PROSTATE CANCER

AR — the link between transcription and translation

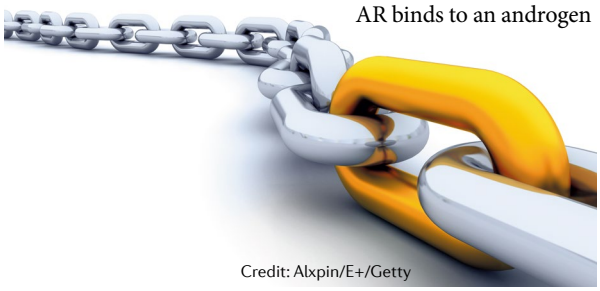
> the relationship between AR and translation initiation is crucial for maintaining rates of protein synthesis in prostate cancer

The androgen receptor (AR) negatively regulates protein synthesis and low AR abundance increases translation, promoting tumour proliferation in prostate cancer, according to newly published data. This unexpected relationship revealed a druggable target for low-AR disease.

Liu and colleagues observed that a decrease in AR abundance resulted in increased de novo protein synthesis in a castrated mouse model of *Pten*-deficient prostate cancer. Furthermore, castration decreased eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4EBP1), which inhibits the formation of the eIF4F translation initiation complex.

In vitro, 4EBP1 expression was considerably decreased in LNCaP cells in which AR had been eliminated. Moreover, AR and total 4EBP1 expression positively correlated in 29 LuCaP patient-derived xenografts.

To determine the regulatory relationship between AR and 4EBP1 expression, the researchers reintroduced androgens into cells derived from the castrated model of *Pten*-deficient prostate cancer to restore AR expression and activity, which completely rescued *4ebp1* mRNA expression and decreased de novo protein synthesis. Chromatin immunoprecipitation sequencing and functional validation revealed that AR binds to an androgen response element encoded in the first intron of *4EBP1* in both mouse and human prostate cancer.



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To investigate whether AR controls the translation initiation complex, the investigators optimized proximity ligation assays for both eIF4E–eIF4G and eIF4E–4EBP1 interactions. Interactions between eIF4E and eIF4G increased and between eIF4E and 4EBP1 decreased in tumours from castrated *Pten*-deficient mice, resulting in a net increase in the formation of the eIF4F translation initiation complex and protein synthesis. The physiological consequences of this effect were increased tumour growth, cell proliferation and disease aggressiveness in a *Pten*-deficient mouse model of prostate cancer subjected to long-term castration.

Ribosome profiling showed that translation efficiency was increased in a subset of mRNAs, which was associated with castration and increased eIF4F complex formation. The majority of mRNAs in this subset were found to have a guanine-enriched sequence, which the researchers termed the guanine-rich translational element (GRTE). The GRTE was found to be a specific 5′ UTR *cis*-regulatory element that has a role in enhanced translation of specific mRNAs when eIF4F is hyperactive.

Gene set enrichment analysis showed that the translationally regulated mRNAs clustered into distinct biological processes such as signal transduction, translation and cell proliferation. Protein, but not mRNA, expression of KLF5, DENR, CACULI and rpS15 was increased in organoids derived from primary prostate cancer cells from castrated *Pten*-deficient mice. In organoids containing doxycycline-inducible, non-phosphorylatable 4EBP1, abundance of these proteins, but not their mRNAs, decreased on treatment with doxycycline.

In vivo assays revealed that increased formation of the eIF4F complex enhances and maintains cell proliferation and initiates AR-low prostate cancer. In vitro, AR-low prostate cancer cell proliferation was decreased to a greater extent than that of AR-intact cells on inhibition of eIF4E. Treatment with small-molecule inhibitors of the eIF4E–eIF4G complex decreased tumour growth and improved survival in AR-low, but not AR-normal, models of human prostate cancer. In patient samples, decreased 4EBP1 expression is observed in samples from men with AR-low castration-resistant prostate cancer (CRPC).

Together these results suggest that the relationship between AR and translation initiation is crucial for maintaining rates of protein synthesis in prostate cancer. The abundance of 4EBP1 is controlled by AR, affecting eIF4F complex formation. This study revealed a vulnerable druggable link between mRNA transcription and translation in AR-deficient prostate cancer.

Andrew Hsieh, corresponding author, tells *Nature Reviews Urology* "AR functions through more than just its control of transcription. It also shapes the proteome through mRNA translation."

"Inhibition of translation initiation might improve the efficacy or long-term potency of enzalutamide and abiraterone for patients with CRPC," he explains. "AR levels could be a biomarker of responsiveness to drugs that inhibit translation initiation," Hsieh continues, concluding "clinical-grade inhibitors of the eIF4F translation initiation complex or its activity are urgently needed."

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