Project 3: Regulation of adipogenesis and adipocyte fate by inflammatory signalling

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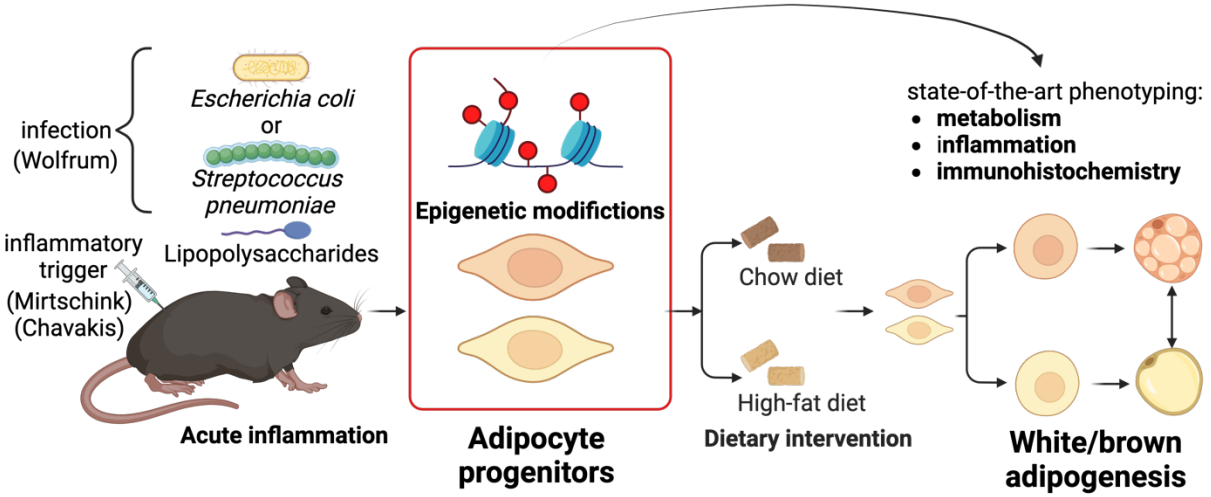

Figure 1. *Infection/inflammation may promote epigenomic remodelling in adipocyte progenitors that could lead to altered white/brown adipogenesis. Created with BioRender.com.*

Background: Obesity is accompanied by altered function of precursor populations in the white and brown adipose tissue (WAT and BAT respectively) that may lead to adipose tissue changes, such as hyperplasia (increase in cell number) and/or hypertrophy (increase in cell size), fibrosis and reduced beige and brown thermogenic adipogenesis. These alterations in adipocyte precursor function hence underlie obesity-related metabolic dysregulation of the adipose tissue promoting obesity-associated metabolic disease (1-3). Evidence from epidemiologic studies suggests that preceding inflammatory events, such as earlier infection and/or antibiotic exposure increases the risk of obesity in childhood and in adult life (4, 5). While this has been partially attributed to altered microbiome, the exact mechanisms remain unclear. Specifically, it is less well understood how inflammatory signalling, triggered e.g. by a preceding infection or inflammation may affect adipocyte precursor fate and their subsequent reactions to an obesogenic high-caloric diet. We (Chavakis and Mirtschink group) are interested in how inflammation in the adipose tissue may affect the development of metabolic dysregulation (2, 6). In addition, we have substantially contributed to the understanding of the new immunological principle of trained immunity, which defines a form of inflammatory memory. Specific inflammatory triggers may induce, via epigenetic rewiring, a higher preparedness of innate immune cells, which then show stronger responses upon a future secondary challenge (7-9). Interestingly, inflammatory memory has been described in parenchymal cells as well (10). The Wolfrum group aims to identify adipocyte precursor populations for both WAT and BAT in vivo and furthermore, to elucidate molecular mechanisms driving preadipocytes proliferation, commitment and differentiation as well as activity of mature white and brown adipocytes. In this context, we have recently identified a rare subpopulation of adipocytes that increases in abundance at higher temperatures and regulates the activity of neighboring adipocytes through modulation of their thermogenic capacity (11). Additionally, we have shown that seasonal or experimental cold exposure induces epigenetic reprogramming of the sperm resulting in hyperactive BAT in the offspring and in improved adaptation to over-nutrition and hypothermia (12).

