Melanoma epidemiology, biology and prognosis

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1. Introduction

Melanoma is a cancer arising from the malignant transformation of melanocytes. These pigment-producing cells derive embryologically from pluripotent neural crest stem cells. During foetal development they not only predominantly migrate to and differentiate within the epidermis, but also to other extra-cutaneous pigment-containing sites such as the eyes, meninges, oesophagus and mucous membranes. Three subtypes of melanoma can therefore be characterised: cutaneous melanoma (the most common) arising from melanocytes in the epidermis, mucosal melanoma from melanocytes residing in the mucous membranes and uveal melanoma from melanocytes residing in the ocular stroma. In this chapter we will consider each of these melanoma subtypes in turn, highlighting the differences in epidemiology, biology and prognosis between them.

2. Cutaneous melanoma

2.1. Epidemiology

Cutaneous melanoma is by far the most common melanoma subtype, accounting for in excess of 90% of cases of melanoma [1]. Melanoma is reported as the 19th most common cancer worldwide, with estimated age-standardised incidence rates of 2.8–3.1 per 100,000 [2]. There is considerable variation in incidence between countries, with the highest rates reported in Australia (37 per 100,000) and the lowest in South-Central Asia (0.2 per 100,000). This trend is attributed to variations in racial skin phenotype, as well as differences in sun exposure around the world; in the United States (US), for example, 98.2% of cases are reported amongst white-skinned individuals [1].

Europe lags behind Australia and the United States in terms of incidence rates, but the statistics demonstrate that even within Europe incidence rates vary widely [3]; Switzerland has the highest rates (19.2 cases per 100,000) with Greece recording the lowest (2.2 cases per 100,000). There is also evidence of clear North–South and East–West incidence gradients across the continent. The reason for such marked intra-continental variation in incidence is unclear and may well be associated with differences in affluence and consequent recreational sun exposure. However, it is also likely to be (at least in part) related to discrepancies in cancer registration [4] between different countries, in particular in Eastern Europe.

Unfortunately the incidence of cutaneous melanoma around the world has been rising annually [5–7], at a rate faster than that of any other malignancy. This is of particular concern given the unusual age demographics of the disease. Unlike other solid malignancies, where the majority of cases are diagnosed at over the age of 65, melanoma affects a higher proportion of younger patients, with a median age of diagnosis of 57 years. Age-specific incidence rates increase steadily from the third to the ninth decades of life. There is a female preponderance in younger age groups (4:10 in 20–24-year-olds) which changes to a male preponderance (16:10 in >85-year-olds) after a sharp increase in incidence amongst males from the age of 55 onwards [8]. Estimates from the United States [9] quote a lifetime risk of melanoma as 1 in 56 for women and 1 in 37 for men, with UK estimates at 1 in 60 for women and 1 in 61 for men [10], further highlighting global differences. Australia/New Zealand has the highest global melanoma mortality rate (3.5/100,000) followed by North America (1.7/100,000) and then Europe (1.5/100,000) [3]. Overall, mortality rates are higher amongst men than women [11], perhaps because of the later presentation of disease.

Several risk factors thought to be significant in the development of cutaneous melanoma have been identified by epidemiological studies. These can be grouped into environmental factors and genetic factors, but there is clearly interplay between both genetics and the environment to account for such a wide variation in disease demographics.

Pigmentation has an indisputable and significant influence on skin susceptibility to malignant change. The melanocortin 1 receptor (MC1R) is a melanocyte cell-surface receptor that induces pigment production (via the signalling cascade recruitment of MITF) following activation by its ligand, alpha-melanocyte-stimulating hormone (MSH) [12]. There are

many polymorphisms of the MC1R gene, resulting in the numerous skin-colour phenotypes seen in humans; variants such as the red hair, fair-skinned phenotype express low pigmentation, with a consequent increased sensitivity to ultraviolet (UV) light and associated increased melanoma risk [13].

