Homeostasis of monocytes and lung interstitial macrophages is regulated by collagen domain-binding receptor LAIR1 *in vivo*

06/06/2022

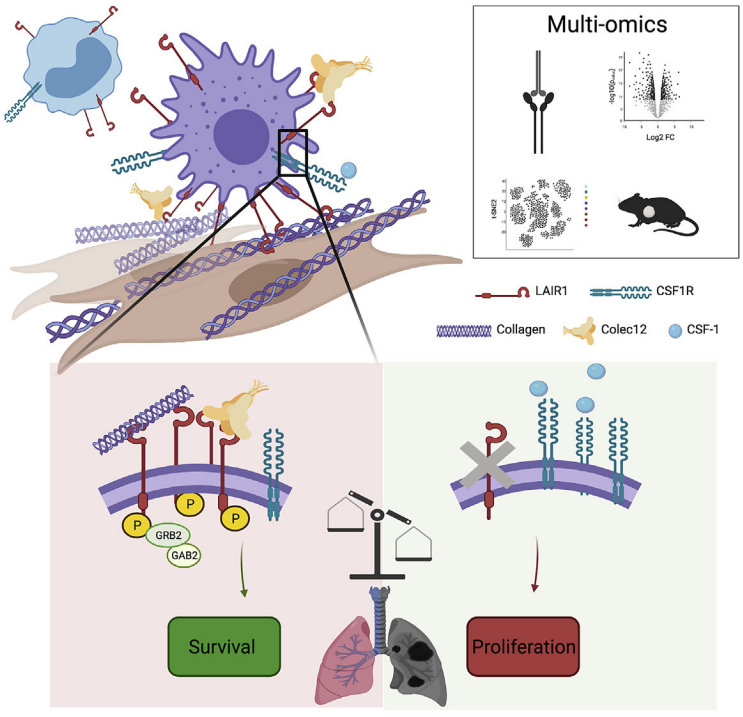
Monocytes and macrophages play important roles in tumor growth and progression[2,3]. Myeloid cells interact with the extracellular matrix (ECM) at all life cycle stages. But the molecular mechanisms and signaling pathways involved in myeloid cell interactions with ECM and tissue stroma are poorly understood. Collagen is a major ECM component that forms a biophysical framework for tissues. Here, Keerthivasan et al.[1] examined the role of the collagen receptor LAIR1 in myeloid biology.

LAIR1 is highly expressed in the myeloid lineage

LAIR1 expression levels were first examined in healthy tissues to identify the primary source of expression in humans. Across blood sample, LAIR1 showed the strongest correlation with myeloid genes (FCER1G, EMR1, HK3, FCGR1A, CD163, and CD14), as compared to lymphoid genes CD3E and NCAM1 (CD56). Compared with DC subsets CD141^{+} cDC1 and CD1c^{+} cDC2, LAIR1 transcript levels were higher in plasmacytoid DCs (pDCs), monocytes, and CD141^{-}CD1c^{-} DCs.

The authors analyzed then LAIR1 protein expression in various immune cell types in murine blood and lung by flow cytometry. In mice, classical monocytes (Ly6C^{hi}CX3CR1$^{lo–mid}$CCR2^{+}) are recruited to tissue and tumor sites and differentiate into macrophages and secrete inflammatory cytokines. Non-classical monocytes (Ly6C^{lo}CX3CR1^{hi}CCR2^{-}) primarily function to scavenge damaged cells and debris from the luminal side of vascular endothelium[4,5] as well as the parenchyma of several tissues[6,7]. LAIR1 expression was higher in Ly6C^{-} monocytes compared with other immune cells in murine blood and lung. In lung, Ly6C^{-} monocytes even exhibited at least 5-fold higher LAIR1 expression compared to Ly6C^{+} monocytes and other immune cells.

Collagen1 and Colec12 are high affinity binding partners of LAIR1



Given the elevated expression of LAIR1 on monocytes, the authors tried to characterize its receptor interactome and gain insights into its functions in the extracellular milieu. Proteomic definition of the LAIR1 interactome identified stromal factor Colec12 as a high-affinity LAIR1 ligand. This affinity was similar to LAIR1's tight interaction with Collagen1.

Observing the robust phosphorylation of the LAIR 1 ITIM (immunoreceptor tyrosine-based inhibitory motif) domain upon Colec12 and Collagen1 binding, Keerthivasan et al. next utilized a quantitative proteomics assay to comprehensively profile signal transduction events downstream

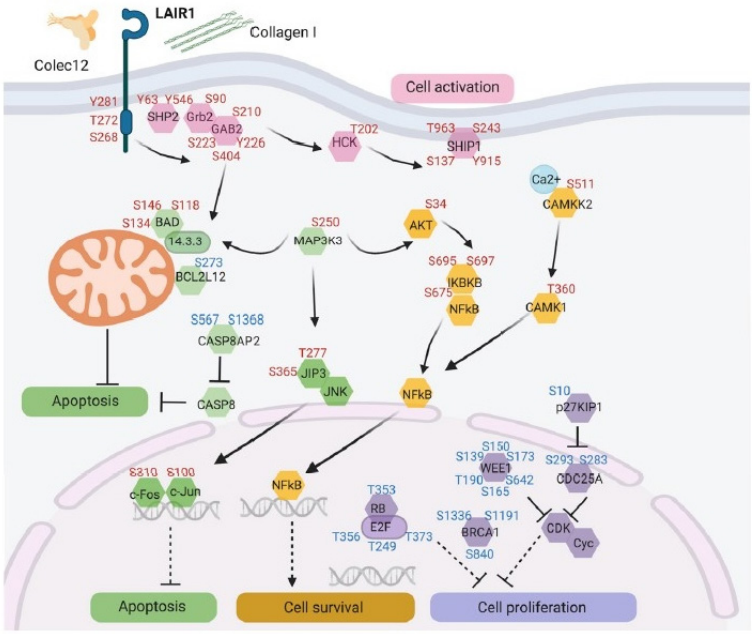
of LAIR1. Wild-type and LAIR-1 deficient THP-1 cells were stimulated with recombinant Collagen1 or Colec12 proteins. Proteomic profiling of LAIR1 signaling triggered by Collagen1 and Colec12 highlighted pathways associated with survival, proliferation, and differentiation in THP-1 cells.

