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Disparity between Melanoma and Non-Melanoma Skin Cancer

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Abstract

Sun exposure is the primary environmental risk factor for melanoma and non-melanoma skin cancer. Non-melanoma skin cancer conforms to the expected site distribution of the most exposed body sites, but the pattern of site distribution with melanoma is more complex. Melanoma is a more aggressive tumour and shows more resistance to therapeutics because of its different cell of origin but some aspects of its site distribution remain elusive. The term melanoma in this discussion applies to cutaneous melanoma only.

1. Introduction

The time has come to appreciate that there are major disparities in incidence, site of predilection and basic nature of melanoma and non-melanoma skin cancer (NMSC). For too long the nature of these two entities have been linked together under a single label, and this has been unhelpful, particularly in relation to understanding the pathogenesis of melanoma.

NMSC relates to the keratinocyte and melanoma to the melanocyte, two very different cell types although they function together as a unit in skin protective measures. Keratinocytes are of ectodermal embryological origin. Born on the basal layer of the epidermis, moving up through the strata of the epidermis as they complete their differentiation to be shed at the surface a month, or so later.

The melanocyte, however, arises from the neural crest, in neuro-ectoderm at the margin of the neural tube. It develops from a melanoblast, a pluripotent precursor that migrates to the skin from its origin and takes its place along the dermo-epidermal junction and hair follicle as a fully differentiated, low proliferative and an extremely long-lived cell, in contrast to the keratinocyte. I consider the melanocyte a specialised neural receptor, placed in the skin to detect solar radiation, and being given some autonomy from the central nervous system to sense environmental conditions and adapt appropriately by providing

protective melanin to its surrounding keratinocytes through a system of autocrine and paracrine messaging. “During vertebrate evolution, the process of photoperiodic regulation has been transferred along with the responsible cells from the nervous system into the skin i.e. closer to the surface of the organism, where it then produced secondary functions like photoprotection via skin/ hair melanogenesis or a remote control of selected functions of visceral organs” [1].

The melanocyte has particular biological features that allow it to persist in the dangerous organism/environment interface over most of the lifespan of the body. Pluripotency along with migratory machinery means that with malignant transformation there can be reanimation of embryological potentialities that can result in very malignant behaviour. This is combined with cellular antiapoptotic pathways that allow for its long lifespan, giving it particular resistance to therapeutic measures. Cellular receptors and intercellular molecular cascades communicate to bypass introduced blocking agents through adaptive mechanisms. Effectiveness of antiapoptotic capacity allowing the accumulation of multiple mutations supporting malignant behaviour with transformation from melanocyte to melanoma and a reanimation of the proliferative and migratory nature of its progenitor.

For melanoma and NMSC, both tumour types show an increasing incidence, but stable or decreasing mortality, over time. Rising rates of NMSC are caused by a combination of increased outdoor recreational activity, changes in clothing style, increased longevity, and immunosuppression. The relationship between sun exposure and melanoma incidence is less clear [2]. The highest incidence rates of melanoma are reported from Queensland, Australia but with stabilised mortality rates. Tumour thickness is the most significant prognostic factor in primary melanoma with an ongoing trend to thin melanomas at the time of diagnosis. Campaigns for prevention and early detection have altered site distribution and thickness at presentation but remain necessary through public heath messages and specialised skin cancer clinics.

