The prerequisite for muscle differentiation is to withdraw cells from cell cycle. Being able to evoke two opposing effects insulin is both mitogen and differentiation factor because it stimulates cell proliferation and myotube formation in skeletal muscle myogenesis. Our previous results have shown that mitochondrial activity increased in response to insulin in differentiating muscle cells (PAWLIKOWSKA et al., 2006). Moreover, protein kinase kinase/extracellular-signal-regulated kinase (MAPKK/ERK-MEK) inhibitor PD98059 accelerated, whereas either the phosphatidylinositol 3-kinase (PI-3K) inhibitor LY294002 or blockage of mitochondrial respiration both abrogated insulin-mediated myogenesis.

Our present study points to the mitochondrial transmembrane protein called hyperplasia suppressor gene/mitofusin2 (HSG/Mfn2) which regulates both mitochondrial fusion (demonstrated by perinuclear mitochondria clustering) and insulin-dependent myogenesis in vitro. The molecular mechanism of this phenomenon is unknown, although immunoprecipitation studies indicate that during insulin-mediated myogenesis Ras protein (upstream activator of MAPK/ERK1/2 cascade) interacts with HSG/Mfn2 in muscle cells. Interaction of Ras with Mfn2 continued unless insulin was present and was blunted after PD98059 co-treatment. It indicates that insulin-mediated myogenesis is augmented by inhibition of MEK, most likely by the lack of mitogenic signals opposing muscle differentiation. We suggest, that insulin stimulates Mfn2 protein expression which in turn binds to Ras and inhibits MEK-dependent signalling pathway. At the same time PI-3K-dependent signalling pathway is boosted, mitochondrial respiration increases, and the rate of myogenesis is accelerated.

References
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Not only insulin stimulates mitochondriogenesis in muscle cells, but mitochondria are also essential for insulin-mediated myogenesis. Cell Prolif. 39 (2006), 127-145