Editorial Commentary

Protein translation controlled by the androgen receptor in prostate cancer: a novel therapeutic option?

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Liu *et al*. identified recently a novel role of the androgen receptor (AR) as a repressor of mRNA-specific translation through increased expression of 4E-BP1 (eukaryotic translation initiation factor 4E (eIF4E)-binding protein), a key factor in eukaryotic translation (1). The link between AR signaling and its interaction with 4E-BP1 expression is an interesting signaling cross-talk in prostate cancer (PCa). Authors explored the observation that androgen-activated AR decreases translation in PCa, reduces PCa tumor growth and improves survival in preclinical models (1). 4E-BP1 in its hypo-phosphorylated form represses the translational initiation by binding to eIF4E, a key driver of translational initiation and elongation. Various kinases were shown to hyper-phosphorylate 4E-BP1, which results in release from eIF4E and subsequent cap-dependent translation (2). Importantly, the androgen dihydrotestosterone increases the level of 4E-BP1 (1). Also eIF4E is regulated by phosphorylation. The phosphorylated form of eIF4E is more active and increases tumorigenicity. Notably, in PCa the phosphorylation of eIF4E is increased (2). The protein levels of each, 4E-BP1 and eIF4E, their interaction, as well as the cross-talk with the androgen-activated AR paves a novel AR signalling pathway in translational control.

An important issue in understanding PCa tumorigenesis is the need for detailed analysis of the progression of PCa from a curable stage to the fatal cancer. PCa is associated with a high mortality rate ranking among the top causes of cancer deaths in men (3). The localized primary PCa is treated successfully in initial phases of tumorigenesis by radical prostatectomy and/or radiotherapy. However, some tumors advance to invasive form (4). Studies indicate that the androgen-activated AR plays an outstanding role for the development and growth of the normal prostate and also in promoting tumorigenesis of PCa (5). Therefore, androgen deprivation therapy (ADT) mostly by chemical castration in combination with AR-antagonists is applied for treatment to inactivate the transcriptional transactivation of the AR (4). Unfortunately, contrary to the primary successful treatment, the advanced PCa growth becomes androgen-independent, so called castration-resistant prostate cancer (CRPCa) (6). However, CRPCa remains dependent on AR signaling and therefore the new generation of AR antagonists is, at least initially, beneficial to repress AR signaling also in CRPCa (7-9).

Nevertheless, CRPCa remains fatal due to development of therapy resistance. In later stages during tumorigenesis PCa becomes more independent of the AR signaling and might reduce AR protein level. Consequently, loss or a reduced AR level will lack or have reduced ability to express 4E-BP1 and consequently reduced ability to inhibit translational including oncogenic mRNAs. This effect might be compensated in future by co-treatment with translation inhibitors (10).

The AR is a member of steroid hormone receptors belonging to the nuclear hormone receptor superfamily. Similar to other members of this family, the AR is a ligand

controlled transcription factor (11). In the absence of hormone, the AR is localized in the cytoplasm bound in a complex with multiple chaperones (heat shock proteins), which incapacitate AR to translocate into the nucleus (12). The ligand binding, being either an agonist or an antagonist, changes the receptor's conformation and dissociates the AR from heat shock proteins. The AR dimerizes and the majority of the AR translocates into the nucleus where it interacts with other transcription factors or binds to androgen response elements (AREs) in the promoter and enhancer regions of target genes. On the other hand a small fraction of androgen-activated AR interacts with cytosolic factors such as the non-tyrosine kinase Src and the serine/threonine kinase PKB/Akt (13). This interaction controls the AR-mediated induction of cellular senescence in PCa (13) and might mediate signal transduction into the nucleus. The recruitment of co-regulators and transcriptional complexes by the activated nuclear AR results in transactivation or inhibition of gene expression (14). The number of factors, which interact with and modulate AR transcriptional function, is steadily augmenting. These factors include coactivators, corepressors and chromatin remodeling proteins (15).

Unlike an extensive body of work regarding AR to regulate transcriptional level of mRNA and also lncRNA, the role of AR to control translation is poorly understood.