As implied above, the main environmental factor implicated in the development of cutaneous melanoma is UV radiation. The incidence of melanoma is highest in equatorial regions, and decreases with increasing distance from the equator [14,15]. This directly corresponds with UV light exposure, particularly UV-B levels [16–18], and occurs regardless of skin type. Although a direct causal link has not been established, epidemiological studies [17,19] have repeatedly demonstrated an association between the pattern and timing of sun exposure and melanoma. The majority of cutaneous melanomas arise on sporadically (rather than chronically) sun-exposed skin, in sites and individuals more prone to sunburn. The highest rates are seen in individuals with repeated intense sun exposure. This theory is further strengthened by the observation that patients with melanoma who actively reduce their sun exposure after initial diagnosis are consequently at reduced risk of developing a second primary melanoma [20]. On the contrary, individuals with dark skin, or skin that darkens easily in response to sunlight but does not burn, have demonstrably lower rates of melanoma [17]. Patients with xeroderma pigmentosum (XP) commonly develop cutaneous (and conjunctival) melanomas [21]; these individuals have a genetic inability to repair UV-induced DNA damage, providing further support for the significance of UV radiation in melanomagenesis.

The age at which sun exposure and/or sunburn occurs also appears to be important. Systematic review [19,22,23] has strongly associated intermittent childhood or adolescent sun exposure with a higher risk of melanoma. In particular, individuals experiencing more than five episodes of severe sunburn had a two-fold increased risk of melanoma [24,25].

Although the melanomagenic effects of UV-B exposure are well evidenced, UV-A exposure is not without risk [26]. Long-term follow-up of psoriasis patients has demonstrated that those receiving UV-A therapy are at increased risk of developing melanoma [27]. Sunbeds emit UV-A radiation; a meta-analysis of studies [28] exploring melanoma incidence following sunbed use reported a 75% increase in risk in individuals under 35 with a history of sunbed use. Further studies support this finding, drawing clear associations between melanoma risk and the amount of sunbed usage, particularly from a young age [29–31]. The association was felt to be sufficiently conclusive for UV light from sunbeds to be formally classified as a human carcinogen [28,32]; unfortunately, despite this evidence and consequent public health warnings, sunbed tanning remains popular.

No other conclusive environmental risk factors – including (unusually) smoking – have been identified. Smoking, a common carcinogen, has not been independently associated with melanoma [33]. Interestingly, however, there is an association between melanoma and comorbidities: for example, individuals who are immunosuppressed (due to organ transplantation) are at demonstrably higher risk of melanoma, including recurrence in individuals with resected primary melanomas prior to transplantation [34,35]. Also, patients who have other skin malignancies (basal- or squamous-cell carcinomas) are at higher risk of melanoma development [36] and subsequent disease-related death [37].

It is also important to consider individual genetics when determining personal risk. Clearly genetic factors such as race and skin phenotype affect risk, as discussed earlier, but it has also been estimated that approximately 10% of melanomas are familial in origin [38]. Some of these occur in specific syndromes – such as familial atypical multiple mole and melanoma syndrome (FAMMM) or dysplastic naevus syndrome (DNS) – wherein individuals have multiple and phenotypically variable moles at high risk of malignant transformation, thereby presenting an almost guaranteed lifetime melanoma risk. Many individuals will not meet the diagnostic criteria for these syndromes but still have numerous naevi, often a reflection of cumulative sun exposure. Observational studies suggest a strong association between high naevus counts and melanoma [39,40]. A personal history of cutaneous melanoma is also a known risk factor for further melanoma primaries [41–43].

2.2. Biology

Aside from these familial syndromes, advances in gene analysis technology have allowed the investigation of less common but high-risk alleles that also appear to contribute to cancer risk in individuals. Linkage studies focused on families with a high incidence of melanomas [44–46] identified a melanoma susceptibility locus on chromosome 9p21, subsequently found to represent the gene locus for CDKN2A [47,48]. This gene locus undergoes complex transcription (from alternate reading frames) and thus encodes two proteins, p16 and p14ARF; the majority of mutations affect the former protein [49,50].

p16 normally interacts with and inhibits cyclin-dependent kinase 4 (CDK4). During the normal cell cycle, CDK4 complexes with cyclin D, resulting in phosphorylation of the retinoblastoma (Rb1) protein, in turn releasing E2F-1 and thus allowing it to induce S-phase gene synthesis; p16 therefore acts as a negative regulator of the cell cycle [47,50]. Mutations affecting this important protein disrupt its inhibitory function, thus deregulating the cell cycle. They are therefore thought to prime melanocytes for malignancy. Evidence [51–53] also exists for a pro-melanomagenic effect of germline mutations affecting CDK4 and Rb1 directly. p14ARF also has an important role in down-regulating p53 activity (through increased activation of MDM2), thus also acting as a tumour suppressor; disruption of this activity through mutations could also be tumourigenic [54].

