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Adipose tissue development, metabolism and endocrine function are essential for the efficient storage of lipids in adipocytes and for normal systemic metabolism. Obesity alters adipose tissue function and impairs the efficient storage of triglycerides in adipocytes, leading to ectopic deposition of lipids and metabolic impairment in non-adipose tissues. Adipose tissue macrophages (ATMs) through their inflammatory function have been implicated in the development of obesity-induced adipocyte dysfunction and complications, including type 2 diabetes, non-alcoholic fatty liver disease and dyslipidemia. Studies funded by this grant have revealed that obesity leads to the accumulation of macrophages in adipose tissue of obese rodents and humans, that adipose tissue macrophages contribute substantially to local and systemic obesityinduced inflammation and that the macrophage content of adipose tissue is tightly correlated with metabolic derangements associated obesity.

The non-inflammatory or trophic functions of macrophages that modulate adipose tissue development and metabolism have been less well characterized. In other tissues, including bone, the central nervous system and liver, resident macrophages through complex paracrine loops play essential roles in the development and maintenance of parenchymal cells. Some of our recent observations suggest similar communication exists between adipocytes and ATMs. During the current grant period, we found that adipocyte lipolysis rapidly leads to ATM accumulation, that depletion of macrophages in adipose tissue from obese individuals increases basal lipolysis, that ATMs are the primary source of both insulin-like growth factor-1 (Igf1) and lipoprotein lipase (Lpl) in obese adipose tissue and surprisingly that obesity rather then inducing a classical inflammatory program in ATMs activates a program of lipid uptake and lysosome biogenesis. From these data emerge a dichotomous picture of ATMs in which their action on adipocytes and adipose tissue function is the balance of their inflammatory and trophic functions. In an effort to provide a more complete picture of ATM function we propose three aims focused on elucidating aspects of the trophic interactions: 1) To study the role of lipolysis in the chronic recruitment and accumulation of ATMs in obesity 2) To determine the role of ATM lysosomes and autophagy in function ATMs and adipose tissue metabolism 3) To characterize the role of ATM-derived IGF-1 and LPL in adipose tissue development and metabolism.

Achieving the goals of this proposal will identify critical processes and molecules required for ATM accumulation and function. Success will also provide important insights into adipose tissue physiology, and by identifying the molecular mechanisms that regulate macrophage accumulation and function in adipose tissue, identify potential novel strategies to reduce obesity-induced adipocyte dysfunction and its attendant complications.
