The microphthalmia transcription factor (MITF) contributes to castration resistance via an actionable translation mechanism in lethal prostate cancer

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Deciphering transcription factor-dependent signaling networks and molecular mechanisms that rewire the cancer cell may provide actionable therapeutic targets to improve patient survival. Here, we show that the master regulator microphthalmia transcription factor (MITF) is downregulated in advanced lethal prostate cancer (PC) patient samples and has a major role in regulating a subset of biologically relevant signaling pathways that control PC growth and confer resistance to androgen deprivation therapy (ADT).

Mechanistically, MITF directly represses protein synthesis by regulating the assembly of the translation initiation complex, which impacts on the protein levels and activity of key PC drivers, such as MYC and AR. Since AR overexpression is a frequent adaptive trait that confers resistance to ADT, we investigated if low MITF levels contribute to castration resistance. Indeed, knockdown of MITF in the hormone therapy sensitive cell lines, LNCaP and VCaP, allowed PC cells to proliferate when cultured in charcoal-stripped serum medium. Likewise, the proliferation of MITF knockdown cells was higher than control cells in presence of 1nmol/L dihydrotestosterone (DHT) than when cultured with 10nmol/L DHT. Most notably, in vivo, subcutaneous tumors generated from shMITF LNCaP and VCaP luciferase tagged cells continued to grow in castrate mice as measured by photon flux and tumor volume. Altogether, these results indicate that low MITF cells continue to proliferate under ADT, suggesting that the MITF signaling axis contributes to the acquisition of castration resistance. Finally, based on the regulatory function of MITF on translation initiation, we unveil that the pharmacologic inhibition of protein synthesis decreases tumor growth, sensitizes PC tumors to ADT and improves survival most robustly in low MITF expressing patient-derived preclinical models.

Overall, this study sheds insight into the role MITF has in the pathogenesis of lethal PC and identifies an actionable mechanism that may transcend into effective combined therapeutic strategies.