Aims: In this project, we hypothesize that inflammatory memory of adipocyte precursors may affect the later development of pathologic obesity. We will assess if a preceding inflammatory event may epigenetically modify adipocyte precursors, which then react in a different fashion to a future obesogenic high-caloric diet. Using mouse models of acute and chronic inflammation or acute infection we aim to study whether (i) an earlier inflammatory trigger, e.g. LPS (Chavakis, Mirtschink) or (ii) an earlier infection (Wolfrum) affects white and brown adipocyte precursors with regards to their functions, such as proliferation and differentiation,

thereby contributing to obesity and metabolic dysfunction at later time points. To this end, we will thoroughly assess the temporal dynamics of adipose tissue composition and function.
Approach: Acute inflammation will be induced in young adult mice by systemic LPS injection (Chavakis, Mirtschink). As infection models, *Streptococcus pneumoniae* induced pneumonia or *Escherichia coli* induced enteritis will be used in young mice as well (Wolfrum). After resolution of inflammation or clearance of the infection, mice will be fed a high fat diet (HFD) or a normal diet (ND) as control for different periods. The subsequent experimental work with lean and obese mice will include comprehensive state-of-the-art phenotyping to evaluate systemic metabolism e.g., by glucose and insulin tolerance tests, indirect calorimetry, lipidomics analysis and metabolomics analysis in adipose tissue, analysis of inflammation (using e.g. flow cytometry, multiplex measurements of cytokines) as well as thorough immunohistochemistry, assessing for adipocyte hyperplasia and hypertrophy. The major focus will be on analysis of adipocyte precursors and their fate. Genome-wide transcriptomic and epigenomic analyses will be performed with a particular focus on genes related to proliferation, differentiation and metabolism. Early and late adipocyte progenitors will be traced in vivo using tamoxifen inducible Cre systems as well as EGFP models (available in the Wolfrum laboratory) allowing direct labelling and hence quantification of adipocyte precursor maturation as well as adipocyte formation. These approaches will allow us to quantify changes in adipocyte precursor populations in our models of altered adipose tissue functionality. Complementary to these lineage-tracing approaches, we will employ single nuclear analysis at different time points to assess the dynamics of early and late adipocyte progenitor abundance.

Topics for the PhD studentships will be:

Ad i) Comprehensive characterization of adipose tissues and populations therein under normal and obesogenic conditions upon earlier inflammatory challenge (Dresden)

Ad ii) Comprehensive characterization of adipose tissues and populations therein under normal and obesogenic conditions after earlier infection (Zurich)

Work to be performed in Dresden: The Chavakis/Mirtschink group will investigate adipose tissue and particularly adipocyte progenitors in lean and obese mice in response to earlier inflammatory challenges using systemic LPS administration. Moreover, our in house metabolomics facility, NMR spectroscopy as well as mass spectrometry, will support metabolomic analyses of samples generated at both sites.
Work to be performed in Zurich: The Wolfrum group will perform analysis of adipose tissue and adipocyte progenitors in lean and obese mice following earlier infection (lung infection by *Streptococcus pneumoniae* and *Escherichia coli*-induced enteritis) and will engage lineage tracing approaches to study early and late adipocyte progenitors in vivo.

Added value through the collaboration between Dresden & Zurich: The Chavakis/Mirtschink and Wolfrum laboratories each have unique expertise, respectively, in innate immunity/immune-metabolism and in the molecular mechanisms and cellular heterogeneity of adipose tissue. Combining these complementary areas of expertise will provide knowledge on the possible involvement of inflammatory memory on adipose tissue composition and function, as possible contributors to metabolic dysregulation.

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