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MICROANATOMICAL ANALYSIS AND QUANTIFICATION OF PLASMA CELL NICHE INTERACTIONS IN THE BONE MARROW

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Introduction

Long-lived plasma cells (PCs), responsible for the production of long-term antibody titers, have been shown to survive in the bone marrow for months to years in the absence of antigen. They are supported by a special microenvironment, the PC survival niche. Various cell types have been reported to contribute to this niche by providing survival factors, e.g. CXCL12-producing reticular stromal cells. Additionally, hematopoietic cells have been shown to mediate PC survival in vivo, amongst them megakaryocytes and eosinophils, but the spatiotemporal dynamics of the various niche components in the tissue remain elusive.

Aims

The aim of our work is to analyze the cellular and molecular composition of plasma cell survival niches in the bone marrow in situ.

Methods

In order to unambiguously quantify the localization of PCs, we are analyzing bone marrow cryosections and whole mounts for PCs, stromal cells, vasculature and accessory niche cells. Additionally, we have developed a computer modeling approach which allows us to distinguish random co-localization from non-random cell positioning.

Using these approaches, we have previously shown that PCs directly contact reticular stromal cells in a non-random fashion, while 30% of PCs are found in 10 µm vicinity to eosinophils, which represent only transient contributors to the niche. We have now analyzed PC localization in relation to mineralized bone, bone marrow vasculature and hematopoietic cell types in 3 dimensions and found that PC niches are situated at large distance to sinusoids.

Results

Semi-automated 3D analyses of whole mounts allow for a comprehensive and unbiased quantification of PC localization and their possible interactions with accessory niche cells in the bone marrow. We show that the survival niche for long-lived PCs is located distant from sinusoidal blood vessels, in contrast to what has been reported for the hematopoietic stem cell niche. We are now testing ways to mobilize PCs from their niches, which should result in shifted PC localization - from vessel-distant to peri-sinusoidal spaces. We are further exploring ways to perform multiplexed histological analysis using multi-epitope ligand cartography (MELC) in the bone marrow in order to further characterize the plasma cell niche.