Transcriptional control of macrophage diversity and plasticity in metabolic health and disease

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Gruppens kerneforskningsområder

Obesity is associated with a dramatic remodeling of e.g. liver and adipose tissue composition, and macrophage infiltration into these tissues in this context was for long thought to be purely detrimental for metabolic health via release of inflammatory mediators. However, it has recently become clear that the macrophage population in these tissues display a remarkable degree of heterogeneity during obesity, and different subpopulations have been proposed to confer protection in this context.

We have further recently shown that tissue resident macrophages contribute to fasting ketogenesis in healthy mice, highlighting the complex context-dependent interplay between macrophages and metabolic cell types. Moreover, metabolic rewiring of macrophage function in obesity may have implications for anti tumor immunity and immune therapy, and tumor growth can conversely trigger hyperactivation of macrophages and other immune cells leading to severe metabolic dysfunction and tissue wasting (i.e. cancer cachexia).

We are interested in understanding how these interplays are controlled and focus specifically on identifying the transcription factors in macrophages that initiate beneficial or detrimental changes in gene activity in response to changes in hormonal, nutritional, and inflammatory cues.

For this purpose, we combine mouse models and viral delivery of genome editing systems with flow cytometry and single cell technologies to assess transcription factor function in a cell type/single cell resolved, high throughput manner. We further aim to employ single cell sequencing data and methodologies to generate synthetic viral drivers capable of targeting specific macrophage populations and transcriptions factors, for assessment of their importance for overall physiological homeostasis.

Overall, our research is focused on understanding the transcriptional mechanisms controlling metabolic rewiring of macrophages, thereby also outlining potential macrophage directed therapeutic strategies.

Er du interesseret i at skrive projekt i gruppen, så kontakt :
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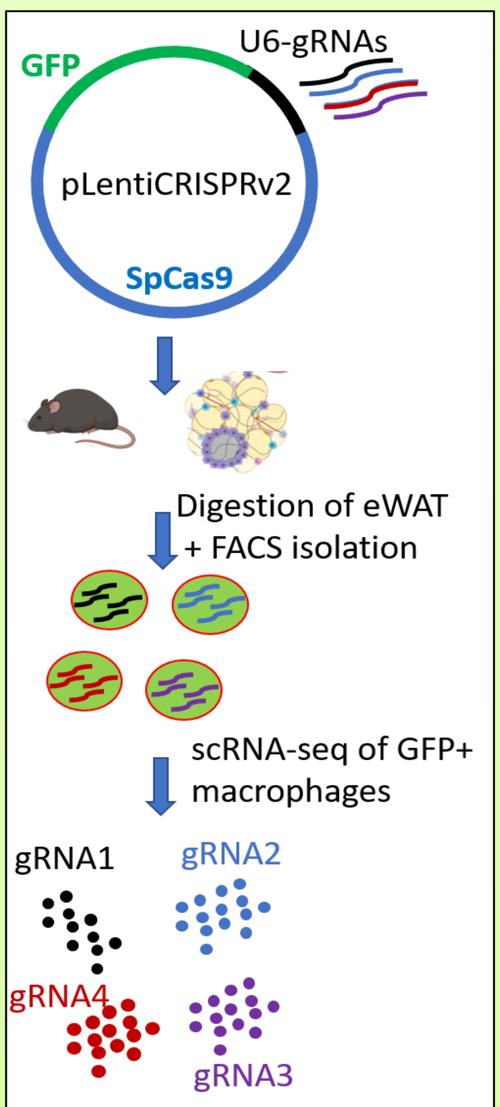

