Antagonist antibodies targeting LAIR1 promotes inflammatory phenotype in myeloid cells and activate lymphocytes

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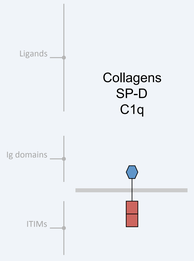
Introduction

New strategies are needed to improve responses to current T-cell checkpoint inhibitors, and one of them is to reprogram the immunosuppressive tumor microenvironment. Some tumors are highly infiltrated by myeloid cells that are known to inhibit T cell responses by diverse mechanisms. Thus new strategies to reprogram myeloid immunosuppressive cells are urgently needed.

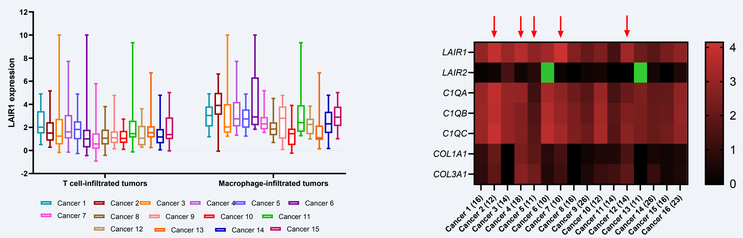
Leukocyte-associated Ig-like receptor (LAIR)-1 is an inhibitory receptor broadly expressed on immune cells such monocytes/macrophages, dendritic cells, T, B and NK cells. Upon binding to its known ligands collagen and C1q, LAIR1 promotes anti-inflammatory phenotypes of myeloid cells as well as inhibits activation of T and NK cells. Blocking LAIR1 interaction with its ligands could potentially re-activate the immune system and improve current cancer immunotherapy. We have studied the relevance of targeting LAIR1 in cancer by utilizing antagonistic antibodies that block LAIR1 binding to its ligands.

LAIR1: an inhibitory receptor

- Type I transmembrane glycoprotein with a single extracellular Ig like domain and two ITIMs in its cytoplasmic tail.
- LAIR1 expression: Lymphocytes T and B, NK, NKT, monocytes/macrophages, dendritic cells.
- LAIR1 ligands: Collagen, C1q and SP-D.
- LAIR1 function: Negatively regulate immune cell activation through interaction with its ligands.
- LAIR1 KO mice: Increased number of splenic B cells, regulatory T cells and DC. With age, there is an increase of activated and memory T cells.
- C1q and collagen have been shown to promote immunosuppressive signals through LAIR1.

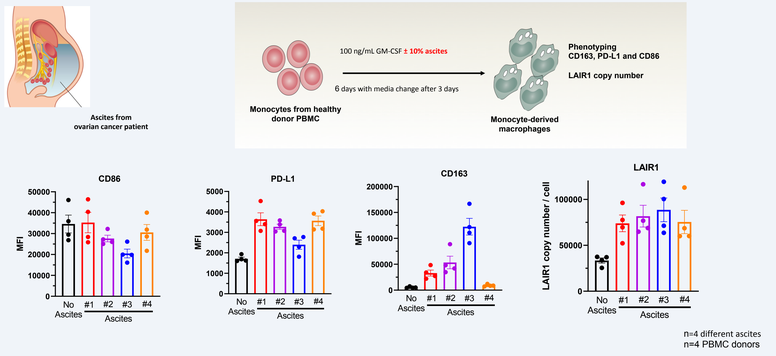


LAIR1 is highly expressed in many macrophage-infiltrated tumors.



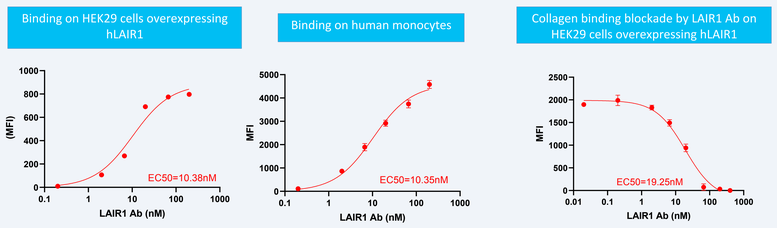
Used a defined Macrophage or T cells signature genes to identify macrophages or T cell-enriched tumors in TCGA database

LAIR1 is highly expressed on M2-Like macrophages induced by human ovarian cancer ascites

