

## DIFFERENTIAL EXPRESSION OF NOVEL ADIPONECTIN RECEPTOR-1 TRANSCRIPTS IN SKELETAL MUSCLE OF SUBJECTS WITH NORMAL GLUCOSE TOLERANCE AND TYPE 2 DIABETES

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**Objective:** Adiponectin receptor-1 (AdipoR1) expression in skeletal muscle has been suggested to play an important role in insulin resistance and diabetes. We aimed at evaluating the presence of novel AdipoR1 splice variants in human muscle and their regulation under physiological and pathophysiological states.

**Research Design and Methods:** AdipoR1 5'UTR mRNA transcripts, predicted from bioinformatics data, were evaluated in fetal and adult human tissues. Expression and function of the identified transcripts were assessed in cultured human skeletal muscle cells and in muscle biopsies obtained from individuals with normal glucose tolerance (NGT) and type 2 diabetes (T2D) (n=49).

**Results:** Screening of potential AdipoR1 5'UTR splice variants revealed a novel highly abundant muscle transcript (R1T3), in addition to the previously described transcript (R1T1). Unlike R1T1, R1T3 expression was significantly increased during fetal development and myogenesis, paralleled with increased AdipoR1 protein expression. The 5'UTR of R1T3 was found to contain uORFs that repress translation of downstream coding sequences. Conversely, AdipoR1 3'UTR was associated with enhanced translation efficiency during myoblast-myotube differentiation. A marked reduction in muscle expression of R1T3, R1T1 and R1T3/R1T1 ratio was observed in individuals with T2D, as compared with NGT subjects, paralleled with decreased expression of the differentiation marker myogenin. Among NGT subjects, R1T3 expression was positively correlated with insulin sensitivity.

**Conclusions:** These results indicate that AdipoR1 receptor expression in human skeletal muscle is subjected to posttranscriptional regulation, including alternative splicing and translational control. These mechanisms play an important role during myogenesis and may be important for whole body insulin sensitivity.