that can regeneratelimbs, such as amphibians and reptiles, showed that tissue regeneration required nerve innervations.[15] Johnston et al went on to investigate the role the peripheral nervous system in skin repair in adult mammals. They found that there were cells of neural crest origin expressing Sox2 in nerve terminals around the hair follicle bulge and following injury, induced in nerve derived cells. Post-injury these Sox2-positive cells were scattered through the regenerating dermis. They suggested that these cells were de-differentiated Schwann cell precursors. Their data demonstrate that Sox2 regulates skin repair controlled by these neural crest-derived precursors and they play a general role in mammalian tissue repair.[16]

Peripheral nerve damage repair

A beautiful example of the adaptive capacities of neural crest-derived cells is demonstrated with the repair potential of the Schwann cell, one of the sub-lineages of the neural crest and the common axonal glial support cell of the PNS, in response to nerve damage. Following nerve injury, the Schwann cell reverts to a progenitor-like state with stem cell-like plasticity, through activation of cell-intrinsic transcriptional programs. The initial part of the process is called Wallerian degeneration, wherein Schwann cells lose contact with their neuron, undergo trans-differentiation which enables alternative gene expression programs that turn off myelination and aid break down of the myelin sheath and neuron distal to the neurotrauma. They also encourage immunomodulation through the release of chemo-attractive cytokines. This trans-differentiated Schwann cell is called a repair Schwann cell (rSC) Figure 5. Post-injury, this is followed by axonal repair and return to normal Schwann cell function with re-establishment of the myelin sheath.

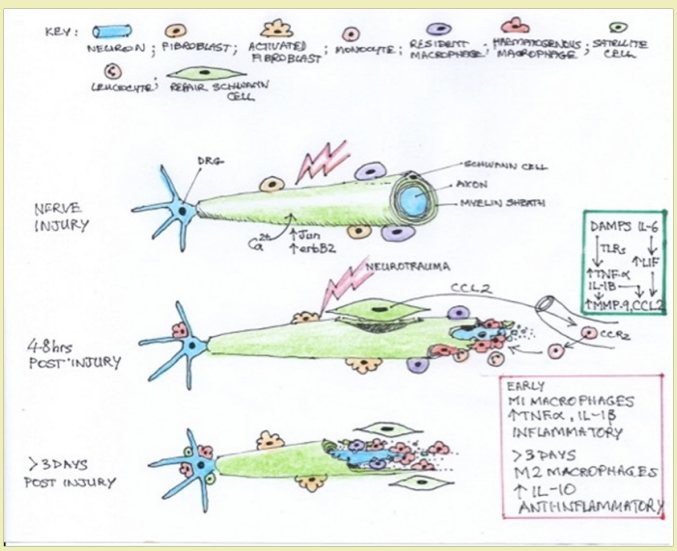

Figure 5: Cells and molecules involved in Wallerian degeneration.

Within minutes of axonal injury Ca^{2+} enters the nerve initiating axonal breakdown. DAMPS stimulate de-differentiation of Schwann cells, through upregulation of Jun and erbB2. TLR signalling by de-differentiated Schwann cells upregulate pro-inflammatory molecules (green box). Increased TNFα and IL-1β upregulate MMP-9 and CCL2 and within hours fibroblasts upregulate IL-6 and GM-CSF. Repair Schwann cells respond to IL-6 from fibroblasts further upregulating CCL2. Neutrophils infiltrate briefly within day 1. By 3 days post-injury macrophages have accumulated, phagocytosing the myelin debris, resulting from ongoing degenerative processes. There are two sites of action of macrophages in response to nerve injury, the distal nerve and around the injured neuronal bodies. They also contribute to inflammation by production of TNFα and IL-1β. Phagocytosis is augmented by resident macrophages. M1 markers are present early but become M2 markers beyond day 3, and remain elevated for 14 days. Once myelin degeneration is complete there is an upregulation of anti-inflammatory IL-10 leading to downregulation of pro-inflammatory cytokines. Removal of debris, which is inhibitory to regenerating axons, is a prerequisite for successful regeneration. CCL2, chemokine C-C motif ligand 2; DRG, dorsal root ganglion; DAMPS, danger-associated molecular patterns; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; Jun, gene for transcription factor AP-1; LIF, leukaemia inhibitory factor; MMP-9, matrix mellatoproteinase-9; TLF, toll-like receptor; TNFα, tumour necrosis factor α. (adapted from Defrancoesco-Lisowitz 2015).

Immunomodulation

As well as changes in gene and transcription factor expression, there is also immune modulation. rSCsacting together with fibroblastssecrete cytokines promoting infiltration of immune cells, particularly myeloid regulatory cells, coordinating and supporting nerve repair and promoting wound healing, including non-neuronal tissue.

