Mesenchymal stromal cell diversity and regulation of immune cell development

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Background

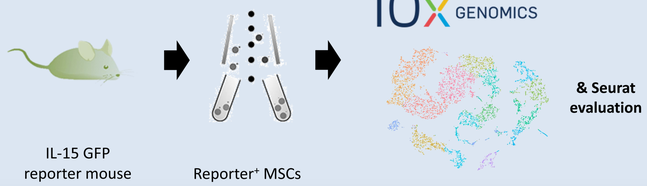
Bone marrow (BM) mesenchymal stroma cells (MSCs) provide distinct **lineage-instructive differentiation and survival signals** for hematopoietic stem and progenitor cells, such as CXCL12 and IL-15 (1). Hematopoietic stem cells (HSCs) for example reside and self-renew in CXCL12-rich perivascular MSC niches. While macrophages and dendritic cells are major IL-15 expressors, studies have shown that they are not sufficient to support maintenance of IL-15 dependent immune cell subsets such as NK, ILC1 and memory T cells in the BM (2)**, indicating the presence of other IL-15 sources**.

Hypothesis

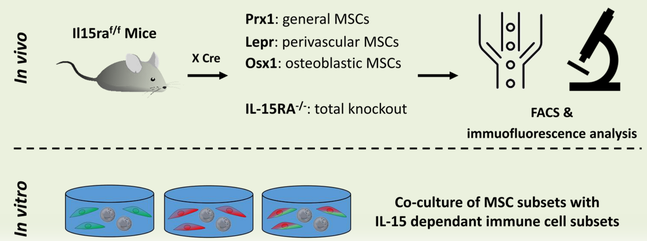
Heterogeneity among cytokine-/chemokine-expressing BM MSCs governs functional specialization, such as expression of distinct lineage-instructive differentiation signals for immune cell development ("**developmental niches**") or distinct survival/adhesion signals for (memory) immune cells ("**survival niches**").

Aims

Aim 1: Single-cell profiling of IL-15⁺ BM MSC subsets



Aim 2: Functional relevance of IL-15⁺ BM MSC subsets



Results

Our conditional KO experiments indicate a physiological relevance of IL-15+ MSCs for CD8+ memory T cell maintenance and NK cell development / maintenance. Nevertheless, the LepR expressing subset, which represents stem cell-like MSCs does not seem to be the causative subpopulation. The high co-expression of LepR on IL-15 GFP+ MSCs indicates a potential role of a rare, more mature LepR- IL-15+ MSC subset.

IL-15 GFP⁺ MSCs express LepR and locate close to hematopoietic cells

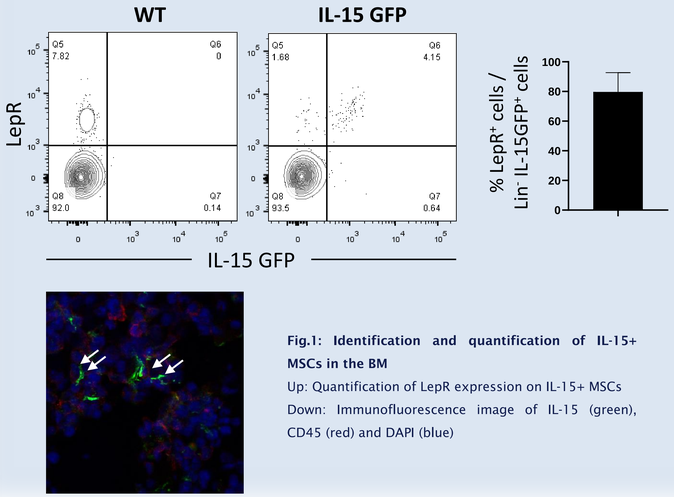


Fig.1: Identification and quantification of IL-15+ MSCs in the BM
Up: Quantification of LepR expression on IL-15+ MSCs
Down: Immunofluorescence image of IL-15 (green), CD45 (red) and DAPI (blue)

Deletion of IL15RA in MSCs impairs NK cell but not ILC1 development

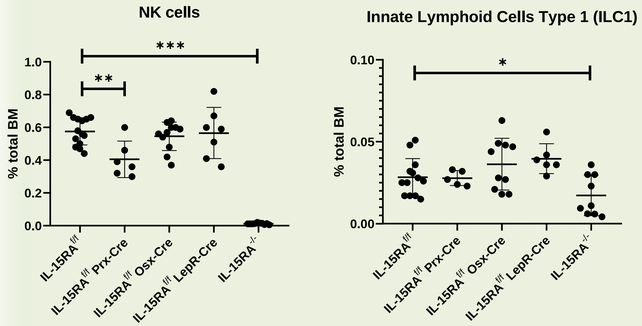
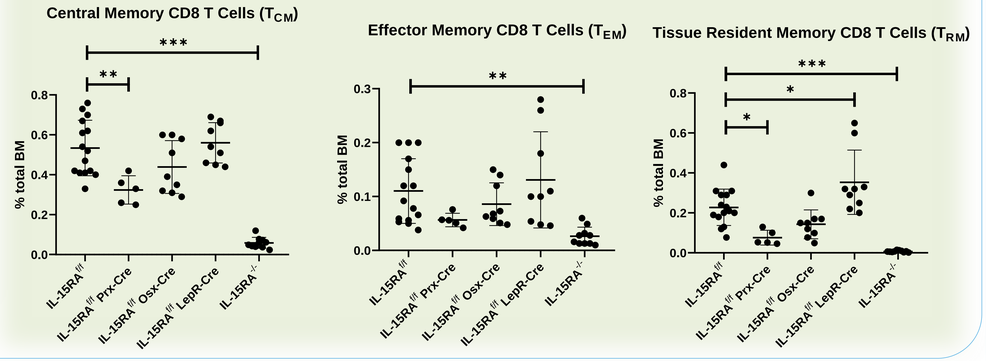


Fig.2: Percentage of group 1 ILCs and memory CD8+ T cells following conditional KO of all MSCs (Prx), osteoblastic MSCs (Osx) and LepR+ MSCs vs controls in the BM. . Mean ± s.e.m. are shown. Mean ± s.e.m. are shown. ** P < 0.01 and *** P < 0.001 (unpaired two-tailed Student's t-test).

Deletion of IL15RA in MSCs impairs survival of memory CD8⁺ T cell subsets



Conclusion

Our results indicate a physiological role of non-stem-like IL-15+ MSCs in development and maintenance of IL-15 dependent immune cell subsets. scRNAseq data will give further information about their identity as well as crosstalk mechanisms. The output will be validated via co-culture experiments.
With these investigations we will increase the understanding of stromal cells as regulators of immunity and immunological memory.

References

(1) Cordeiro Gomes, A. et al. Hematopoietic Stem Cell Niches Produce Lineage-Instructive Signals to Control Multipotent Progenitor Differentiation. ***Immunity*** 45, 1219-1231, doi:10.1016/j.immuni.2016.11.004 (2016).

(2) Mortier, E., et al. Macrophage- and dendritic-cell-derived interleukin-15 receptor alpha supports homeostasis of distinct CD8+ T cell subsets. Immunity 31, 811-822, doi:10.1016/j.immuni.2009.09.017 (2009).

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