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## **Understanding and Overcoming Immune Suppression in the Tumor Microenvironment**

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In cancer and various infectious and chronic inflammatory diseases, the quality and quantity of immune cells can be used to predict clinical outcome. For example, the number and location of activated cytotoxic CD8 T cells within human tumors are remarkably accurate prognostic indicators of patient survival. However, immune effector cells including CD8 T cells and NK cells are often functionally paralyzed within the tumor microenvironment due to the expansion of suppressive cell populations such as CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> regulatory T cells, myeloid-derived suppressor cells (MDSCs), tolerogenic dendritic cells or tumor-associated macrophages, and the expression of various suppressive factors including TGF- $\beta$ , IL-10 and PD-L1. In general, immunotherapies targeting the treatment of cancer and chronic infections focus on enhancing the immune response by activating and expanding effector cells and/or blocking or eliminating the suppressive cells and their products. Recent studies from our lab have shown that myeloid cell infiltrates can differ significantly between cancers and often exhibit varied suppressive mechanisms. We are currently working on novel approaches to block the immunosuppressive and tumor-promoting activity of tumor-infiltrating myeloid cells. Other promising approaches to immunotherapy for cancer directly target cytotoxic lymphocytes. One such strategy employs IL-15/IL-15R $\alpha$  complexes which are considerably more potent than IL-15 alone in expanding cytotoxic lymphocytes (NK and CD8 T cells) that express the IL-2/IL-15 receptor beta-chain (CD122). We recently demonstrated that short-term treatment with IL-15/IL-15R $\alpha$  complexes is highly effective in reducing established tumor burden and restoring the function of tumor-resident CD8 T and NK cells. However, continuous cytokine therapy improved survival only modestly and failed to control tumor outgrowth. Recent work in our laboratory has shown that long-term cytokine therapy with IL-15/IL-15R $\alpha$  complexes leads to a preferential impairment in NK cell function. Our studies indicate that NK cell dysfunction may result from chronic stimulation via CD122, expansion of myeloid-derived suppressor cells, or both. Our results have important clinical implications for the design of immunotherapies and vaccines using multiple doses of immunostimulatory agents.

### References

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