LAIR1 deficiency in myeloid cells leads to aberrant proliferation and apoptosis

The researchers next generated Lair1$^{-/-}$ mice to examine the role of LAIR1 in monocytes and macrophages *in vivo*. Lair1 deletion led to a reduction in the frequency and number of Ly6C^{-} monocytes, but an increase in the frequency of Ly6C^{+} monocytes in bone marrow and lung. LAIR1 signaling may influence the developmental transition from classical to non-classical monocytes. This switch was associated with altered proliferation and apoptosis of non-classical monocytes from bone marrow and altered heterogeneity of interstitial macrophages in lung.

LAIR1 expression by myeloid cells is associated with improved clinical outcomes in melanoma

Considering the changes in monocytes and TRMs in lungs of Lair1$^{-/-}$ mice, Keerthivasan et al. examined the role of LAIR1 deficiency in tumor metastasis. They injected B16/F10 luciferase tumor cells intravenously via tail vein and monitored tumor growth. After 7 days, metastatic foci were 2 times more abundant and luciferase counts 2-3 times higher in the lungs of Lair1$^{-/-}$ mice. Myeloid-specific LAIR1 deficiency promoted metastatic growth in this melanoma model. In contrast, LAIR1 deficiency did not impact subcutaneous growth of B16 melanoma. These results suggest that LAIR functions in a myeloid cell-autonomous manner to restrain metastatic tumor growth in lung.



The researchers next asked whether homeostasis of Ly6C^{-} and Ly6C^{+} monocytes was altered in Lair1$^{-/-}$ lungs bearing B16 tumors. Thanks to cytometry analysis, they found that Lair1$^{-/-}$ Ly6C^{-} monocytes exhibited an enrichment in p53 and apoptosis pathways, while Lair1$^{-/-}$ Ly6C^{+} monocytes exhibited increased activity in angiogenesis and IL2-STAT5 pathways.

Ly6C^{-} and Ly6C^{+} monocytes also showed differences with respect to pathways activated in tumor compared to healthy lung. Blood Ly6C^{-} and Ly6C^{+} monocytes in tumor bearing mice also showed increased CSF1R (CD115) expression in Lair1$^{-/-}$ condition. Finally, the authors investigated the correlation of LAIR1 with myeloid cell signatures and identified Ly6C^{-} monocytes and macrophages as the most likely source of LAIR1 expression in metastatic melanoma. Moreover, LAIR1 expression was found to be associated with improved clinical outcomes in human metastatic melanoma.

Of note, human cells developed in our BRGSF-HIS (human immune system) mouse model express human specific inhibitory receptors such as LAIR1. In the spleen as in the bone marrow, LAIR1 was found to be expressed on all tested leukocytes, and highly expressed on effector T cells and in CD16^{-} natural killer cells.

References:

1. Keerthivasan S, Şenbabaoğlu Y, Martinez-Martin N, Husain B, Verschueren E, Wong A, Yang YA, Sun Y, Pham V, Hinkle T, Oei Y, Madireddi S, Corpuz R, Tam L, Carlisle S, Roose-Girma M, Modrusan Z, Ye Z, Koerber JT, Turley SJ. Homeostatic functions of monocytes and interstitial lung macrophages are regulated via collagen domain-binding receptor LAIR1. 2021, *Immunity* 54, 2021 July 13; 1511-1526
2. Biswas SK, and Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat. Immunol.* 11, 2014; 889–896
3. Sarkar A, Kim MV, Bivona MR, Liu ., Pamer EG, and Li MO. The cellular and molecular origin of tumor-associated macrophages. *Science* 344, 214; 921–925
4. Audoy-Rémus J, Richard J-F, Soulet D, Zhou H, Kubes P, and Vallières L. Rod-Shaped monocytes patrol the brain vasculature and give rise to perivascular macrophages under the influence of proinflammatory cytokines and angiopoietin-2. *J. Neurosci.* 28, 2008; 10187–10199
5. Auffray C, Fogg D, Garfa M, Elain G, Join-Lambert O, Kayal S, Sarnacki S, Cumano A, Lauvau G, and Geissmann F. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Science* 317, 2007; 666–670
6. Landsman L, Bar-On L, Zernecke A, Kim KW, Krauthgamer R, Shagdarsuren E, Lira SA, Weissman IL, Weber C, and Jung S. CX3CR1 is required for monocyte homeostasis and atherogenesis by promoting cell survival. *Blood* 113, 2009; 963–972
7. Tacke F, Alvarez D, Kaplan TJ, Jakubzick C, Spanbroek R, Llodra J, Garin A, Liu J, Mack M, van Rooijen N. Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J. Clin. Invest.* 117, 2007; 185–194