This response, however, also acts to control immunosuppressive potential of the tumour immune-environment. Martyn et al found that melanoma-treated Schwann cells, but not control Schwann cells, enhanced myeloid-derived suppressor cell's (MDSC) ability to suppress T cell proliferation *in vitro*. They also determined that the mechanism was related to an increased expression of myelin-associated glycoprotein (MAG), an inhibitor of axonal growth selectively localised in Schwann cells.[17] The invasion of the melanoma cell mass causing nerve injury accelerates the growth of melanoma resulting from modulation of the local microenvironment by Schwann cell-derived repair cells. Promotions of epithelial to mesenchymal transition (EMT)-transcription factors activate tumour cells as well as the Schwann cell, increasing mobility and transmigration. This process of immunomodulation is seen in a number of other diseases, including Leprosy, Tasmanian devil facial tumour disease and some autoimmune neuropathies.

Melanoma cells reprogram Schwann cells

Melanoma invasion of the dermis may destroy or displace nerves. While neurodegenerative processes are occurring within the tumour. Gene expression by nerves and Schwann cells at the tumour edge phenotypically mimic response to neurotrauma. Most intra-tumoural nerve or Schwann cell markers are strongly expressed by melanoma cells.[18] Chronic cancer-induced reprogramming of the Schwann cells in the tumour milieu is characterised by a non-resolving neurodegenerative process unlike normal tissue regeneration, being reminiscent of the concept of a non-healing wound. These melanoma-induced transactivated Schwann cells have enhanced plasticity, mobility, extracellular matrix reorganisation, and macrophage attraction. This creates a paradigm where Melanoma cells reprogram Schwann cells, initiating nerve injury response in surrounding tissues. Having a common neural crest progenitor, they share signalling axes with the peripheral nervous system including response to neurotrophic factors. This results in accelerated tumour growth *in vivo* due to modulation of the local microenvironment by activated Schwann cells. In relation to NRG signalling, Schwann cells secrete NRG-1 and express epidermal growth factor-like receptors (ErbB2 and 3 dimerise to produce a high affinity receptor) in response to axon damage, suggesting autocrine interaction. Autocrine regulation of cell proliferation and differentiation has been reported in other tissues and carcinomas. This autocrine activation of the ErbB receptor complex by NRG-1 has also been observed in non-small cell lung cancer, accelerating tumour growth and affecting prognosis.[19]

Dorsal root ganglia neurons, located within the melanoma-harbouring dermatome, also express markers of nerve injury. Considering that axons and glia exist in a constant state of interaction, it is therefore likely that both axons and glia participate in the nerve repair response triggered by melanoma. Dorsal root ganglia may further promote tumour growth *in vivo*.[20]

Pro-survival role of MITF in melanoma

Melanoma is a therapy resistant malignancy due, in part, to numerous mechanisms supporting cell survival. Several genes mediating pro-survival functions have been identified as direct targets of Microphthalmia-associated transcription factor (MITF), a melanocyte-specific mediator also recognised as an oncogene in melanoma. Mutated BRAF and other proteins deregulated in melanoma influence MITF expression and activity.

In melanoma, elevated oncogenic signalling with hyperproliferation and regulatory disruption causes DNA damage that needs to be balanced by pro-survival mechanisms in these malignant cells. Common cancer cell strategies are enhanced DNA repair[21] and resistance to apoptotic signals.[22] In melanoma, these cells derive from melanocytes, characterised by pre-existing pro-survival mechanisms as an adaptation to the extrinsic threat of ultraviolet radiation and intrinsic production of highly reactive intermediates of melanogenesis. Both of which have the potential to disrupt intracellular homeostasis.

A range of transcriptional factors contribute to the melanoma pro-survival phenotype. MITF plays a central role with a number of transcriptional factors promoting or inhibiting MITF expression Figure 6.

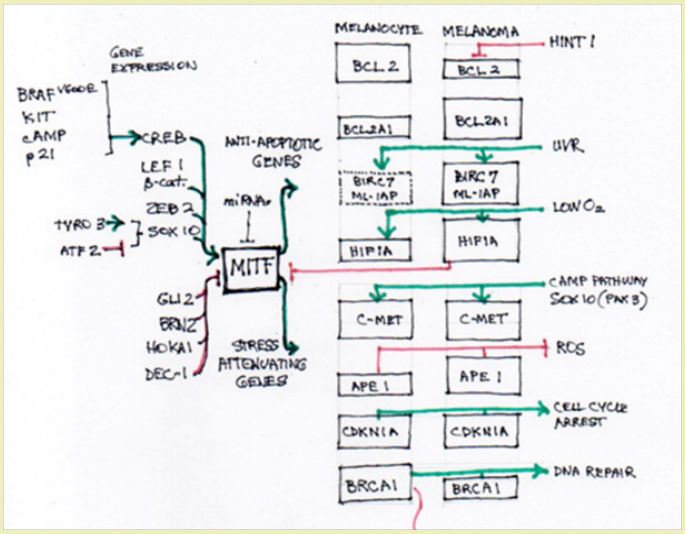

Figure 6: Regulation of MITF expression and pro-survival effects in melanocytes and melanoma cells. (Adapted from Hartman 2015).