2. Site Distribution

Sun exposure is the main environmental risk factor for both melanoma and NMSC. The relationship between sun exposure and melanoma incidence is, however, more complex. Squamous cell carcinoma, for example, occurs mostly on the face and backs of hands and forearms, and thus, is clearly associated with excess sun exposure. Cutaneous melanoma occurs frequently not only on chronically exposed sites such as the face but even more commonly on the back in Australia, predominantly a fairer skinned population of Anglo-Celtic heritage. There is evidence that the relationship between melanoma and patterns of sun exposure varies according to age, site and morphology [3,4]. After adjusting for surface area, rates of melanoma tend to be highest on intermittently exposed sites in the under 40-year age group. That is the trunk for males and the lower limb for females. It seems paradoxical that melanoma should occur frequently on skin covered with clothing [5-7], and rates are higher with indoor rather than outdoor workers [8-10], unless it is appreciated that regular sun exposure is necessary to allow for adequate adaptive skin protective processes and changes. Over 60 years of age, melanoma is most common on the more chronically exposed sites, in common with NMSC, such as the head and neck [11]. David Whitman et al found that head and neck melanomas were statically significantly more likely to occur in people with fewer naevi but with more solar keratoses and a history of solar keratosis treatment in the past. They also occurred in people with higher levels of occupational sun exposure. This led to his proposal of a divergent pathway hypothesis [3]. A model built from epidemiological [12] and animal studies [13] hypothesising two pathological pathways to melanoma. He suggests that early exposure initiates transformation in melanocytes and that factors that drive development vary according to phenotypic and environmental conditions experienced

by the patient. This led him to hypothesise that naevus prone individuals tend to induce melanocytes to proliferate without necessity for further exposure, particularly patients with numerous or ontogenetically unstable melanocytes on the trunk [14,15], whereas in patients with a lesser tendency to naevus growth their melanocytes required further exposure to drive the development of melanoma. He found that, amongst this group, melanomas will tend to arise on sun exposed body sites at older ages and be associated with solar skin damage and history of NMSC lesions. This hypothesis was supported by an Australian case-control study of the distribution of naevi and solar keratoses with melanoma of the head and neck, finding substantially fewer naevi and more solar keratosis than in patients with melanoma on the trunk or legs [16].

3. Divergent Pathways for Early or Late Onset Melanoma

American investigators interrogated statistics from a SEER9 database for melanoma (cutaneous malignant melanoma) from 1975-2004 linking melanoma histopathology with somatic and germline genetic variants, sun-exposure and anatomic body site concluding that there are divergent pathways for early- and late-onset melanomas, again supporting David Whiteman's divergent pathway hypothesis [3]. Early onset melanomas possibly representing gene-sun exposure interactions, occurring early and/or intermittently among susceptible individuals. Whereas late onset may reflect accumulated life-long exposure in comparatively less-susceptible individuals [4].

4. Adéle Green's Hypothesis

Adéle Green proposed a theory of site distribution of melanoma from observations of the distribution of naevus-related melanomas in Queensland, Australia. She found the variation in the proportion of melanomas with adjacent naevi not explainable by regional variation in naevus density suggesting variable susceptibility of naevi to malignant change and explaining the high incidence of melanomas on less sun-exposed areas such as the back, as well as on chronically exposed sites such as the face and supporting her hypothesis that melanocytes have differential response to mitogenic stimulus of sunlight according to anatomical site [12].

5. Australian Childhood Naevus Study

An Australian childhood naevus study observed density and size of naevi at different body sites in relation to age, phenotype, latitude and other measures of ultraviolet exposure. In Queensland, at least, gender differences in naevus density on the back and lower limbs, unrelated to sun exposure, were similar to gender differences for melanoma. Small naevi (2 mm - 4 mm) were most dense on the arms, whereas large naevi (>5 mm) were most dense on the posterior trunk where they were related to age, decreased latitude, male sex and freckling. Their findings support Green's hypothesis of site-specific differences in naevus proliferative potential [17].

6. Childhood Sun Exposure as a Risk Factor for Melanoma

Whiteman and Green collaborated on a review of epidemiological studies to determine the strength of evidence suggesting that childhood is a particular period of susceptibility to the carcinogenic effects of solar radiation [18].

The concept of a "critical period" in childhood for the initiation of cancer had already been demonstrated in leukaemia and cancers of the breast and thyroid among survivors of nuclear fallout in Japan, Belarus and the Marshall Islands [19]. Tissues that undergo post-natal development are especially vulnerable to environmental carcinogen exposure in childhood [20] with peak melanocytic activity in early life [14]. This concept having obvious implications for primary prevention.

