Immune Cell Types

682 **PKC AGONISM RESTRICTS INNATE IMMUNE SUPPRESSION, PROMOTES ANTIGEN CROSS-PRESENTATION AND SYNERGIZES WITH AGONISTIC CD40 THERAPY IN BREAST CANCER**

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Background Immunotherapies that reinvigorate T cell responses have transformed the treatment of many cancers showing unprecedented durable antitumor responses. However, most patients do not respond to immunotherapy due in part to immunosuppression. Immunotherapy non-responders have high levels of circulating myeloid-derived suppressor cells (MDSCs)-an innate cell population that expands in pathological conditions such as cancer and suppresses T cells via production of immunosuppressive factors. In contrast, immunotherapy success is dependent on the ability of antigen-presenting cells (APCs) to cross-present tumor antigens to cytotoxic T cells. Immunogenic cross-presentation by APCs requires a specific subtype of dendritic cells (DCs) called conventional DC1 (cDC1) which are dysfunctional in cancer. Novel ways to increase cDC1 function are promising and under active investigation. One of these ways is ligation of CD40 which is primarily expressed by myeloid cells and its agonism leads to myeloid cell activation. Thus, targeting MDSCs while simultaneously expanding cross-presenting DCs represents a promising strategy that, when combined with agonistic CD40, will likely result in long-lasting protective immunity.

Methods Using in vitro, ex vivo, in vivo and adoptive transfer systems, we investigated the effect of PKC agonists PEP005 and prostratin on MDSC expansion, differentiation to APC-like cells and recruitment to the TME. MDSC suppressive capacity was investigated using functional coculture assays with CD8+ T cells. Furthermore, we assessed the effect of PKC agonists on MDSC cross-priming capacity using in vitro coculture assay with OT-I CD8+ T cells as well as adoptive transfer experiments. We also investigated the effect of PKC agonists on cDC1 expansion from the BM in vitro and in vivo. Finally, we tested the efficacy of PKC agonism in combination with agonistic CD40 using the E0771 murine breast cancer orthotopic mouse model.

Results Herein, we show that PKC agonists decreased MDSC expansion from hematopoietic progenitors in the BM and induced M-MDSC differentiation to an APC-like phenotype that expresses cDC1-related markers and the transcription factor Irf8. Simultaneously, PKC agonists favored cDC1 expansion at the expense of cDC2 and plasmacytoid DCs (pDC). Functionally, PKC agonists blunted MDSC suppressive function of T cells and promoted MDSC cross-priming capacity. Finally, combination of PKC agonism with agonistic CD40 mAb resulted in a marked reduction in tumor growth while synergistically increased intratumoral activated CD8+ T cells and tissue-resident memory CD8+ T cells.

Conclusions In sum, we propose a novel promising strategy to simultaneously target MDSCs and promote APC function that may have potential clinical relevance in cancer patients.

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