GUEST LECTURE SERIES

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Targeting of thermogenic adipose tissue in cardiometabolic

Promoting brown adipose tissue (BAT) activity has been recognized as an innovative therapeutic approach to improve obesity and metabolic disease. Whilst the circuitry underlying thermogenic activation of BAT is well understood, the processes underlying rheostatic regulation of BAT to maintain homeostasis and avoid excessive energy dissipation remain ill-defined. Increasing cyclic adenosine monophosphate (cAMP) biosynthesis by virtue of Adenylyl Cyclases (ADCY) proteins, which are strongly linked to human cardiometabolic disease, is key for BAT activation and we here demonstrate that adenylyl cyclase 3 (ADCY3) is key for cAMP generation and BAT function in obesity. Further, by combining (full-length) RNA-seq with H3K4me3 profiling, we report novel, cold-inducible promoters that generated a 5' truncated Adcy3 mRNA isoform (Adcy3-at) during cold. Translated ADCY3-ATs protein are structurally conserved between rodents and primates, indicating that transcriptional rewiring via alternative promoter commissioning is key for thermogenic fat function across species. We found that transgenic, which specifically lack ADCY3-AT, display increased energy expenditure and are resistant against obesity and ensuing metabolic imbalances, and present fundamentally novel molecular insights into how novel cold-inducible proteoforms such as ADCY3-AT can limit the adverse consequences of uncurbed cAMP activity during long-term BAT activation. At the end, I will also present unpublished data on a novel class of small molecule inhibitors that promote energy expenditure via brown and beige fat activation and which exhibit profound beneficial effects in rodent models of obesity.