MITF regulates anti-apoptotic and stress attenuating genes. Gene expression promoting, green; Gene expression inhibiting, red. Target genes are expressed in melanocytes/melanoma cells at different levels (box sizes).

ML-IAP is not normally present in melanocytes (dashed box) but can be expressed in response to UVR, in a MITF dependent manner.

Additional regulators can interfere or support expression of MITF target genes.

APE1, apurinic/apyrimidinic endonuclease 1; BCL2, B-cell leukaemia/lymphoma 2; HIFIα, hypoxia inducible factor 1α; HINT1, histidine triad nucleotide binding protein 1; MITF, microphthalmia-associated transcription factor; ML-IAP, melanoma inhibitor of apoptosis; ROS, reactive oxygen species.

BRAFv^{600E} can also be a positive or negative regulator. Depending on expression levels and post-translational modifications. MITF in melanoma cells can either promote differentiation or proliferation. High activity promotes differentiation, preceded by p16- and p21-mediated G1 cell cycle arrest. Low activity results in a stem cell-like, invasive phenotype. MITF, the master regulator of the melanocyte lineage during development has its activity enhanced by genetic/epigenetic changes generated within the melanoma. The transcript expression can also be regulated by the microenvironment via micro RNAs (miRNAs). Cellular context and tumour microenvironment influence MITF expression and activity resulting in modulation of melanoma cell phenotype Thus, MITF can be expressed at different levels in distinct subpopulations of a heterogeneous tumour mass. Melanin synthesis is considered the major mechanism protecting skin from damaging effects of UVR but MITF also promotes other cell survival strategies independent of melanin synthesis.

Discussion

I am a clinician with a special interest in melanoma and as such you are continually struck by the potential aggressive and lethal nature of invasive melanoma and its resistance to therapeutics. There are some striking differences in behaviour between it and its non-melanoma skin cancer relatives. Obviously, the melanocyte as the cell of origin rather than the keratinocyte and inevitably the neural crest origin of the melanocyte and its malignant offspring the melanoma cell. During evolutionary development aspects of the Neural crest began to appear in early chordata and eventually reached full expression in vertebrates. Protochordates were thin transparent sessile filter-feeders sitting in burrows on the sea floor but with evolutionary development grew in size, became more mobile, a prominent head with a concentrated array of sensors and a jaw with teeth. These changes are possible through the elaboration of the Neural crest cells. These cells are pleuri-potent, heterogeneous and mobile. They were responsible for a cellular movement out of the central nervous system to provide a peripheral neuroendocrine system with peripherally placed sensors in the skin, including the melanocyte. With this came co-opting of other systems and cells and changes of function to suit new needs and environmental niches. The key word here is adaptability and is provided by these Neural crest cells. The pigment cell which began life as an accompaniment of a photosensitive cell in the ocellus, the light sensing Hesse organ of the filter feeder, is now a peripheral sensor in the skin responsible for camouflage and protection of the keratinocytes from the new threat of ultraviolet radiation. A photo-sensory protein, Melanopsin, is still present in the melanocyte but it is now used for circadian rhythm control a change in function but also a clue to its evolutionary origins. Associated with these changes was an ability to repair and regenerate. The peripheral glia is responsible for support of neuronal tissue and closely related to their CNS cousins but of Neural crest origin, now having the ability to repair nerve damage that the CNS glia and neurons do not have. When faced with nerve injury these peripheral glial cells can change gene expression programs, de-differentiating to a progenitor phenotype with a different range of functions, changes in levels of communication and release of cytokines attracting macrophages, immune cells of the central system, adding another layer of plasticity to the

existing immune and inflammatory changes. The keratinocyte has a short, one month, life-span. The melanocyte is more long-lived and is subjected to years of ultraviolet radiation exposure. The melanocyte has a range of unique survival mechanisms but may eventually succumb to a series of mutational events leading to melanoma. The melanoma cell mass shares potential gene expression programs of the other Neural crest cells and as such can show heterogeneity, plasticity and adaptability of its cell mass in response to a perceived threat, resulting in resistance to therapeutics.

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Conflicts of interest

Author declares that there is no conflict of interest.

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