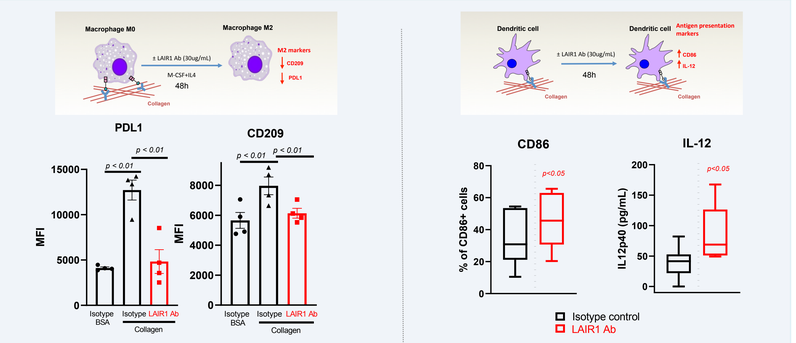


LAIR1 antagonist antibody

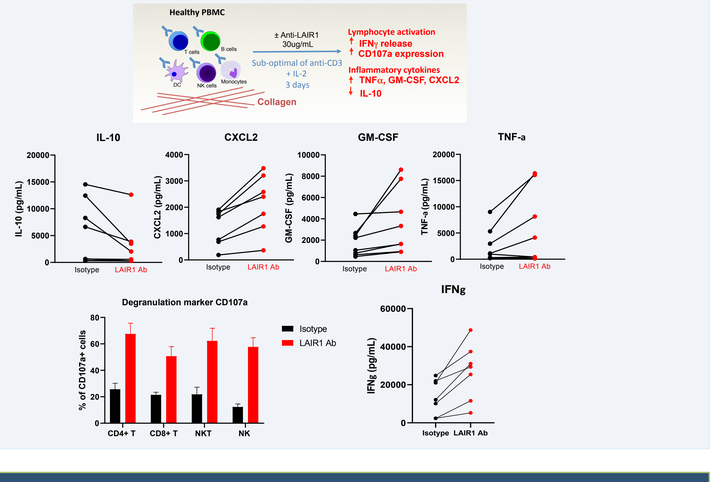
- High affinity (K_D=0.97 nM, Gator™)
- No binding to other LILRA/B family members
- No binding to GPVI (Glycoprotein VI), a receptor for collagen expressed in platelets
- Blocks LAIR1/collagen interaction



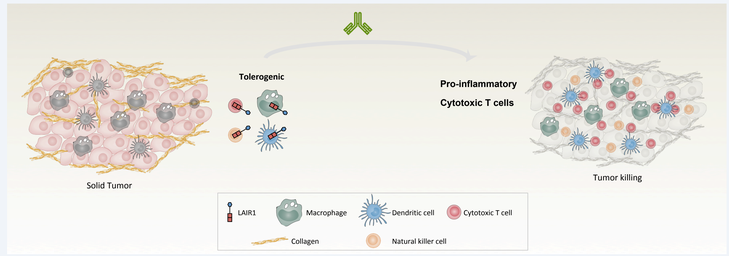
LAIR1 Ab inhibited collagen-induced immunosuppressive phenotype of myeloid cells.



Blocking LAIR1 interaction with collagen induces pro-inflammatory cytokines release and lymphocyte activation.



Proposed MoA of targeting LAIR1 in tumor microenvironment.



Summary

Analyses of TCGA database suggested that LAIR1 gene expression is highly expressed in most of the tumors infiltrated by macrophages, especially the ones that have high levels of collagen and C1q, both ligands of LAIR1. LAIR1 is highly expressed on M2-like macrophages differentiated *in vitro* from monocyte cultivated with human ovarian cancer ascites. We have generated an humanized monoclonal antibody against LAIR1 to block its interaction with its ligands such as collagen. *In vitro*, blocking the LAIR1 interaction with collagen decreased the expression of two M2 markers, PD-L1 and CD209 on monocyte-derived M2 macrophages. Also, LAIR1 Ab treatment of monocyte-derived dendritic cells increased the expression of the co-stimulatory protein CD86 and promote the release of IL-12, a crucial cytokine for lymphocyte activation. Finally, LAIR1 Ab induced the release of pro-inflammatory cytokines (TNFα, GM-CSF and CXCL2) and decreased the release of anti-inflammatory cytokine (IL-10) from human PBMC. LAIR1 Ab treatment increased lymphocyte activation (CD107a expression) and IFNγ release from human PBMC. All these data suggest that blocking LAIR1 binding to its ligands could potentially block myeloid immunosuppression and induces the activation of T cells. Thus, targeting LAIR1 have potential to modify tumor myeloid immunosuppressive functions and increase checkpoint immunotherapy response.