Project 2: Hyaluronan matrix in bone marrow adipose tissue: implications for the development and progression of insulin resistance

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Background: Hyaluronan (HA), a major component of the extracellular matrix (ECM), is synthesized by three different HA synthases (HAS) that assemble HA from activated sugar precursors. Therefore an interrelationship between HA and glucose metabolism is considered and is further indicated by excessive deposition of HA occuring in white adipose tissue (WAT) and skeletal muscle in T2DM. [1].[2] Further, HA matrix directly affects adipogenesis in WAT and is possibly involved in WAT inflammation in T2DM via the recruitment of immune cells into WAT.[2]

Brown adipose tissue (BAT), known for its thermogenic properties, is also increasingly recognized for its importance in the regulation of metabolic homeostasis. Recently we identified HA as a regulator of BAT function. [3]

Bone marrow AT (marrow AT, MAT) is in cellular, molecular and functional aspects clearly distinct from WAT and BAT. Importantly, MAT contributes to systemic metabolism, osteogenesis as well as hematopoiesis via its specific endocrine and paracrine actions and it has been reported that MAT increases in T2DM. [4]

HA is a pivotal component of the bone marrow stromal microenvironment and has been reported to be of importance for bone marrow hematopoiesis. However, the role of MAT-ECM for MAT function as well as the possibility of cross-talk between the different AT compartments (MAT – BAT – WAT) in the context of early IR and T2DM remain to be defined.

Own previous work: Functions of HA matrix and mechanisms of immunomodulation were addressed in multiple metabolic and inflammatory disease models. Specifically it was shown that HA matrix is essential for infarct healing by orchestrating the macrophage and the fibroblast response and on the other hand HA is a modulator metabolic homeostasis and insulin sensitivity by directly effecting BAT activity.

Aim of the project: In this project the role of HA in MAT and its role for inflammation during the early phase of T2DM and insulin resistance (I/R) will be unravelled. Ultimately, therapeutic implications will be tested in a murine model of IR and obesity

Work program: Changes in the HA-matrix in MAT and their functional effects on MAT secretory profile of MAT as well as on immune responses will be characterized during disease initiation and progression in a murine model of diet-induced obesity and IR. Effects of ubiquitous and AT-specific HAS-knockout on MAT and the metabolic responses during IR will be evaluated. Finally, HA synthesis will be inhibited pharmacologically and the effects on MAT-ECM, MAT function and systemic metabolic control during development of IR will be examined.

References:

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4. Hamrick, M.W., et al., *Leptin treatment induces loss of bone marrow adipocytes and increases bone formation in leptin-deficient ob/ob mice.* J Bone Miner Res, 2005. **20**(6): p. 994-1001.