

Muscle miR-27a is Decreased During Diabetes and is Regulated by Calcineurin Signaling

Munoz, ER., Folk, AL., Rahnert, JA., Wang, XH., Price, SR., Jeka, JJ., Park, JY., Hudson, MB. Temple University, Philadelphia, PA, Emory University, Atlanta, GA

Skeletal muscle atrophy occurs during a variety of conditions including diabetes. Elevated levels of muscle myostatin (MSTN) play a central role in the development of muscle atrophy during these conditions. Recently, research has focused on understanding the control of myostatin in skeletal muscle during both atrophy and hypertrophy.

Specifically, recent evidence indicates that microRNA-27a (miR-27a) can target MSTN mRNA and decrease MSTN protein in muscle cells. However, the mechanisms that controls the level of miR-27a in muscle during atrophy-inducing conditions are unknown.

PURPOSE: To investigate how miR-27a is regulated during muscle atrophy.

METHODS: Acute uncontrolled type I diabetes was induced in rats by a single IV injection of 125/mg streptozotocin (STZ), and muscles were harvested 3 days later. Since elevated glucocorticoids mediate some atrophy-inducing effects during diabetes experiments were also performed in C2C12 muscle cells incubated with dexamethasone (DEX; 100 nM). In both muscle and muscle cells miR-27a was measured via qPCR using U6 as a control miR. **RESULTS:** In gastrocnemius muscles of diabetic rats miR-27a was decreased $40\pm 3\%$ (mean \pm SEM), a finding consistent with the reported elevation in MSTN during diabetes. Similarly, treatment of C2C12 myotubes with DEX also reduced the level of miR-27a $68\pm 3\%$ within 0.5 hr and this suppression was sustained at $>51\%$ for 48 hr. The miR-23a/miR24-2/miR-27a cluster was previously reported to be regulated by Calcineurin (CnA) signaling and we have previously shown that CnA activity in skeletal muscle is reduced during diabetes and in muscle cells following DEX treatment. Therefore, we investigated the relationship between CnA activity and miR-27a in muscle cells. Infection of muscle cells with an adenovirus to overexpress a constitutively active form of CnA increased miR-27a by $35\pm 3\%$, showing CnA directly regulates miR-27a in muscle. **CONCLUSION:** These results are consistent with a model in which atrophy-inducing conditions regulate MSTN production in skeletal muscle in part by reducing the level of miR-27a via a mechanism that involves decreased CnA signaling. Thus, miR-27a appears to play a pivotal role in the pathogenesis of muscle atrophy during conditions such as diabetes.

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