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Project Summary/Abstract
Obesity is a burgeoning epidemic that affects approximately one third of the American population. Current treatments have low long-term efficacy or require surgery. Recent research showing the ability of nonshivering thermogenesis (NST) to reduce obesity in rodents and the presence of thermogenic adipocytes in humans provides a potential novel strategy for developing obesity therapies. NST maintains body temperature duringa cold challenge in parth through the action of brown adipose tissue (BAT). Current models suggest white adipose tissue (WAT) derived fatty acids, products of neutral lipases including adipose triglyceride lipase (ATGL/PNPLA1). Acid lipases have not previously been implicated in NST; however, recent studies implicate lysosomal acid lipase (LIPA) in the regulation of lipolysis in WAT. Unexpectedly, our preliminary data show that temperature challenges activate lysosome function in BAT and that whole body genetic ablation of LIPA impairs thermogenesis, rendering mice unable to defend body temperature in response to a cold challenge. Moreover, these lysosomal functional changes appear to be specific to the BAT, not the WAT. Despite these findings, many questions regarding this novel lysosomal-dependent NST and the role of lysosomal and neutral lipases in producing fatty acids required for thermogensis remain. We hypothesize that LIPA provides fatty acids for uncoupled oxidation in BAT either through endogenous lipids within brown adipocytes or secondarily through macrophages. Aim One will test whether lysosomal and specifically LIPA function is required in the brown adpocytes for NST. We will use a combination of techniques: first, a BAT transplant to test whether BAT with intact LIPA can rescue the cold sensitive phenotype of the LIPA knockout mice, and second, a brown adipocyte-specific LIPA knockout mouse. Cold challenge of the tissue specific model and the transplant will allow us to determine the importance of LIPA in brown adipocytes. In Aim Two, we will assess the contribution of the nutral lipase ATGL in BAT to NST. A published study of ATGL used a Cre-line that deleted in white adipocytes, brown adipocytes, and macrophages that are each implicated in NST function. We will generate a brown adipocyte-specific ATGL knockout line. Cold challenging these mice will provide functional evidence of the role of ATGL in BAT NST maintenance. Successful completion of the proposed studies will define the contributions of acid and neutral lipases to BAT dependent NST.