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Sommario	Regeneration of skeletal muscle is a complex process that requires the activation of quiescent adult stem cells, the satellite cells, which are resident in hypoxic niches in the tissue. This process is mainly regulated through a group of transcription factors known as the hypoxia-inducible factors (HIFs). In particular, HIF-1α activation has been described as beneficial for the cell to overcome an hypoxic insult, while it has been observed that its chronic activation completely inhibits skeletal muscle differentiation. Therefore, oxygen deprivation and HIF-1α may play a role in activating the initial steps of the regeneration process. Herein, we investigated whether a 24h pre-conditioning under physical (1% O2) or chemical (IOX2 and FG-4592, two commercial PHDs inhibitors) hypoxic culture conditions could alter the differentiation of C2C12 myoblasts. In this thesis work we report that a controlled stimulus can trigger HIF-1α, activating MyoD through the non-canonical Wnt/β-catenin pathway and resulting in muscle hypertrophy. In particular, results show that both an hypoxic and a chemical pre-conditioning promotes the increase of all differentiation markers and the up-regulation of the non-canonical WNT pathway involved in myogenesis. Moreover, HIF-1α silencing significantly reduced cell differentiation, down-regulating MyoD and MHC as well as the expression of WNT7a.

	Finally, we studied the mechanism of WNT7a activation mediated by HIF-1α. Our results showed that HIF-1α activation induced an enhancement of WNT7a promoter activity, therefore we focused on the identification of the HIF-1α binding sequences localized on WNT7a promoter. Two different regions of over-lapping were identified by ChIP experiments, validating that HIF-1α directly binds WNT7a promoter and regulates its gene expression. In conclusion, we demonstrated the crucial role played by HIF-1α during skeletal muscle differentiation, and our results revealed that PHDs inhibitors could be used to mimic the effects obtained under hypoxic conditions. In addition, we define HIF-1α as a new possible candidate to induce the activation of WNT7a, which characterized the hypertrophic phenotype of the skeletal muscle. Altogether these results support the notion that HIF-1α plays a pivotal role in activating the regeneration process and may suggest new perspective for novel therapeutic targets in the treatment of several muscle diseases.
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