The actual prevalence of CDKN2A mutations is difficult to quantify. In melanoma family studies estimates have ranged from 20% to 57% [50], but in the general population are thought to be considerably lower, in the region of 1.2–2.9% [55]. Gene penetrance estimates are further complicated by the knowledge that the environmental factors discussed earlier further modulate risk in individuals with CDKN2A. Establishing the relative risk contribution from genes is therefore more challenging. There may also be interaction between genetic mutations to modulate melanoma risk further; for example, some MC1R gene variants can increase the penetrance of CDKN2A mutations, thus increasing risk further

[56,57]. A link between CDKN2A melanoma and other malignancies (e.g. pancreatic cancer) has also been demonstrated [58–60].

BRCA2 is well associated with increased risk of breast malignancies, but its role in melanoma is not fully established. Given that some studies [61] suggest an increased risk of melanoma in the presence of mutations in this gene, whereas others [62] have been unable to demonstrate this, no sound conclusions can be drawn regarding this gene. Other genes are also being investigated; genome-wide association studies [63–65] have identified several loci that may correlate with increased melanoma risk, but the biological mechanism of many of these has not yet been established.

Genetic mutations affecting protagonists of the mitogen-activated protein kinase (MAPK) pathway have been found in many tumour types. This key cell signalling pathway is activated by ligand binding to a cell-surface receptor tyrosine kinase (RTK), which in turn activates RAS. The RAS family of G proteins consists of three isoforms, the most important of which is NRAS. NRAS activation results in further pathway signal transduction through phosphorylation (and consequent activation) of the RAF proteins BRAF and CRAF [66]. Homo- or hetero-dimer formation of RAF molecules ultimately leads to the activation of extracellular signal-regulated kinase (ERK) which in turn acts on numerous targets to promote cell growth and survival, as well as controlling further MAPK pathway signalling by inducing the expression of negative regulators [67], and directly inhibiting proteins such as CRAF [68].

Mutations affecting this pathway are present in the vast majority of cutaneous melanomas, predominantly affecting the NRAS (approximately 20%) [69] or BRAF (approximately 40–50%) proteins [70]. In the case of BRAF, the vast majority of mutations constitute a single amino acid substitution from valine to glutamic acid at codon 600 (V600E), resulting in a constitutively active BRAF protein that is consequently able to signal in a continuous and unopposed fashion down the MAPK pathway, thus promoting melanomagenesis and preventing apoptosis [71,72]. Interestingly, a similar proportion of naevi also contain BRAF mutations, implying that these alone are not sufficient for malignant transformation [73].

It is hypothesised that whilst melanocyte acquisition of a BRAF mutation is not the founder event for oncogenesis, it occurs early in the development of invasive melanoma and further enhances the effects of other oncogenic stimuli; thus it facilitates malignant transformation, rather than initiating it. BRAF mutations are more commonly seen in melanomas arising in intermittently sun-exposed sites, implying that UV light (as described earlier) may be one such stimulus. Additionally, as there is significant interaction between intracellular signalling pathways, further genetic aberrations affecting the PI3 kinase pathway, for example, may also be sufficient to induce melanoma development. Once developed, however, there is clear tumour dependency on persistent activation of the MAPK pathway [72].

2.3.   Prognosis

Prognostic factors in cutaneous melanoma have been closely studied; they include histopathological characteristics, patient characteristics, biochemical measures and most recently genetic mutations. Each of these will be considered in turn.

The American Joint Committee on Cancer (AJCC) staging system [74] is globally acknowledged as an invaluable tool in predicting outcomes for patients diagnosed with melanoma. It is based on data derived from analysis of tens of thousands of cutaneous melanoma patients; the current seventh edition was introduced early in 2010 and incorporated new factors not previously used in the estimation of melanoma prognosis.

