Pharmacological activation of the HIF-1α signaling pathway regulates satellite cells fate during aging through histone lactylation

ShT-03.1-3

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Sarcopenia is a multifactorial disease characterized by progressive loss of skeletal muscle mass and function in the elderly, associated with reduced muscle satellite cells (SCs) function and tissue oxygenation. The hypoxia-inducible factor-1α (HIF-1α) plays an essential role in the cellular response to oxygen levels by determining the switching of the glucose pathway from oxidative phosphorylation to glycolysis, thus acting as a regulator of cellular energy metabolism. In this context, we have previously reported that the HIF-1α pathway is strongly downregulated in human skeletal muscle biopsies from sarcopenic patients. This study aims to determine the role of pharmacological activation of HIF-1α, using the prolyl-hydroxylases inhibitor FG-4592, on the fate of mice satellite cells during sarcopenia and establish whether this treatment can counteract the switch of SCs metabolism to glycolysis. The results showed that treatment with FG-4592 increased the gene expression of all glycolytic enzymes, resulting in an enhancement in lactate production associated with the activation of anaerobic glycolysis. The main effect of this metabolic change is a decrease in the proliferation rate of treated SCs, reflecting an alteration of their cell cycle. Indeed, the progression of SCs in phase S of the cell cycle is severely impaired, which may be caused by an epigenetic modification in chromatin. The results revealed that lactate, a crucial metabolite mainly in muscle tissue, can also induce histone lactylation that alters the gene expression and fate of SCs. Indeed, treatment with FG-4592 promoted the expression of PAX7, the main marker of SCs, leading to the hypothesis that the treatment may increase the self-renewal power of SCs. In conclusion, these results support the notion that pharmacological activation of HIF-1α may counteract the development of sarcopenia by activating muscle regeneration.