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).

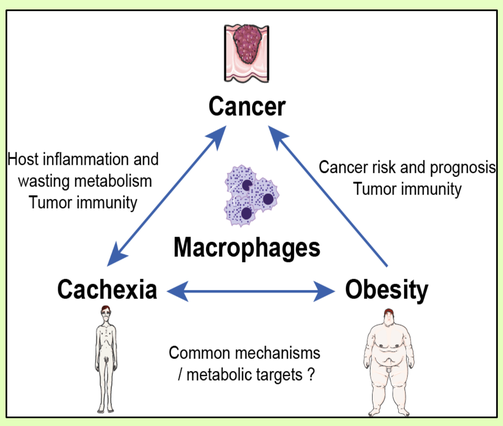
We are interested in understanding how these interplays are controlled and focus specifically on identifying the transcription factors in macrophages that initiate beneficial or detrimental regulatory changes in response to changes in hormonal, nutritional, and inflammatory cues.

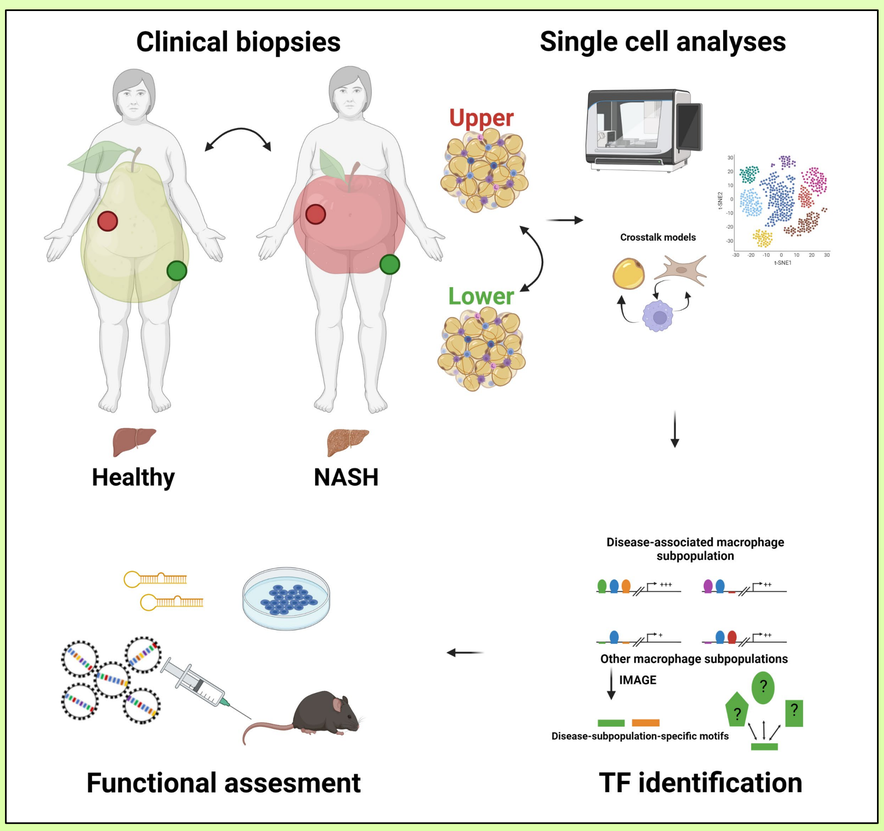
For this purpose, we combine single cell analyses of clinical samples, cell culture studies, and viral targeting strategies in animal disease models. Currently, a key focus is to understand adipose tissue macrophage function in healthy vs unhealthy obesity. We further aim to employ single cell sequencing data and methodologies to generate synthetic viral drivers capable of targeting specific macrophage populations and transcriptions factors.