Histopathological features logically form the main criteria for determining prognosis. Increasing thickness of the cutaneous primary correlates with worsening survival outcomes, dropping from 96% 10-year survival for lesions <1 mm, to 54% for lesions >4 mm; even for lesions <1 mm in thickness, there is further deterioration in outcome between lesions <0.25 mm thickness and those >0.75 mm [75]. Moreover, at each tumour thickness it has been demonstrated that the presence of epithelial ulceration in the primary results in a worse prognosis than if there is no ulceration [76,77]. These two features (tumour thickness and ulceration) are arguably the most powerful independent prognostic factors for cutaneous melanoma [76,78,79]. A third significant pathological feature is the mitotic rate [80,81]; a rate of >20 mitosis/mm^2 results in a 10-year survival of approximately 48% relative to 93% in those individuals with <1 mitosis/mm^2. Other features of the primary associated with higher risk of relapse or metastases are high tumour vascularity (i.e. new vessel formation at the base of an invasive melanoma) [82,83] and lymphovascular invasion (tumour invasion of the dermis microvasculature) [84]; the evidence for these factors is not as conclusive as that for those discussed earlier.

The site of the primary also has important prognostic implications; those arising centrally (trunk, head and neck) tend to carry a worse prognosis than those arising on the limbs (lower < upper) [76,85,86]. Additionally, cutaneous melanoma can metastasise to lymph nodes. The presence of lymph-node disease has adverse prognostic implications, with further variation depending on the burden of nodal disease – both in terms of micrometastatic versus macroscopic disease – and the number of lymph nodes involved. The presence of microscopic lymph-node disease results in 10-year survival rates of 63%, but if macroscopic disease is present this drops to 47% [76,87]. Similarly, there is a 10% 5-year survival deterioration with an increase in the number of nodes involved (from 1 to 3) [87]; for those with macroscopic metastases this increased risk is independent of other primary tumour characteristics. Metastases to other sites have adverse prognostic implications. Satellite cutaneous lesions reduce survival by a similar proportion to lymph-node metastases [88], with worsening prognosis with metastases to the lung and further deterioration with any other organ involvement [74,76].

In terms of patient characteristics, it is well established that age is an independent prognostic factor, with worsening outcome associated with increasing age [76,89,90]. Interestingly, for early-stage (I–II) melanoma, female gender also has positive prognostic implications [78,91–93], possibly related to the higher number of thin, non-ulcerated, extremity

lesions diagnosed in women. The histopathological factors previously discussed are more prognostically significant than gender.

With regard to biochemical features, serum lactate dehydrogenase (LDH) is well recognised as an independent prognostic factor in cutaneous melanoma; in multivariate analysis [74,94] a raised LDH level predicts approximately 50% lower survival rates in patients with distant metastases. Other serum prognostic biomarkers have also been studied; the most promising, S100 protein levels, correlate with survival in patients with resected locoregional disease [95,96], with high levels predicting a significantly worse outcome than with normal levels.

The increased use of gene expression profiling is also providing further genetic prognostic clues. The BRAF gene mutation – which as previously described is integral to melanoma pathogenesis – has been investigated as a prognostic marker too. It appears to be linked to known prognostic factors such as age and site of primary, whilst also being unrelated to factors such as site of metastasis and LDH [97]. In advanced disease, meta-analyses have demonstrated that the presence of a BRAF mutation is independently associated with a worse survival outcome [97–99]. The data in this area continue to evolve.

3. Uveal melanoma

Uveal melanoma is the most common primary ophthalmic malignancy in adults and is associated with resistance to available treatments and poor prognosis. The incidence of uveal melanoma in Europe has been estimated as between 2 and 8 per million [100] and the median age at presentation ranges from 55 to 60 years of age [101,102]. Both US [103] and European [100] studies report that the incidence rate has been stable since the 1970s, and disappointingly there has been no improvement in survival over this time period. There is regional variation within Europe with an increase in incidence from South to North, leading to the hypothesis that ocular pigmentation may be protective [100]. Other incidence studies support this hypothesis.

