Postdoc **Hande Topel Batarlar**, PhD, MSc

Place of employment University of Southern Denmark, Department of Biochemistry and Molecular Biology

Principal supervisor: Master of Basic Science Jarl-Wilhelm Kornfeld, University of Southern Denmark, Department of Biochemistry and Molecular Biology

Title of project: The Role of Proto-Adipokine AOC3 During Adipose Tissue Dysfunction in Metabolic Diseases

ABSTRACT

Fat cells or adipocytes are centrally involved in regulation of healthy metabolism by storing food-derived calories for times of need. Interestingly, in metabolic diseases like obesity and T2D, (dysfunctional) adipocytes contribute to disease through aberrant endocrine crosstalk and promote aberrant coordination of energy metabolism in distant organs like liver, muscle and brain. Adipocytes secrete factors termed 'adipokines' that coordinate energy balance through activation of signaling pathways and modulation of gene regulation in recipient tissues. Whereas most adipokine are secreted by classical exocytosis, a non-canonical secretion mechanism termed 'ectodomain shedding' exists, which has been poorly investigated in the context of metabolic regulation. Here, cell membrane-tethered isoforms of adipokines ('proto-adipokines') are released into the circulation through cleavage by surface-bound proteases called 'sheddases'.

Unpublished data from our lab has revealed the existence of a novel regulatory circuit on adipocytes, where one of the major sheddases, termed BACE1, processes the membrane-tethered form of the multifunctional amino oxidase 3 (AOC3) protein, thereby giving rise to circulating levels of soluble AOC3 (sAOC3) proteoform which has potent functions in immune cell attraction and activation. During Metabolic Disease, we observe aberrant activation of this BACE1-AOC3 axis, selectively on adipocytes, suggesting that elevated levels of (adipose-derived) sAOC3 plays a key role in translating adipose tissue dysfunction into systemic impairment of energy homeostasis in mouse and human obesity.

In this project, I plan to molecularly investigate the proteolytic processing mechanism of AOC3 through BACE1 in adipocytes using advanced super-resolution STED microscopy techniques and genetically engineered cell systems for BACE1-AOC3 activation and, mouse lines to address the *in vivo* function of elevated AOC3/sAOC3 expression for paracrine and endocrine regulation of adipose tissue function and metabolic control. I will address the role of BACE1- AOC3 signaling in human adipocyte cell systems, and explore its biomarker properties by probing adipose tissue biopsies from obese and T2D human patients for BACE1-AOC3 signaling alterations.