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PROJECT SUMMARY

The rising tide of obesity represents a public health crisis due to its strong association with a panoply of disease conditions, notably including insulin resistance leading to type 2 diabetes. Although the mechanism linking obesity and insulin resistance remain controversial, an attractive hypothesis posits that the excess lipid of obesity strains the handling capacity of adipocytes, which then, through various proposed mechanisms, foments insulin resistance. The idea of harnessing the ability of the adipocyte to burn off its own surplus lipid has gained popularity in recent years due to a renewed interest in the study of brown adipose tissue in adults as well as the finding that white adipose tissue can undergo "browning" changes. The proposed project seeks to establish a better understanding of the role of key insulin-responsive transcription factor FoxO1 in the regulation of adipocyte browning. I have already found in a brown-adipocyte cell line as well as in cultured white primary adipocytes that overexpression of FoxO1 selectively represses the expression of "brown" genes – those necessary for engaging in thermogenic lipid oxidation – while leaving unaffected "pan-adipocyte" genes. In order to determine whether these observations hold up in vivo and their potential medical applications, I have generated mice lacking FoxO1 specifically in adipocytes, termed the "A-FoxO1" model. I therefore describe in this proposal two Specific Aims centering on the characterization of the A-FoxO1 model. First, I propose a thorough metabolic phenotyping of the A-FoxO1 mouse, including biometrics (e.g., body weight, body composition, adipose-tissue depot weights) and assays of insulin sensitivity at both the levels of whole-body (e.g., glucose tolerance testing, insulin tolerance testing) and the cell (e.g., activation of insulin signaling pathway components). Next, I will test the adipocyte browning response in A-FoxO1 mice by subjecting animals to cold (4ºC), room temperature (22ºC), or thermoneutrality (30ºC) for various time periods and then performing gene-expression and histologic analyses of white and brown adipose tissue depots. A potentially differential browning response in the absence of FoxO1 suggests a potential application to diet-induced obesity. I will therefore perform the temperature exposure experiments again following highfat feeding of A-FoxO1 and WT mice and determine whether A-FoxO1 mice differ significantly in their sensitivity to insulin. Particularly of interest is a potential difference in insuiln sensitivity that manifests even at room temperature, suggesting a practical application to human obesity. Finally, I will isolate and culture both A-FoxO1 and WT primary preadipocytes ex vivo in order to perform detailed biochemical and cell biologic studies of the mechanism underlying the putative regulation of adipocyte browning by FoxO1. These studies represent a set of challenging but reasonable goals that will not only contribute significantly to my development as a scientist but may also prove valuable in the continuing struggle against obesity