In the USA the majority of cases occur in the white population [103]; there is a low incidence in South African black populations [104] and in Far East Asian populations [105]. Case–control studies provide further supportive evidence that lighter skin [106] and iris [107–109] colours are a risk factor for the development of uveal melanoma. The role of UV-B radiation in the pathogenesis of uveal melanoma is less clear as studies rely on self-reported retrospective data on exposure to sunlight. Some case–control studies have reported a weak positive relationship between lifetime UV-B exposure and uveal melanoma [106,110], whereas others have reported no relationship [111,112]. Despite this the use of sunlamps is recognised as a significant risk factor for the development of uveal melanoma [106,109].

3.1. Biology

Disruptions in a number of tumour suppressor genes and/or activation of oncogenes have been implicated in the development of uveal melanoma. Disruption of the activity of the retinoblastoma (Rb) tumour suppressor gene leads to uninhibited progression of melanocytes through the G1–S phase of the cell cycle, resulting in deregulated cell proliferation. Cyclin D4, either by over-expression [113] or lack of inhibition by the tumour suppressor gene INK4a [114], phosphorylates Rb resulting in its inactivation [113]. The p53 tumour suppressor gene is often functionally inhibited by the over-expression of HDM2 resulting in the inhibition of apoptosis [115]. Also PTEN, a negative regulator of the PI3K-AKT pathway, is frequently inactivated or down-regulated in uveal melanoma leading to increased cell proliferation and survival [116].

More recently mutually exclusive mutations in GNAQ and GNA11, genes encoding the alpha subunit of heterotrimeric cell surface G proteins, have been reported. These alpha subunits are involved in mediating signals between G-protein-coupled receptors and downstream effectors such as protein kinases A and C [117]. Mutations in codon 209 of GNAQ and GNA11 have been reported in approximately 46–49% [118,119] and 32% [120] of patients, respectively, and lead to constitutive activation of the G protein alpha subunit and activation of the MAPK signalling pathway (in human melanocyte cell lines), driving cell proliferation [118]. The majority of substitutions at codon 209 of GNAQ and GNA11 involve substitutions of glutamine by leucine or glutamine by proline [118,120]. Mutations at codon 183 of GNAQ and GNA11 also occur, although less frequently, and involve the substitution of cytosine by thymine [118,120] which is characteristic of ultraviolet-radiation-induced mutations [121], thereby supporting the role of UV-B radiation in the pathogenesis of a minority of uveal melanomas. As mutations in GNAQ and GNA11 are common in uveal melanoma, targeting these or downstream effectors such as protein kinase C [122] or members of the MAPK signalling [123] pathway are promising potential therapeutic options. However, the presence of these mutations is not correlated with the development of metastatic disease.

Inactivating somatic mutations of the gene coding for BRCA1-associated protein-1 (BAP1) have been found in up to 85% of metastasising uveal melanomas [124]. BAP1 is a deubiquitinating enzyme (DUB) encoded at the 3p21.1 locus [125]. It regulates cell growth by mediating ubiquitination of the nuclear transcription regulator, host cell factor 1 (HCFC1) [126], and stabilises the BRCA1–BARD1 tumour suppressor complex [127]. Also families with germ-line mutations of BAP1 have been identified with an increased incidence of both uveal and cutaneous melanoma, as well as other malignancies [128–130].

Vascular endothelial growth factors (VEGFs) are a family of five proteins which bind to VEGF receptors (VEGF-Rs) on endothelial cells and promote angiogenesis. Increased VEGF expression is involved in the pathogenesis of a number of solid malignancies. The expression of VEGF is increased in hypoxic environments [131], and raised VEGF-A levels have been found in the aqueous humour of eyes with uveal melanoma [132,133]. Significantly increased levels of VEGF-A have been reported by some groups in patients with metastatic disease [134], although not consistently [135]. The role of VEGF in the pathogenesis of uveal melanoma requires further clarifi-

cation, but trials of anti-angiogenic agents of patients with melanoma, including uveal melanoma, are underway.