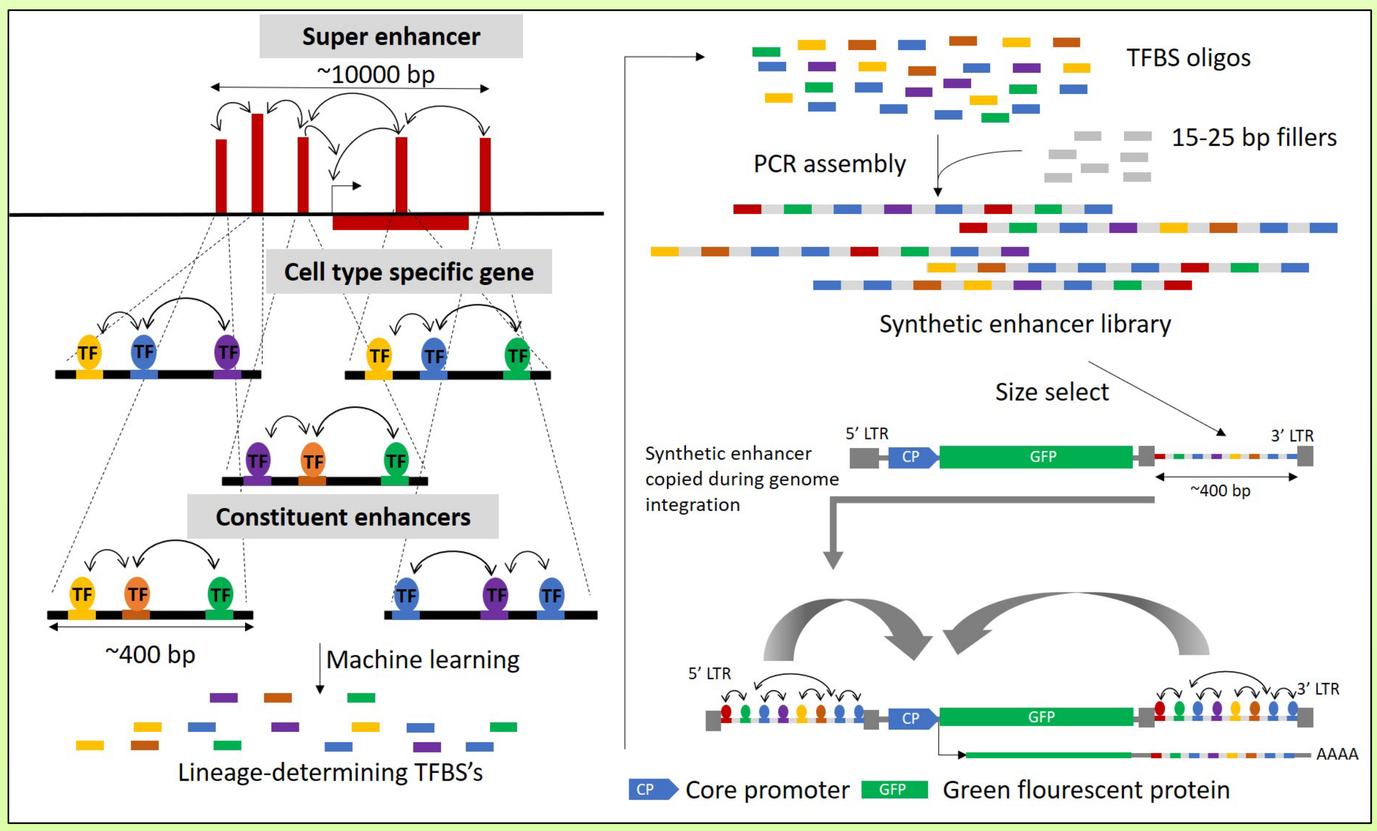
Overall, our research is focused on understanding the transcriptional mechanisms controlling metabolic rewiring of macrophages, thereby also outlining potential macrophage directed therapeutic strategies.

Functional Genomics & Metabolism

Er du interesseret i at skrive projekt i gruppen, så kontakt : sfs@bmb.sdu.dk







Projekter	Beskrivelse
Transcriptional regulation of adipose tissue macrophage plasticity and function in healthy obesity	We are applying bulk and single cell sequencing analyses to adipose tissue biopsies from obese individuals with varying degrees of metabolic complications, such as development of fatty liver or non-alcoholic steatohepatitis. In this context, we are also investigating the molecular mechanisms underlying the protective effects of fat storage in lower body depots (pear shape) compared to storage in upper body depots (apple shape). Machine learning will be used 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 in cell culture models and eventually in animal models for assessment of their contribution to overall metabolic homeostasis.
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 subsets. The generated synthetic drivers will be inserted into self-transcribing 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 manipulating transcription factor expression in specific macrophage subsets.