With this in mind they systematically reviewed epidemiological literature in relation to timing of sun exposure to melanoma risk looking at ecological and case-control studies.

There are obvious inherent difficulties in measuring and comparing historical sun exposure recall resulting in a clearer picture emerging from ecological rather than case-control studies. They accepted as higher quality the evidence from ambient exposure studies that high levels of sun exposure in childhood are associated with substantial increases in risk of melanoma. However, they also accept that the effects of adult exposure cannot be dismissed. This was specifically addressed in two studies showing that age of migration from countries of low to high exposure gave stronger evidence than duration of residence [21,22].

The results of these studies led them to develop their model of initiation-promotion-progression of melanoma.

- Initiation phase-melanocytes can be transformed in early life through ultraviolet radiation (UVR) which is determined by host susceptibility factors.
- Promotion and progression phase-progression to neoplasm through either further UVR and associated with p53 expression, NMSC and appearing on exposed sites, or a naevus pathway associated with naevus density and freckling propensity [11].

7. Sex-Site Interaction

Anderson et all's age-related differing cancer pathways for melanoma [4] showed that sex, site and histopathology are age dependent effect modifiers of melanoma risk, however they should also have considered sex-site interactions [23].

It is fair to say that sex-specific risk patterns of melanoma by site are rarely studied because there is an assumption that differences in melanoma between the sexes are not considered to be biologically relevant. A Swedish study, however, observed a striking difference in age-distribution of trunk melanoma between the sexes. Incidence rates displayed a steady increase with age in men but plateaued in women from perimenopausal ages [24]. This age-distribution in trunk melanoma in women mirrors age changes in breast cancer rates around menopause suggesting a modulatory role of sex hormones. The role of hormones in melanoma is not well understood although melanocytes are known to express oestrogen receptors [25]. Melanomas on intermittently exposed sites such as the trunk present frequent *BRAF* mutations, strongly associated with *Melanocortin 1 receptor* (*MC1R*) polymorphism, the expression of this gene modulated by endocrine sex hormones [26].

8. Aetiology

There is aetiological heterogeneity of melanoma development and tumour progression with possible links between advancing age, solar exposure patterns and constitutive molecular changes. Recent molecular studies have linked melanoma

histopathology with somatic and germline genetic variants, sun exposure and anatomic body site [4]. Lentigo maligna melanoma associated with proto-oncogene *KIT* mutations and p53 overexpression. Presenting as late onset combined with chronic sun damaged skin from life-long high exposure patterns [11,27,28]. Whereas early onset and less sun damaged skin is associated with somatic *BRAF* or *N-RAS* mutations and germline *MC1R* variants in some populations [29-32]. Although not all clinicians acknowledge the importance of melanoma histopathological classification, e.g. Bernie Ackerman's unifying concept [33]. Also, 40% of approximately 100,000 melanomas in SEE9 remaining unclassified and the American Joint Committee of Cancer staging for Melanoma does not include subtype in their currant prognostic scheme. Therefore, the clinical relevance of histopathology for melanoma remains uncertain.

9. Determinants of BRAF Mutation in Melanoma

Maldonado et al found that BRAF mutations were statistically significantly more common in melanomas occurring on intermittently sun exposed skin than otherwise. This contrasted with melanomas on chronically sun damaged (CSD) skin and relatively or completely unexposed skin, such as palms, soles, subungual sites and mucosal surfaces where the BRAF mutation is rare [29].

Genetic alterations identified in melanomas at different sites and with different levels of sun exposure indicate that there are distinct genetic pathways in the development of melanoma and this may underly well recognised differences in risk factors and behavioural patterns [34].