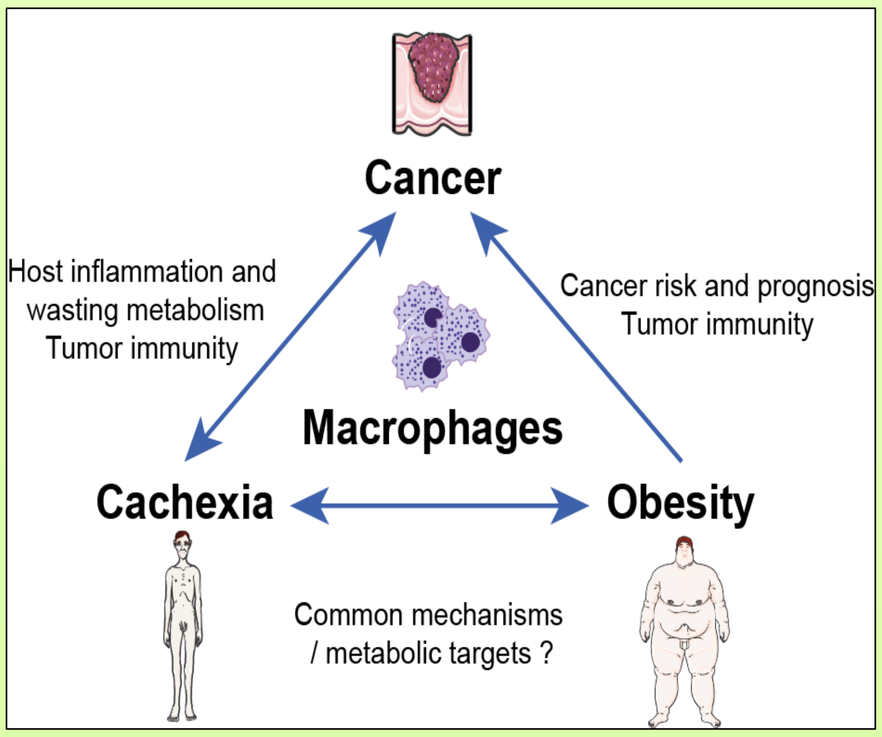

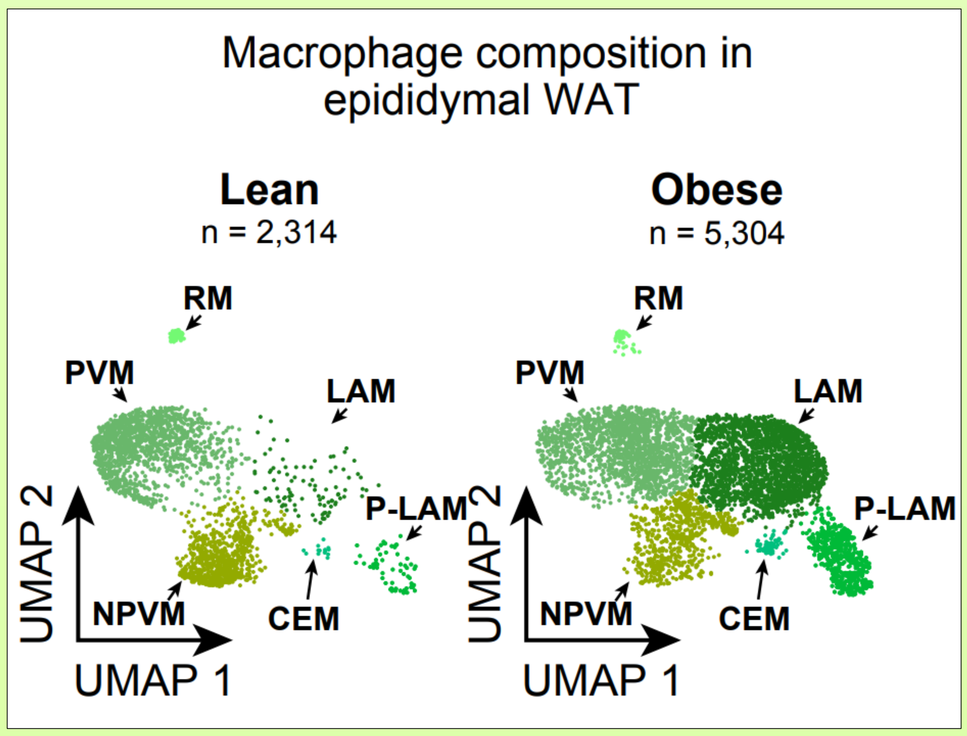

Projekter	Beskrivelse
Transcriptional regulation of macrophage plasticity in obese adipose tissue	In this project, we will apply machine learning approaches to single cell RNA-sequencing data generated from adipose tissue of obese mice to identify regulatory sequences controlling the identity and function of specific macrophage subsets and the transcription factors binding to these motifs. Transcription factors will be functionally assessed using lentiviral delivery of Cas9 and guide RNAs libraries combined with cell sorting and/or (single cell) sequencing.
Generation of synthetic viral drivers for targeting specific macrophage subsets	In this project, we will randomly combine different regulatory sequences potentially controlling the identity of specific macrophage subset. The generated synthetic drivers will be inserted into selftranscribing lentiviral reporters, which will be injected into mice. Cell sorting and/or (single cell) sequencing will be used to identify drivers with the desired potency and specificity. These will be used to deliver RNAi or genome editing systems to assess the physiological consequences of targeting the same transcripition factor in all cells of a specific macrophage subset.