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Commentary

Immune–pigment dynamics in uveal melanoma

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Abstract

In uveal melanoma (UM), increased M2 macrophage infiltration and high tumor pigmentation are well-established adverse prognostic features, yet their biological interplay remains underexplored. Emerging evidence indicates that these characteristics frequently coexist in genetically high-risk tumors, particularly those with monosomy 3 and BAP1 loss. This commentary proposes that highly pigmented tumor cells and M2-polarised macrophages form an integrated, immunosuppressive tumor ecosystem that promotes immune tolerance and tumor progression. Recognizing immune–pigment coexistence provides a refined framework for prognostic assessment and highlights microenvironmental interactions as potential targets for future therapeutic strategies in UM. Understanding these dynamics may improve risk stratification and development of targeted therapies.

Introduction

Uveal melanoma is an ocular cancer that frequently metastasizes to the liver despite effective local tumor control [1]. In contrast to cutaneous melanoma, UM exhibits limited responsiveness to immune checkpoint blockade, underscoring fundamental differences in tumor immunobiology and immune–tumor interactions [2,3]. These differences have prompted growing interest in understanding how the tumor microenvironment (TME) contributes to disease progression and therapeutic resistance. Substantial evidence indicates that UM prognosis is not governed solely by genetic alterations within tumor cells but is profoundly shaped by microenvironmental features, particularly immune infiltration and tumor pigmentation [4–7]. Among immune cell populations, tumor-associated macrophages (TAMs) consistently correlate with adverse outcomes, paradoxically marking aggressive disease rather than effective antitumor immunity [4–6]. In parallel, high tumor pigmentation proven to be a high-risk histopathological parameter closely associated with poor survival [8–10]. Recent studies suggest an association between macrophage infiltration and high tumor pigmentation, particularly in tumors with chromosome 3 loss or BAP1 inactivation [10–13]. These observations argue against viewing immune infiltration and high pigmentation as independent prognostic markers. Instead, they support that macrophages and high pigmentation could coexist to shape the TME and influence clinical outcome. This commentary explores the relationship between high pigmentation and M2 macrophage polarization in UM in the context of monosomy 3 and BAP1 loss.

Commentary

Macrophages are among the most abundant immune cells in the UM microenvironment and have repeatedly been associated with unfavorable prognosis [4–6]. Early histopathological analyses demonstrated that increased macrophage density correlates with larger tumor size and reduced survival [5]. Subsequent studies confirmed that macrophage infiltration is particularly prominent in tumors exhibiting epithelioid morphology and chromosome 3 loss [4,12]. Importantly, macrophage-rich infiltrates in UM do not translate into effective tumor rejection. This distinguishes UM from

many other malignancies in which immune infiltration predicts favorable outcome. Macrophages are commonly classified into basic phenotypic types, such as M1 and M2, yet in UM, tumor-associated macrophages (TAMs) demonstrate extensive functional heterogeneity, shaped by factors within the TME, including local signaling factors, pigmentation, and cellular interactions [6,14]. M1-polarized macrophages are potent effector cells which can be antibacterial, anti-tumorigenic, and antiangiogenic. By contrast, M2-polarized macrophages contribute to wound-healing processes, angiogenesis, and debris removal (scavenger function) and are thus inflammatory (immune suppressive) and pro-angiogenic. Instead, they are associated with immune suppression, reduced cytotoxic lymphocyte activity, and tumor progression [6,15–17]. UM promotes the formation of a premetastatic niche in the liver by reprogramming the TME, particularly TAMs, to create conditions favorable for metastatic colonization. In our study TAMs were assessed in different fields of tumors using immunohistochemistry in total 82 UM patients. All UM patients were included in our study except patients who received radiotherapy or chemotherapy. IHC scoring was done by immunoreactive scoring (IRS) and the average IRS of the M2/M1 ratios was 2. M2/M1 ≥2 was considered a high expression whereas M2/M1 <2 was considered a low expression. Using the Chi square test, a high M2/M1 macrophage ratio showed a statistically significant association with distant metastasis. Notably, 8 of the 9 metastatic cases exhibited high M2/M1 expression, and three of these patients died. These findings are consistent with prior reports demonstrating a correlation between increased macrophage density and metastasis-related mortality in UM [18]. This aligns with established mechanisms whereby immunosuppressive myeloid cells, including M2-like macrophages and myeloid-derived suppressor cells (MDSCs), are critical orchestrators of the pre-metastatic niche, enabling metastatic seeding and outgrowth [19].