10. Melanocortin 1 Receptor and Braf Mutations

Landi et al hypothesise that the high frequency of BRAF mutations that occur in the non-chronic sun exposure pattern group of melanomas is due to a susceptibility factor that occurs with a higher frequency in Caucasian populations [31]. The Melanocortin 1 receptor (MC1R) is G-protein coupled receptor on melanocytes that responds to α-melanocyte stimulating hormone (αMSH) secreted in response to UVR [35]. The MC1R gene is highly polymorphic in Caucasians [36], variants associated with a variable degree of receptor dysfunction resulting in signalling defects that can produce fair skin, freckling and red or fair-haired individuals [37] and associated with a melanoma risk factor [38] beyond pigmentation due to associated defects in DNA repair pathways and antioxidant enzyme mobilization [39] (FIG. 1). They found that BRAF mutations were 6-13X more frequent with at least one *MC1R* variant allele as compared to wild type. Overall, melanoma was higher by a risk factor of 3.3 with any variant allele but even higher with multiple variant alleles [34].

Wakamatsu et al determined that diversity of pigmentation in human melanocytes is due to differences in the type as well as the quantity of melanin. Eumelanin but not always pheomelanin content correlates with the visual phenotype and eumelanin correlates with the ethnic background and *MC1R* variant alleles do not necessarily alter this phenotype but still relate to increased sensitivity to UV-induced DNA damage.

Over half the Australian population carry at least one variant allele and this is independent of their degree of pigmentation so this higher risk cannot be dismissed in individuals with a darker skinned phenotype [40].

