THE GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) INHIBITS SKELETAL MYOGENESIS BY COUNTERACTING MYOD ACTIVITY

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Myogenesis is characterized, at a molecular level, by the activation of transcription factors named muscle related factors (MRFs) and myocyte enhancer factors-2 (MEF-2), which promote myoblast exit from cell cycle and fusion of myoblast into myotubes. This process is self-sustained by the release of insulin-like growth factor-1, while other molecules, such as myostatin, limit muscle formation and help to keep a pool of reserve cells (satellite cells) in an undifferentiated state. However, the intracellular mechanisms that regulate the fine tuning of myoblast differentiation are not completely understood.
GILZ is a small molecule known to be a glucocorticoid effector in T cells, where it counters activation signals and exerts anti-inflammatory effects. Its expression is not restricted to T cells and comprehends mesenchymal derived tissues such as skeletal muscle.
Preliminary data indicate that GILZ can interact with histone-deacetylase (HDAC)-1, which is an important myogenic regulator. MyoD, the best known MRF, is HDAC1-bound when inactive, and myogenic stimuli promote HDAC1 removal and MyoD acetylation: this allows MyoD association with chromatin regulators, such as CBP/p300 and SWI/SNF, and consequent induction of myogenin, the main inducer of terminal differentiation.
GILZ expression is developmentally regulated being reduced during early differentiation stages and successively re-induced. We found that GILZ inhibits myogenesis when over-expressed in C2C12 myoblast cell line. Our data indicate that GILZ suppresses myogenin induction and, consequently, the myogenin target gene myosin heavy chain, a late differentiation marker. Moreover, morphological analyses revealed a significant inhibition of myotube formation. We investigated MyoD activity on myogenin promoter and found that GILZ suppresses MyoD transcriptional activity in a dose dependent manner; intriguingly, GILZ can directly interact with MyoD.
Based on these observations, we hypothesize that GILZ recruits HDAC1 to MyoD target loci and speculate that this process physiologically happens in later stages of myogenesis, thus contributing to the fine tuning of differentiation. Therefore, GILZ might represent a pharmacological target to sustain an effective recovery after muscle injury.