Tumor pigmentation has long been incorporated into histopathological descriptions of UM, yet its biological significance has historically been underappreciated. Multiple studies have demonstrated that heavily pigmented tumors are associated with adverse prognostic features, including epithelioid cell type, increased mitotic activity, and reduced survival [8,9]. More recent genomic analyses have strengthened the association between pigmentation and high-risk genetic alterations, particularly chromosome 3 loss and BAP1 inactivation [10–13]. These findings suggest that high pigmentation is an active component of biological pathways driving tumor aggressiveness, rather than a passive or secondary feature. We performed pigmentation grading in UM patients at both clinical and histopathological levels. Clinical grading of pigmentation involved an indirect ophthalmoscopic fundus examination. Histopathological grading of choroidal pigmentation was conducted on H&E slides by evaluating the percentage of melanin present in melanoma cells. Melanin content equal to or less than 30% was designated as 'grade 1', indicative of low pigmentation. Melanin content ranging from 31% to 70% and exceeding 70% were categorized as 'grade 2' and 'grade 3', respectively, both representing high pigmentation. In our previous study, transmission electron microscopy revealed that at the ultrastructural level, highly pigmented UMs contain abundant premelanosomes and dedifferentiated melanosomes, suggesting disrupted melanosome biogenesis and turnover compared with low-pigmented UMs [20]. Pigment accumulation may influence tumor architecture, cell–cell interactions, and immune accessibility. Dense pigmentation may modify tissue organization in ways that indirectly shape immune surveillance. The microphthalmia-associated transcription factor (MITF), a key regulator of melanocyte development and melanogenesis, promotes pigmentation by transcriptionally regulating several melanocytic markers, including tyrosinase-related protein 1 (TYRP1), tyrosinase-related protein 2 (TYRP2), and silver protein (SILV) [11]. Notably, previous study also demonstrated that high expression levels of TYRP1, TYRP2, SILV, and MITF were associated with poor prognosis in patients with UM [20].

One of the most striking observations in UM biology is the frequent spatial and quantitative overlap between macrophage infiltration and tumor pigmentation. Rather than acting independently, these features could reinforce one another within a shared tumor ecosystem. This synergistic relationship likely fosters a tumor microenvironment with a dysregulated redox state, a common vulnerability in aggressive cancers that can be exploited therapeutically [21]. We found high M2/M1 expression was significantly associated with high pigmentation and immunoexpression of all pigmentation markers (MITF, TYRP1, TYRP2, SILV). In addition to high pigment-derived effects on macrophages, reciprocal signaling may also occur within the tumor microenvironment. In our current research, ultrastructural studies have identified macrophages containing phagocytosed melanosomes in high pigmented UMs, providing direct evidence of physical interaction between immune cells and pigmentary components [20]. High pigmented tumor cells produce abundant melanosomes which are engulfed by macrophages. These macrophages contribute to immune suppression and tumor support, facilitating ongoing tumor growth. Consistent with this paradigm, our study identified elevated circulating levels of interleukin-10 (IL-10) in UM patients which was performed by ELISA on pre operated UM serum samples. A high concentration of IL-10 was statistically significant with the high M2/M1 expression. IL-10 is a key downstream effector of M2 macrophages and a central regulator of immunosuppression, facilitating immune evasion and contributing to the progression of advanced melanoma [22]. Although strong associations exist between monosomy 3, BAP1 loss, high pigmentation, and macrophage infiltration, the precise molecular mechanisms linking these features remain incompletely defined.

The convergence of tumor pigmentation, macrophage infiltration, and chromosome 3 alterations underscores the importance of genetic context in shaping the UM microenvironment. Monosomy 3 and loss of BAP1 are among the most powerful predictors of metastatic risk and are consistently associated with tumors that exhibit inflammatory yet profoundly immunosuppressive phenotypes [11–13,23,24]. UM cases harboring chromosome 3 loss frequently demonstrate both increased tumor pigmentation and a higher density of infiltrating macrophages [10,12]. Rather than exerting a direct effect on immune cell behavior, these genetic alterations may reprogram tumor cell biology in ways that promote pigment accumulation and immune tolerance, thereby constraining effective immune surveillance. In our cohort, high pigmentation was observed in 28 UM cases, of which 19 exhibited monosomy 3, representing a statistically significant association. Moreover, monosomy 3 in highly pigmented tumors was significantly associated with increased immunoexpression of melanogenesis-related markers, including TYRP2, SILV, and nuclear MITF, alongside a predominance of M2 over M1 macrophage markers which was performed by Spearman's rank-order correlation analysis. Collectively, these findings suggest that chromosome 3 loss orchestrates a TME characterized by enhanced melanogenesis and macrophage-driven immunosuppression, contributing to UM progression and metastatic potential.

The close relationship between macrophage infiltration, pigmentation, and genetic alterations has important implications for prognostication in UM. Single biomarkers considered in isolation may fail to capture tumor complexity. In contrast, integrated assessment of immune composition, pigmentation status, and chromosomal alterations provides a more refined risk stratification framework. High macrophage density combined with high tumor pigmentation identifies a subset of UMs with particularly poor outcomes, even when tumor size and stage are accounted for [4,5,10]. Conversely, tumors with low pigmentation and limited macrophage infiltration often follow a more indolent course.

Such composite evaluation may be especially valuable in populations with lower baseline metastatic risk, where traditional prognostic models may underestimate long-term danger. Beyond prognostic implications, the interaction between tumor pigmentation and macrophage biology may also hold therapeutic relevance. Strategies targeting melanogenesis pathways could potentially modify pigment production and alter the tumor microenvironment. Similarly, therapeutic approaches aimed at repolarizing TAMs from an M2-like immunosuppressive phenotype toward a more pro-inflammatory state may enhance antitumor immune responses. Additionally, disrupting pathways involved in melanosome uptake or phagocytic signaling, may represent another avenue for therapeutic intervention. Although these concepts remain largely exploratory in UM, understanding immune–pigment dynamics may help guide the development of future microenvironment-targeted therapies. Incorporating immune–pigment interactions into prognostic algorithms could improve patient counselling and surveillance strategies.

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