3.2. Prognosis

Major aberrations in karyotype are frequently observed in uveal melanoma [136]. Monosomy 3 is the most common and is reported in approximately 50% of cases treated with enucleation [137]. It has been found to correlate with clinical features of poor survival – such as large tumour size, tumours of the ciliary body [138] and epithelioid cytology [139] – and is also closely associated with the development of metastatic disease [140]. Such patients with monosomy 3 uveal melanoma have a poor 5-year survival [141]. This may be due to loss of tumour suppressor genes located on chromosome 3, including BAP-1. It is likely that loss of chromosome 3 is an early event in tumourigenesis, predisposing to other cytogenetic aberrations such as gain of 8q [142]. This is found in around 40% of cases and corresponds to the locus for the MYC proto-oncogene [143]. Together these cytogenetic abnormalities are more common in ciliary body tumours [144] and are associated with the development of metastatic disease [143]. Gain in chromosome 6p is associated with a better prognosis. It has been observed in approximately 25% of tumours and exclusively in tumours without monosomy 3 [143].

More recently gene expression profiling has identified two distinct molecular subtypes (classes 1 and 2) of primary uveal melanoma using a three-gene signature, with significant differences in prognosis [145]. This signature identifies genes which are involved in apoptosis, cell growth and angiogenesis. Class 1 tumours are associated with gain of chromosome 6 and are less likely to metastasise, whereas class 2 tumours are associated with monosomy 3 and demonstrate a propensity to metastasise. Consequently the 92-month survival for class 1 and class 2 subtypes differed significantly at 95% and 31% respectively.

4. Mucosal melanoma

Given that the primary function of melanocytes is pigmentation and protection of the skin and eyes against UV radiation, their presence in unexposed sites such as mucous membranes is not fully understood. There is accumulating evidence that melanocytes function as antigen-presenting cells [146,147], and as mucous membranes form a critical antimicrobial barrier, melanocytes at this site may have a role to play as part of the innate immune system [148]. At leptomeningeal sites there is even evidence of a neuroendocrine role [149]. Regardless of their function, mucosal membrane melanocytes are susceptible to malignant transformation in a similar fashion to their cutaneous and uveal counterparts.

4.1. Epidemiology

Mucosal melanoma is the least common of the three melanoma subtypes, accounting for less than 1.5% of all melanomas [1,150]. The incidence rate is similar around the world [151] and estimated at 2.2 [150] and 2.6 [152] cases per million per year in the USA and Europe respectively. Significant regio-

nal variation in incidence across Europe has been reported, with the highest rate (2.7 cases per million per year) noted in Northern Europe, and the lowest (0.88 cases per million per year) in Eastern Europe [152], but this may simply reflect differences in classification and reporting of this rare malignancy. Interestingly, unlike cutaneous melanoma (which demonstrates an annual increase in incidence), the annual incidence of mucosal melanoma has remained relatively stable over several decades [1,150,153].

The incidence of mucosal melanoma varies with both gender and age [150]. The median age at diagnosis is 70, with the exception of oral cavity melanomas which tend to occur in younger patients. Incidence increases with age; over 65% of cases are diagnosed in patients over 60. The incidence in women is almost twice as high as in men, possibly because of the higher rates of genital tract melanomas [1,154,155] amongst women. The absolute incidence of mucosal melanoma in white populations is higher (2:1) than in non-whites [1,150,155,156].

Mucosal melanomas arise most often in the head and neck region, female genital tract and anorectal region [150]. No clear risk factors for mucosal melanoma are known. As mucous membranes are not exposed to the sun, UV radiation is not considered an important aetiological factor. The role of viruses – such as human papillomavirus (HPV) or human herpes virus (HHV) implicated in other oral malignancies – has not been substantiated [157–159]; however, a role for the human immunodeficiency virus (HIV) has been postulated [160,161] for anorectal mucosal melanomas. Inhaled chemical irritants such as formaldehyde [162] are also not thought to be significant carcinogens for this malignancy. It has been reported that smoking is associated with a greater prevalence of pigmented oral lesions [163]. Oral mucosal melanoma is thought to be preceded by oral melanosis in one third of cases [157,164,165], but no clear link to smoking has been identified, particularly at other mucosal sites.

4.2. Biology

The advent of next-generation genomic sequencing has enabled detailed investigation of the molecular biology of this rare melanoma subtype, and provided an insight into its pathogenesis. Unlike cutaneous melanoma, V600E BRAF or NRAS mutations are rare in mucosal melanoma [166,167]. Instead a distinct molecular mutation pattern exists, further differentiating mucosal melanomas biologically from their cutaneous and uveal counterparts.

