Unraveling the Dual Role of NFIX in Cancer-Associated Cachexia and Tumor Biology

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Cancer-associated cachexia is a debilitating disorder characterized by unintentional body weight loss and skeletal muscle wasting, that derives from an imbalance between protein synthesis and degradation, favouring the latter[1-2-3]. Nowadays, no treatment exists to cure this pathology, pointing out the need of finding new targets for novel therapeutic strategies development. Nuclear Factor I X (NFIX) is a transcription factor essential for skeletal muscle biology: it modulates muscle mass by upregulating Insulin-like Growth Factor 1[4], which promotes muscle growth, and repressing Myostatin[5], a negative regulator of muscle mass. This regulatory balance is disrupted in cancer cachexia, and so we asked if NFIX could be a novel central player in this disorder.

With this purpose, NFIX protein levels were assessed in the Tibialis Anterior of the C26 cachectic mouse models, one of the most severe models of cachexia, and a significant NFIX downregulation was observed. Similarly, both *Nfix* mRNA and NFIX protein levels were significantly reduced in an *in vitro* model of cancer cachexia, generated by treating C2C12 myotubes with the Conditioned Medium (CM) from C26 cells. To test whether NFIX overexpression could counteract cachexia, C2C12 myotubes were transduced with a lentiviral vector expressing NFIX under the CMV promoter. Preliminary data demonstrated that NFIX overexpression exerts a protective effect against muscle atrophy *in vitro*.

In parallel, we assessed whether NFIX modulation could affect tumor behaviour, as any therapeutic strategy must avoid promoting its progression. Interestingly, silencing NFIX, using a specific short hairpin RNA, in C26 resulted in reduced proliferation and increased migratory capacity, suggesting that NFIX loss may confer pro-tumorigenic properties, while NFIX overexpression might not improve the tumor fitness.

Overall, our *in vivo* and *in vitro* findings identify NFIX overexpression as a promising strategy to preserve skeletal muscle mass during cancer-associated cachexia without conferring advantages to tumor growth.

References:

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