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Understanding the role of skeletal muscle beyond contraction

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Abstract

Synchronized release and removal of Ca^{2+} from the sarco/endoplasmic reticulum (SR), is the basis of contraction and relaxation of striated muscles. Recent discoveries making it increasingly clear that Ca^{2+}-signaling in the skeletal muscle mediate many additional functions such as metabolic state, mitochondrial biogenesis, thermogenesis etc. Skeletal muscles taken together constitute ~40% of body mass and consume ~60% of energy in mammals including humans. Therefore, muscle metabolism contributes significantly to energy homeostasis.

My talk is focused on a unique Ca^{2+}-handling protein, sarcolipin (SLN). It is a 31 residue single trans-membrane protein found in the sarco/endoplasmic reticulum (SR) of striated muscle tissues and regulate the SR Ca^{2+}-ATPase (SERCA) activity. Using SLN knockout and overexpression mouse models we showed that SLN is the missing-link for muscle-based non-shivering thermogenesis (NST) both during cold and diet. Our studies also provided first time evidence that SLN but not phospholamban (PLB), the better known SERCA regulator, is involved in NST. We have been exploring the detailed mechanism of SLN-mediated NST. Our results show SLN creates an energy demand that promotes mitochondrial biogenesis in skeletal muscle leading to increased utilization of fat and this mechanism is further recruited during diet overload thereby providing protection against obesity. These findings suggest that SLN-mediated NST can be a novel target for manipulation of mammalian energy expenditure towards therapeutic intervention of obesity and diabetes.

Among rodents brown adipose tissue (BAT) is the major known mechanism of NST, in which an inner mitochondrial membrane protein called uncoupling protein 1 (UCP1) mediates thermogenesis. We are also studying the dynamics between these two mechanisms of NST by generating a double knockout (lack both the protein) mouse model. We have data to show that SLN-based and the BAT-based NST mechanisms play synergistic role in cold-induced