Project 5: Role of Interleukin (IL-)6 trans-signaling in meta-inflammation and development of insulin resistance.

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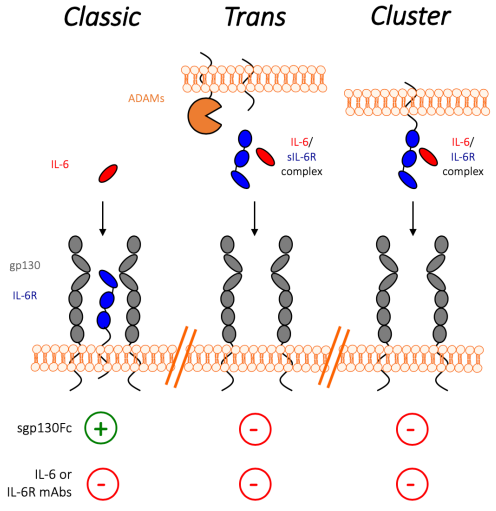
Background: Obesity with type 2 diabetes mellitus (T2DM) is accompanied by a chronic, low-grade metabolic inflammation 'meta-inflammation', characterized by increased interleukin (IL)6 levels. Meta-inflammation may already occur in early developmental stages and impact metabolism and disease progression throughout different stages of life. IL-6 interacts with insulin signaling and controls metabolic processes such as lipid and glucose homeostasis. Interestingly, in skeletal muscle of T2DM patients, IL-6 signaling has been shown to be compromised, indicating links between IL-6- and insulin-dependent signaling pathways.

Own previous work: We have assigned functional roles of IL-6 trans-signaling in the development of chronic inflammation using the specific trans-signaling inhibitor sgp130, whereas classic signaling appears to be mainly involved in hepatic acute phase response and homeostatic, metabolic functions of IL-6. We developed a novel IL-6 trans-signaling mouse model, with exclusive production of the sIL-6R to enable IL-6 trans-signaling and prevent classic-signaling, which complements our experiments using sgp130, which inhibits transsignaling but allows classic-signaling. The trans-signaling sIL-6R mice represent a novel genetic strategy to phenocopy substrate-selective hyper-activation of ectodomain shedding of IL-6R which is mainly executed by ADAM-proteases. Finally, a transgenic mouse strain with a cell autonomous, constitutive active variant of gp130 (CRE-Lgp130f/f) complement the study by using (Cre/lox-based) tissue-specific, time resolved activation of cytokine signaling.

Aim of the project: High-fat diet-induced obesity in young genetically modified mice will uncover the role of IL-6 classic and trans-signaling in obesity-induced meta-inflammation with respect to the early transition from the healthy state to insulin resistance. Analysis of meta-inflammation will be performed in the Scheller lab, whereas metabolic profiling will be done in the Al-Hasani lab. The long-term perspective will comprise the analysis of cell-type specificity to enable tailormade manipulation of IL-6 type cytokine induced meta-inflammation.

Work program: IL-6R-deficient, IL-6-trans-signaling and control mice will be fed a high fed diet (HFD) and analyzed if IL-6 trans-signaling can completely compensate for the loss of classic signaling. Next, conditional IL-6R$^{-/-}$ mice will be analyzed in HFD and compared with SD. Finally, the consequence of constitutive activation of gp130 receptor signaling will be analyzed using Lgp130 transgenic mice. All mice will be subjected to comprehensive metabolic phenotyping, induction of insulin resistance and analysis of meta-inflammation by e.g. recruitment of macrophages into adipose tissue beds and status of M1/M2 polarization. Determination of blood glucose and insulin level under fasting conditions and body composition by NMR. Determination of substrate preference will be made by indirect caliometric measurements followed by final analysis of glucose uptake and fatty acid oxidation in isolated skeletal muscles. Additionally, measurements of glucose and insulin tolerance will be performed followed by a final analysis of contraction power of the isolated skeletal muscles.



References: Fazel-Modares N et al. IL-6 Trans-Signaling controls liver regeneration after partial hepatectomy. Hepatology. 2019; 70(6):2075-91. Scheller J et al. Immunoreceptor engineering and synthetic cytokine signaling for therapeutics. Trends Immunol. 2019; 40(3): 258-272. Floss DM et al. Naturally occuring and synthetic constitutive-active cytokine receptors in disease and therapy. Cytokine Growth Factor Rev. 2019; 47:1-20. Lamertz L et al. Soluble gp130 prevents interleukin 6 and interleukin 11 cluster signaling but not intracellular autocrine responses. Sci Signal. 2018; 11(559).