

Loss of tristetraprolin drives the progression to treatment resistant prostate cancer by altering stress response pathways

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Background: Phenotypic plasticity is a hallmark of cancer and is associated with transition to a treatment resistant state. This plasticity can be driven by a hardwired instinct to survive stresses induced by anti-cancer therapies. This happens by activating the integrated stress response (ISR), which stalls most translation but prioritises stress response pathways. Tristetraprolin (TTP), an ARE (AU-rich element)-binding protein that destabilizes ARE-mRNAs, plays a role in the regulated turnover of many transcripts encoding proteins involved in immune function and cell growth control. TTP also plays a critical role in stress-induced destabilisation of mRNAs.

Methods and Results: Loss of TTP in prostate cancer (PCa) models *in vivo* and *in vitro* results in a more aggressive disease state, characterised by increased p65 (NF-κB) expression and signalling, reduced AR expression, increased expression of synaptophysin, impaired ISR signalling and resistance to androgen deprivation therapy (ADT) by enzalutamide or surgical castration. In multiple patient cohorts, low TTP expression in multiple PCa selects for the most aggressive disease. These patients demonstrate an increased gene signature score of lineage plasticity. In PCa models where TTP has been inactivated, key components of the ISR signalling pathways are partially impaired compared to models with intact TTP, including ATF4, PPP1R15A and G3BP1. This altered ISR has noted changes to mRNA decay rates. In response to acute ADT, TTP gene and protein expression is upregulated, and ISR pathways are activated. However, chronic ADT exposure induces TTP loss and inactivation of ISR components. This indicates that persistent activation of ADT-induced stress responses impairs TTP activation over time, resulting in therapeutic resistance.

Conclusions: Together, our data demonstrates that TTP is an important regulator of prostate cellular identity, and loss of TTP drives progression of a treatment-resistant prostate cancer phenotype. Of particular clinical significance, TTP loss provides a novel therapeutic vulnerability to either prevent or reverse resistance to ADT in PCa patients.

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