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A Novel Treatment for Melanoma: Targeting the MIF/CD74 Inflammatory Pathway

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Abstract

Melanoma is one of the more aggressive skin cancers with a high mortality rate once it metastasizes. New breakthroughs in the treatment of melanoma have come from the introduction of immune checkpoint blockade (ICB). Targets of ICB include programmed cell death protein 1 (PD-1), program death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4). However, these therapies that target ICB proteins are only effective in 30-40% of melanoma cases. Combinations of these drugs can lead to better outcomes but also increase the risk of severe side effects. A new inflammatory pathway is being investigated, the receptor CD74 and its known ligands macrophage migration inhibitory factor (MIF) and its homolog D-dopachrome tautomerase (D-DT). This pathway is highly inflammatory in autoimmune diseases like multiple sclerosis (MS). However, studies in melanoma have shown the MIF/CD74 pathway creates regulatory/pro-tumorigenic macrophages and can potentially induce tumor cell survival through phosphorylated extracellular-related kinase (pERK1/2) signaling. We have developed a partial MHC class II construct, DRQ, that inhibits ligands from binding to CD74 and blocks downstream signaling through CD44 to increase pERK1/2. We hypothesize that DRQ can be used at low doses to treat melanoma. Mice survive significantly longer with metastatic melanoma when treated with a lower dose of DRQ than the higher, immunosuppressive dose, or vehicle. Additionally, B16F10 mouse melanoma cells produce MIF in culture and have a baseline expression of CD44. When the cells are cultured with interferon gamma (IFNg) for 48h, the cells express significantly more CD74 and PD-L1 compared to baseline. These results suggest targeting the MIF/CD74 pathway by inhibiting CD74 with DRQ could provide a novel treatment for melanoma as a monotherapy for patients that fail ICB or as an adjuvant therapy with ICB therapy.