ANTAGONISTIC ANTIBODIES TARGETING LAIR1 ENHANCE T LYMPHOCYTE ACTIVATION AND PROMOTE INFLAMMATORY PHENOTYPES IN MYELOID CELLS

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Background The Leukocyte Associated Immunoglobulin-like Receptor 1 (LAIR1) is an immune inhibitory transmembrane glycoprotein expressed on lymphocytes and myeloid cells. The known ligands for LAIR1 are proteins containing collagen-like domains including collagen, complement component 1q (C1q), and stromal protein Clec12.^{1 2 3} Myeloid-derived suppressor cells (MDSC), tumor associated macrophages (TAMs), as well as collagens, are important contributors of the immune-suppressive tumor microenvironment, and LAIR1 expression is negatively correlated with patient survival in many solid tumors.⁴ These findings prompt us to investigate LAIR1 as a novel immuno-oncology target in collagen-rich tumors. Utilizing LAIR1 antagonist antibodies, we aim to mobilize anti-tumor immunity by changing the collagen-induced tolerogenic state of the immune cells into proinflammatory.

Methods The mRNA expression levels of LAIR1, collagen, and C1q in diverse human cancers were analyzed using the TCGA database. LAIR1 protein expression on tumor infiltrated immune cells were measured by flow cytometry. Human tumor samples were obtained from Cooperative Human Tissue Network (CHTN) by the National Cancer Institute (NCI). Purified human T cells from healthy donors were stimulated with immobilized anti-CD3 in the presence of plate-coated human collagen I. Human monocyte-derived macrophages and dendritic cells (DC) were differentiated with M-CSF+IL-4 or GM-CSF+IL-4, respectively. Immune cell phenotypes were assessed by flow cytometry and cytokine secretion by Luminex.

Results Analysis of the TCGA database using signature genes specific to macrophages, T cells, DCs, and natural killer (NK) cells demonstrate that LAIR1 is highly expressed in most macrophage-infiltrated tumors and certain T cell-enriched tumors. LAIR1 and collagen are co-expressed at high levels in multiple macrophage-enriched tumors. Flow cytometry analysis of infiltrated immune cells from fresh tumor tissues showed that the highest level of LAIR1 protein expression was detected on TAMs, followed by monocytes, monocytic MDSCs, DCs, and lymphocytes. In vitro, LAIR1 antagonizing antibodies enhanced T-cell activation, proliferation, and IFN γ and TNF α production in comparison to isotype controls in the presence of collagen. Blocking LAIR1 interaction with collagen also decreased the expression of M2 markers such as PD-L1 and CD209 on monocyte-derived M2 macrophages. Additionally, treatment of monocyte-derived DCs by these antibodies increased the expression of the co-stimulatory protein CD86 and promoted the release of IL-12, a crucial cytokine for lymphocyte activation.

Conclusions These in vitro data suggest that LAIR1 blockade could potentially reverse T-cell and myeloid immunosuppression mediated by collagen, demonstrating the therapeutic potential of anti-LAIR1 antagonistic antibodies.

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