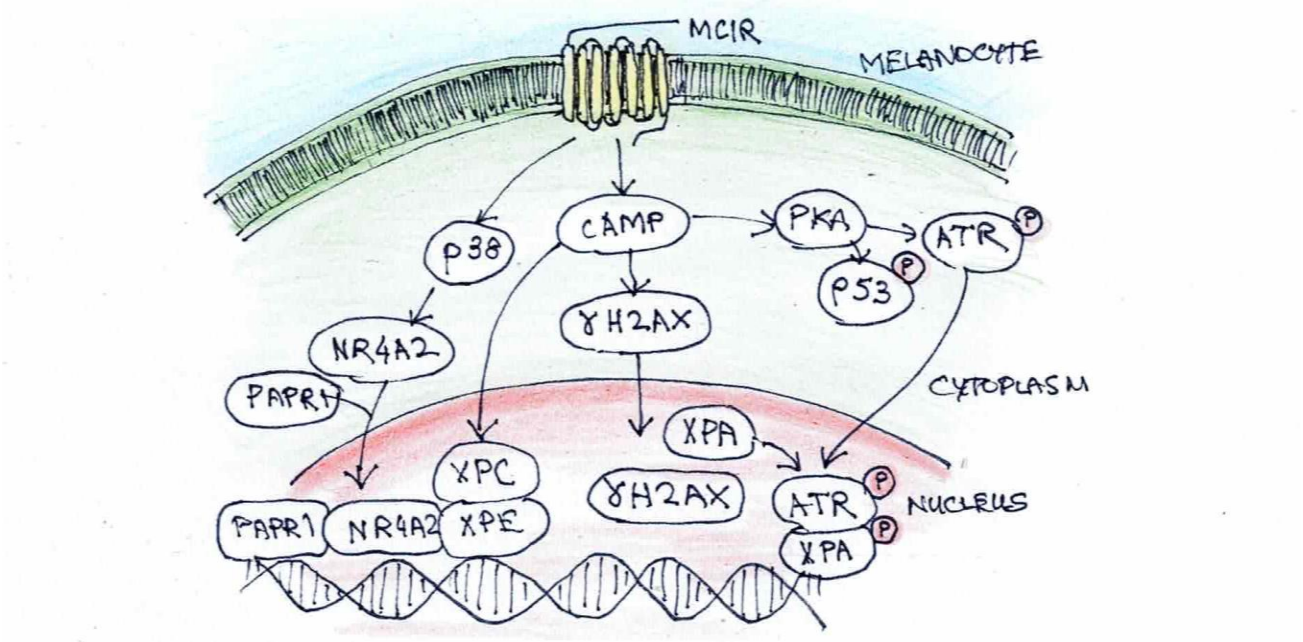

FIG. 1. **MC1R /cAMP signalling cascade promotes melanocyte genomic stability.**

MC1R activation indues translocation of NR4A2 to the nucleus where it colocalises with XPC and XPE (damage sensing proteins) at sites of UV-induced DNA damage. MC1R activation also elevates XPC and ɣH2AX promoting DNA repair complexes. PKA activation promotes phosphorylation of ATR which complexes with XPA in the nucleus following phosphorylation of XPA. The complex translocates to sites of UV-induced damage for enhancement of nucleotide excision repair. ATR, ataxia-telangiectasia and Rad 3-related protein; cAMP, cyclic adenosine monophosphate; ɣH2AX, phosphorylated form of H2A histone family member; NR4A2, nuclear receptor subfamily 4 group A member; PARP1, poly (ADP-ribose) polymerase 1; PKA, protein kinase A; XPA, C and E, xeroderma pigmentosum groups A, C and E. (Adapted from Wolf Horrell et al 2016 [41]).

11. Changes in Site Distribution of Melanoma in Australia

A recent large study in Queensland, Australia observed significant decreases in rates of invasive melanoma in the younger age groups on less frequently exposed body sites. That is the trunk and upper limbs/shoulder for both sexes under the age of 40 years, and among males aged 40-59 years. However, the >60-year age group, the incidence of melanoma is continuing to rise at all sites (apart from trunk), for males on the scalp/neck and upper limbs/shoulders for females. Superficial spreading melanoma is significantly increasing on the scalp/neck and lower limbs, along with Lentigo maligna melanoma, since the late 1990's, at all sites apart from the lower limbs.

They concluded that these results provide indirect evidence for the impact of primary prevention campaigns in Australia that emphasise the use of sunscreens, hats and clothing to avoid excessive sun exposure [42].

12. Conclusion

The melanocyte is a specialised cell of neural origin in communication with both the central nervous system and cells of the local environment. Placed in the skin, the interface between organism and environment, to monitor environmental conditions and risks to make appropriate adaptive and protective changes through pigmentation and DNA repair mechanisms to ensure genomic stability and homeostasis. A cell of adaptation. It needs to be exposed to these environmental conditions and changes to perform its function. This is best achieved through a regular pattern of exposure. The keratinocyte also communicates with its cellular environment and can adapt to UVR damage through increasing cornification, but it has a more static and structural protective role.

Historically there has been controversy as to the nature of the naevus cell. Dermatopathological consensus, based on morphological and biochemical evidence, is now that the naevus cell is a cell of a melanocytic naevus and is purely a melanocyte. The naevus cell undergoing a process of maturation that changes it as it descends into the dermis.

Why then should naevus cells respond differently to the insult of UVR at different sites on the body? Allowing for different levels of UVR exposure, why should covered areas of skin or indoor workers be at higher risk of melanoma development? The answer is that there is lesser opportunity for intermittently exposed skin of these individuals to adapt to their environment, in Australia that is often intense solar radiation. This means introduction of normally intermittently exposed skin to regular mild exposure, preferably early morning or late afternoon exposure, will allow for the initiation of adaptive intracellular cascades the most prominent being the tanning response. Regularity of exposure being more beneficial than intensity of exposure to initiate and maintain protective intra- and inter-cellular networks. The caveat being that over half the Australian population carry a melanocortin 1 receptor variant on their melanocytes that may result in varying degree of MC1R dysfunction resulting in not only subnormal tanning ability but also interference with DNA repair mechanisms and mobilisation of antioxidant systems so regular exposure still needs to be tempered with avoiding intense exposure as much as possible.

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