Capillary remodeling in Obese Skeletal Muscle

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Skeletal muscle comprises ~40% of total body mass and is a main site for the consumption of nutrients (i.e. Glucose, lipids), making it a major regulator of metabolic homeostasis. A critical yet often overlooked factor is the presence of capillaries (small blood vessels) that regulate the distribution of nutrient and oxygen rich blood to support skeletal muscle functions. In fact, an emerging body of research indicates that the expansion (angiogenesis) or regression of the skeletal muscle capillary network independently influence systemic insulin sensitivity, demonstrating the importance of these vessels for metabolic homeostasis. Surprisingly, the regulation of skeletal muscle capillarity in the context of obesity, and potential implications for the pathogenesis of metabolic dysfunction, remains largely unexplored.

My first study explored the potential involvement of the forkhead box O (FoxO) family of transcription factors because they are recognized as potent inhibitors of angiogenesis and have previously been implicated in the progression of metabolic disorders. Using transgenic mice with an endothelial (capillary) cell directed depletion of FoxO, we showed that the absence of FoxO proteins promoted angiogenesis in response to a prolonged (16-week) high fat (HF) diet, resulting in reduced skeletal muscle insulin sensitivity. Analysis of the skeletal muscle transcriptome in HF fed mice revealed an increased pro-angiogenic and lipid metabolism gene profile in FoxO deficient mice, providing further mechanistic insight. In the second study, using leptin receptor mutant mice, we demonstrated that the adipokine leptin (elevated in obesity) is a physiological regulator of skeletal muscle capillarity by promoting the production of the pro-angiogenic factor, VEGFA by skeletal myocytes. These studies indicate that both pro- and anti- angiogenic factors regulate the skeletal muscle capillary network in obesity, and that angiogenesis is an adaptive response to restore metabolic homeostasis in the context of obesity. Furthermore, we identified pericytes (PDGFRβ+) as a nutrient-sensitive cellular source of leptin within skeletal muscle. Ongoing work is focused on elucidating the mechanism(s) regulating leptin production by pericytes.