The proto-oncogene, KIT, is a type III transmembrane receptor tyrosine kinase (RTK) that dimerises upon extracellular binding of its ligand stem-cell factor (SCF), activating its intracellular tyrosine kinase domain and thus the receptor. The activated protein, c-KIT, leads to phosphorylation of a downstream intracellular signalling cascade and the activation of MAPK and phosphoinositide 3-kinase (PI3K) pathways crucial for proliferation, migration, differentiation and survival in many cell types, including melanocytes [168,169].

Although the exact mechanism of KIT signalling in melanocytes is not fully understood, studies have demonstrated that inactivating mutations in KIT can lead to amelanotic disorders [170,171] and prevent normal melanocyte development

and survival [172]. Loss of KIT expression in melanocytes also results in abnormal proliferation and melanocyte mobility [173]. A loss/lack of KIT expression is often seen in progressive melanoma [174,175]. Early studies on the genetic alterations in mucosal melanoma led to the identification of chromosomal aberrations, such as gain of 1q, 6p and 8q [176–178]. Subsequently, detailed studies [179,180] comparing melanomas derived from different anatomical sites demonstrated gain-of-function mutations (such as K642E, D816H and V559A), amplifications or over-expression of c-KIT in 39% of mucosal melanomas. This frequency is reported to vary markedly by site of melanoma; in one study 88% of oral mucosal melanomas were reported as expressing aberrant c-KIT [181], while others [180] reported their highest rates (35%) amongst genital tract melanomas. It was also noted that mutations of KIT did not occur alongside mutations in NRAS or BRAF [180].

Exon 11 mutations (including point mutations, in-frame deletions and insertions) are the most common KIT mutations; the L576P mutation in particular is found in approximately one third of these melanomas [166,179,180]. This region encodes the juxtamembrane domain of the KIT receptor, which performs an auto-inhibitory role. Mutations in this region lead to constitutive receptor activation and consequent abnormal intracellular growth signals, predominantly via the PI3K pathway [182]. Experimental evidence suggests that such activation alone is insufficient for mucosal melanoma genesis, requiring further triggers within the cellular microenvironment (such as hypoxia) in order to induce malignant transformation [182].

There is clearly still much to learn about the biology of mucosal melanoma, but the knowledge gained thus far about KIT mutations is encouraging further research in this area, focused particularly on exploiting this mutation in the pursuit of effective treatment options for this condition. KIT mutations have been successfully targeted in the treatment of other malignancies such as gastrointestinal stromal tumours (GIST), which also demonstrate an increased prevalence of KIT mutations.

4.3. Prognosis

Mucosal melanoma has the poorest prognosis of all the melanoma subtypes considered. Five-year survival estimates range from 25% to 40% [1,152]. Interestingly, patients with KIT mutations appear to have a poorer prognosis than wild-type patients [183].

The site of these melanomas is often occult; early malignant lesions are usually asymptomatic, and any subsequent symptoms are non-specific, resulting in significant diagnostic delay and enabling the lesion to grow and metastasise. Even supposedly early-stage disease deemed to be fully surgically resectable (and thus curable) often has a poor outcome. This is most likely due to the presence of occult metastatic disease at diagnosis. The lack of knowledge regarding disease risk factors means that, in contrast with cutaneous melanoma, strategies to improve mucosal melanoma outcomes must focus on early detection of the disease rather than avoidance of risk factors and prevention of development.

5. Conclusion

The socio-economic burden of melanoma is disproportionate as its incidence is highest amongst younger, economically active individuals. Both inherited, genetic and lifestyle factors have been shown to affect the malignant transformation of melanocytes. More recently it has become clear that cutaneous, mucosal and uveal melanomas are each distinct disease entities with unique clinical behaviours and characteristic molecular abnormalities. This improved understanding has led to the development of new treatment strategies which have started to improve outcomes. However, there is still a long way to go as melanoma, for now, remains an assortment of diseases with a common poor prognosis – particularly for those with advanced disease.

Conflict of interest statement

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