OVERLAPPING AND DISTINCT PATTERNS OF LILRB RECEPTORS SUPPORT COMPLEMENTARY TARGETING APPROACH IN CANCER

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Background: Leukocyte immunoglobulin-like receptors (LILRBs) are cell surface immunoinhibitory proteins that have been recently recognized as therapeutic targets of interest in immuno-oncology. LILRB1, LILRB2 and LILRB4 among them are broadly expressed on myeloid cells; however, their individual expression patterns have been difficult to define due to high sequence homology. To devise rational treatment options, it is important to develop a better understanding of LILRB1, LILRB2 and LILRB4 specific expression patterns as well as functional overlap and differences, as suggested by their diverse ligand binding partners. Here we characterize expression of these receptors on human immune cells in tumor and blood samples across different cancer indications. In addition, we performed pharmacodynamic analysis and unbiased clustering after individual LILRBs (1,2 or 4) were blocked in primary human tumor ex vivo systems to understand the roles of these receptors in complex cellular environments.

Methods: Cell-specific anchoring across multiple single cell RNAseq data sets was performed to characterize temporal and spatial LILRB gene expression on individual cells. Proteins were detected on human tumor specimens using ligand, cell type and LILRB-specific IHC antibodies. LILRB protein levels on immune cells from dissociated human tumors and peripheral blood mononuclear cells (PBMCs) were quantified using flow cytometry. Fresh treatment-naïve human tumor samples were treated with anti-LILRB1, anti-LILRB2, anti-LILRB4 or isotype control antibodies and gene expression analysis was performed on treated samples.

Results: LILRBs (1,2,4) are expressed on myeloid cells but distinct expression patterns also emerge. LILRB1 is expressed by T, B and NK cells; LILRB4 is highly expressed on plasmacytoid dendritic cells (pDCs) and a subset of conventional DCs (cDC2); LILRB2 is prominently expressed on immunosuppressive macrophages as well as monocytes, and within that population, intermediate monocytes display higher levels of LILRB2 than classical monocytes. In complex ex vivo systems, treatment with blocking anti-LILRB molecules induced both overlapping and distinct patterns of gene expression changes.

Conclusions: LILRB1, LILRB2 and LILRB4 each display unique cell-specific expression patterns and blocking their ligand binding activity in ex vivo systems suggests that they have non-redundant functions. Thus, context-dependent inhibition of one or more of these molecules can contribute to the optimal activation of anti-tumor immunity.

Ethics Approval: Human blood and tumor samples were acquired from commercial providers and from the CHTN and NDRI networks respectively. Specimens were collected under each provider’s human subject research institutional review board approved protocols and were fully anonymized or otherwise permanently de-identified to recipient investigators.