Autophagy in Non-Cell Autonomous Regulation of Adipogenesis

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Age-related metabolic disorders often result from the dysfunction in adipose tissue, which is responsible for energy storage and mobilization. Formation of the adipose tissue or adipogenesis involves the differentiation of pre-adipocytes into adipocytes, which requires remodeling of the whole pool of cellular proteins (proteome). Chaperone-mediated autophagy (CMA) is a selective form of lysosomal protein degradation that degrades damaged proteins and remodels the functional proteome for regulatory purposes. CMA activity decreases with age, leading to the extracellular release of undegraded products. Here, I propose a model whereby CMA loss with age in pre-adipocytes leads to the extracellular release of undegraded products that may interfere with adipogenesis and contribute to adipose tissue malfunctioning in aging. I found that media collected from CMA-deficient mouse adipose progenitor cells, when added to differentiating normal pre-adipocytes in culture, increased intracellular lipid storage, suggesting upregulation of adipogenesis. To investigate if similar cell-extrinsic deregulation of adipogenesis occurs in vivo and if it could be driven by CMA blockage in distal tissues, I analyzed white adipose tissue from mice with CMA blockage in neurons and found increased expression of several adipocyte genes, indicating possible upregulation of adipogenesis. My results raise the possibility that decline in CMA with age promotes global changes in the extracellular environment that contribute to non-cell autonomous deregulation of distal organ function. The paracrine and endocrine consequences of CMA failure on adipogenesis identified in my work justify future efforts to restore CMA as a possible therapeutic intervention against the metabolic syndrome of aging.

Awards Won:
Second Award of $2,000