The Role of Liver X Receptors in the homeostasis of Splenic Red Pulp Macrophages and Iron Metabolism.

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Introduction: The liver X receptors (LXRα and LXRβ) are members of the nuclear receptor superfamily of transcription factors. In macrophages, LXRs play essential roles in the coordination of both metabolic and immune responses, such as the transcriptional control of lipid metabolism or the modulation of innate and adaptive immune responses. Tissue resident macrophages are professional phagocytes that orchestrate innate immune responses and have considerable phenotypic diversity at different anatomical locations. In the spleen, there are different macrophage subpopulations, including red pulp and marginal zone macrophages, which play specific roles in homeostasis and disease. Red pulp macrophages (RPMs, identified as CD45+F4/80hiCD11blo by flow cytometry) are specialized cells that are important for the maintenance of Red Blood Cells (RBC) homeostasis, by actively phagocytosing injured and senescent erythrocytes, and thus being critical for the recycling of hemoglobin iron. We have previously reported that LXRs are crucial for the differentiation of splenic marginal zone (MZ) macrophages. Here we now show these nuclear receptors importance in the correct functioning of the red pulp of the spleen.

Material and methods: We used C57Bl/6 LXRαβ-/-, LXRα-/- and wild type mice, to compare the RPM and monocyte subpopulations both in the red pulp of the spleen and bone marrow using Flow Cytometry. Cell Sorting technique allowed us to perform transcriptional profiling, and quantitative PCR to monitor specific gene expression in these cell populations. Iron and hemoglobin concentration was analyzed through nephelometry, and iron distribution in the spleen by Prussian Blue histological staining.

Results: LXRαβ null mice present marked defects in splenic RPM subpopulation, despite elevated proportion of monocytes in the spleen. Presumably as a result of these alterations, iron handling is impaired in LXRαβ-deficient mice, that accumulate excessive iron in the splenic red pulp. In addition, LXRαβ-deficient mice also present defects in F4/80hiCD11blo iron-recycling bone-marrow resident macrophages. Strickingly, transcriptional analysis of RPM population in LXR-null mice showed defective expression of CD163, the hemoglobin scavenger receptor, which results in increased hemoglobin concentrations in the tissue.

Discussion: These results indicate a new role for LXR nuclear receptors in the regulation of iron homeostasis, possibly in part through the generation of an appropriate splenic RPM compartment.