Deciphering Mechanisms of UVR-Induced Tumoral Immune Checkpoint Regulation against Melanoma

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Exposure to solar ultraviolet radiation (UVR) impacts various cellular, genetic, and immunologic responses governing biological and pathophysiologic events including the development of skin cancers. The mechanistic insights into UVR-induced immune tolerance against skin cancers, particularly cutaneous melanoma, have been a great challenge, given the sophisticated regulation of immune checkpoint proteins. A study led by Wang and colleagues has elucidated novel mechanisms of UVR-induced immune suppression, implicated in melanoma immune evasion and progression mediated via upregulation of PD-L1, and reduced CD8+ T-cell–mediated cytotoxicity in HMGB1/TBK1/IRF3/NF-kB–dependent manner. These findings offer new mechanistic insights into UVR-induced melanoma immune evasion and progression.

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and 84% of metastatic samples in patients with melanoma. In addition to the common driver mutations, the somatic mutation burden has been documented to be comparatively high in melanomas than other human malignancies (7). UVR significantly contributes to the accumulation of somatic mutations, which act as neoantigens to elicit antitumor immune responses. Understanding mechanistic insights into immune checkpoint regulation in response to UVR-induced mutational signature could offer new strategies to overcome immune tolerance or to circumvent melanoma immune evasion. Importantly, such strategies can be useful in designing immune checkpoint-based novel combination approaches for melanoma treatment.

The high somatic mutational burden in melanoma has been shown to be associated with long-term clinical benefits including overall improved survival responses to anti–CTLA-4 therapy (8). Wang and colleagues evaluated the significance of UVR-induced somatic mutation burden on antitumor immune responses against melanoma (9). Subsequently, authors generated a mutagenized mouse melanoma model, YUMMER 1.7 [i.e., Yale University Mouse Melanoma (YUMM) Exposed to Radiation], from the parental YUMM 1.7 melanoma cells that harbor three driver mutations (Braf^V600E, Pten^−/−, and Cd8n2a^−/−) by UVR irradiation and expansion of a single cell–derived clone. Implantation of YUMMER 1.7 cells harboring UBV-introduced high somatic mutation burden at low cell numbers exhibited tumor regression compared with YUMM 1.7 cells in immunocompetent C57BL/6J hosts. These data indicated that YUMMER 1.7 cells enhance immunogenicity via eliciting T-cell–mediated functional antitumor adaptive immune responses. This tumor regression was abrogated in immunodeficient Rag1^−/− mice and by the depletion of CD4^+ and CD8^+ T cells or inoculation of higher numbers of YUMMER 1.7 cells in C57BL/6J mice. The increased growth of YUMMER 1.7 tumors was attenuated by anti–CTLA-4 and anti–PD-1 immunotherapy, and their combination resulted in enhanced antitumoral and survival effects (9). Given these findings, further delineation of signaling pathways involved in regulating tumoral immune checkpoints in response to UBV may offer alternative therapeutic strategies for melanoma intervention. Such investigations are also important, given the delineation of transcription factors and upstream mediators such as p53, PTEN, and NF-kB, which regulate PD-L1 expression, and thus, add other pieces to the puzzle of this very ongoing challenge.

Multiple studies have implicated UBV in the induction of oxidative stress via the production of reactive oxygen species (ROS), and cancer cells require high ROS demand compared with normal cells to support their accelerated metabolism and high proliferation rate. A recent study examined the role of nuclear factor E2–related transcription factor (NRF2), which regulates the expression of antioxidant proteins, in melanoma intervention (10). These authors demonstrated that UBV upregulates PD-L1 and NRF2 expression in human primary keratinocytes (HPK) and human primary melanocytes (HPM), and the analysis of human melanoma tissue array also revealed a significant correlation between PD-L1 and NRF2 expression. The question of whether UBV-induced PD-L1 expression or transcription is NRF2-dependent was supported by the findings including that UBV upregulates PD-L1 expression on the dorsal skin including melanocytes of wild-type, but not from Nrf2^−/− mice, and NRF2 overexpression induced and its silencing attenuated UBV-mediated PD-L1 expression in HPK and HPM. Importantly, NRF2 silencing combined with anti–PD-1 therapy resulted in greater suppression of melanoma tumor growth compared with single treatments, respectively (10). These combination treatment–induced effects were mediated via mechanisms including increased infiltration of CD8^+ and CD4^+ T cells as well as reduced Tregs and myeloid-derived suppressor cells compared with NRF2-silencing or anti–PD-1 therapy alone. As the efficacy of silencing NRF2 and anti–PD-1 therapy was relatively similar in inducing antitumor immune responses, these findings suggested the potential of targeting NRF2 as an alternative strategy of PD-1/PD-L1 inhibition for melanoma treatment (10). However, the question of whether UBV exposure can impede the antitumor immunity mediated via NRF2-silencing and/or anti–PD-1 therapy as well as the mechanisms involved in these events remained to be elucidated.

Notably, one of the major limitations of UBV-induced effects on tumoral PD-L1 expression and anti–PD-1–mediated antitumor immune responses was thoroughly addressed by Wang and colleagues (11). The authors demonstrated that UBV-induced secretion of damage-associated molecular patterns (DAMP) molecule, HMGB1, by melanocytes and keratinocytes activated the receptor for advanced glycation endproducts (RAGE). These changes in turn activated NF-kB and IFN regulatory factor (IRF3) pathways in melanocytes to promote PD-L1 transcription (11). Although NRF2 depletion did not affect UBV-induced PD-L1 expression in melanoma cells, NF-kB and IRF3 were found to be indispensable for PD-L1 regulation by UBV in primary melanocytes. These data indicated a cell type–specific mechanism and suggested that within primary melanocytes, UBV may mediate PD-L1 transcription with NRF2 alternatively and/or collaboratively. The findings that deletion of HMGB1/RAGE abolished UBV-induced phosphorylation of TBK1, NF-xBp65, and IRF3 as well as PD-L1 upregulation, validated the role of HMGB1/RAGE in activating the downstream TBK1/NF-xB/IRF3 pathway and PD-L1 induction by UBV. Further studies confirmed that the upstream kinase, TBK1, activated both NF-xB and IRF3, and IRF3 formed a transcriptional complex with NF-xBp65 within PD-L1 promoter to coordinately promote PD-L1 transcription, and that inhibition of the NF-xB upstream kinases, IKKβ or TBK1, attenuated UBV-induced increased PD-L1 transcription in melanoma cells (11). Importantly, the inhibition of PD-1/PD-L1 signaling attenuated the UBV-induced increased growth of melanoma tumors via CD8^+ T-cell–mediated enhanced antitumor immunity. These data indicated that blocking immune checkpoint may also mitigate UBV-induced immune suppression, which resulted in immune evasion of premalignant melanocytes and melanoma cells, leading to melanoma initiation and progression.

Several clinical studies have documented improved checkpoint immunotherapy responses with tumor profiles including PD-L1 positivity, high mutational burdens, tumor-infiltrating lymphocytes such as increased CD8^+ T cells and immune gene signatures against malignancies including melanoma. However, additional evidence is needed to utilize the relevance of such tumor profiles as predictive indicators in selecting patients with cancer for immune checkpoint–based combination treatments and/or correlating their levels with treatment outcomes. Importantly, as novel therapeutic strategies are being actively explored, the validation of cellular pathways such as HMGB1/TBK1/IRF3/NF-xB

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in clinical settings will allow us to determine whether the benefits of alleviating UVR-induced melanoma immune evasion by immune checkpoint inhibition can be replicated pharmacologically as alternative combinational approaches for melanoma treatment.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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