high concentrations of long-acting, pegylated IL-10 have also shown anti-tumor activity. Here we investigated IL-10 and IL-10 receptor-alpha (IL-10RA) expression profiles in normal and tumor tissues as well as the immunological effects of modulating the IL-10 pathway via antibody-mediated blockade of IL-10RA.

Methods IL-10 and IL-10RA mRNA are expressed by several tumors, including renal, lung, breast, and colon cancers. Fluorescent in-situ hybridization revealed that the majority of IL-10RA was expressed by CD3-negative tumor-infiltrating cells, localized in close proximity to T cells in the tumor microenvironment (TME). Immunohistochemistry studies confirmed expression of IL-10RA in the TME, while no expression was detected in healthy tissues. Furthermore, dissociated tumor cells produced biologically active levels of IL-10 in culture.

Results Monoclonal antibodies (mAbs) against IL-10RA prevented IL-10 signaling and enhanced release of IL-12 by monocyte-derived dendritic cells activated with suboptimal LPS concentrations. The effect of IL-10RA blockade was greater than that observed with IL-10 neutralizing mAbs. In mixed lymphocyte reactions and superantigen-driven T-cell activation, IL-10RA blockade enhanced IL-2 secretion by T lymphocytes. Consistent with earlier observations in mouse models, the effect of IL-10RA blockade was nonredundant with blockade of the PD-1/PD-L1 axis, resulting in enhanced IL-2 and interferon-gamma secretion by T cells when both pathways were inhibited. Blockade of IL-10RA during CD3-redirected in vitro killing of tumor cells by PBMC induced IL-12 release as well as upregulation of CD86 and HLA-DR by CD3-negative cells. In vitro dissociated tumor cells, IL-10RA blockade induced release of IL-2, interferon-gamma and other proinflammatory cytokines; additional PD-1/PD-L1 axis blockade further enhanced cytokine release.

Conclusions In summary, antibody-mediated IL-10RA blockade can potentiate immune activation in the dissociated tumor cells and may be a valuable addition to cancer immunotherapies, including redirected T-cell killing and checkpoint blockade.

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