Mechanistically, activation of AR by the androgen dihydrotestosterone increases the protein level of 4E-BP1 via binding of AR to the first intron of *4ebp1*, which harbors a putative ARE (1), linking androgen-activated AR to translational control.

However, 4E-BP1 may exhibit different roles either as an oncogene or a tumor suppressor in different types of cancers.

In luminal breast cancer, the 4E-BP1 encoded gene is frequently amplified. 4E-BP1 and specially the phosphorylated 4E-BP1 form play a prevailing role in breast cancer by mechanisms being different from its role to control cap-dependent translation. Analysis of 4E-BP1 expression in breast cancer patients showed that overexpression of 4E-BP1 is associated with decreased relapse-free survival across all breast tumor subtypes (16), indicating that 4E-BP1 has an oncogenic activity in breast cancer.

On the other hand, 4E-BP1 has a tumor suppressor role in many other types of cancer including more than 80% of head and neck squamous cell carcinomas and colorectal cancer (17,18).

Notably, for PCa patients the levels of both 4E-BP1 and its interaction partner eIF4E influence the overall survival. In PCa patients reduced 4E-BP1 is associated with reduced survival (16), which suggests that 4E-BP1, as a potent inhibitor of translation, has a tumor suppressive role. Also the phosphorylated, inactive 4E-BP1 is associated with more aggressive metastatic PCa. Recently, studies show that the pro-translational factor eIF4E level is significantly overexpressed in advanced PCa compared to benign prostatic hyperplasia (19). In line with this, increased expression of eIF4E is significantly associated with reduced survival of PCa patients (20).

It appears that eIF4E phosphorylation is a strong promoter of translation enhancing the rate of oncogenic mRNAs to increase tumorigenicity (21). Interestingly, for PCa the eIF4E level might be involved in castration resistance and therapy resistance to the first generation AR-antagonists. Knockdown of eIF4E by siRNA in CRPCa cells or using Mnk (mitogen activated protein kinase interacting protein kinase)- inhibitors sensitizes cells to the first generation AR-antagonist bicalutamide that is usually inactive in CRPCa. Accordingly, eIF4E overexpression induces resistance to this anti-androgen. Further, eIF4E phosphorylation increases cap-independent translation, indicating that in CRPCa eIF4E has also cap-independent activity. In line with this, inhibition of eIF4E restores cap-dependent translation (21).

Thus, three main points of eIF4E-activity in PCa were demonstrated. First, eIF4E phosphorylation is increased by inhibition of AR. Second, AR inhibition induced cap-independent translation and increases the eIF4E phosphorylation at S209. Third, PCa tumor growth suppression was observed by simultaneous inhibition of eIF4E phosphorylation and mTOR activation through inhibiting both cap-dependent and -independent translation (22). This is in line with previous studies that reveal a link between increase of eIF4E and an enhanced progression to castration resistance (20).

Evidence suggests that the androgen dihydrotestosterone increases the protein level of 4E-BP1 (1). In addition, AR antagonists stimulate eIF4E phosphorylation (21). These observations link AR signaling to key translation factors in order to inhibit rather a broad-range of translation.

Eukaryotic protein homeostasis, or proteostasis, is required for normal cell health and viability, and is certified by the coordinated control of protein synthesis, folding and degradation. Although the unfolded protein response enables proteostasis to be restored during unfavorable

conditions, PCa cells have hijacked a particular part of this pathway for tumor growth and maintenance (23).

Further studies shall reveal the underlying pathway for synthesis of those proteins preventing the progression of PCa to a castration resistant state.

The article by Liu *et al*. (1) revealed in preclinical *in vivo* models that AR negatively regulates protein synthesis and this pathway is mediated through increased expression of 4E-BP1. The *Probasin-cre;Pten*$^{LoxP/LoxP}$ PCa mouse model with a tissue-specific loss of Pten causes PI3K pathway hyperactivation and PCa formation (24) and was used as a model to study the impact of AR on protein synthesis (1). To modulate AR protein abundance and to reduce androgen levels, mice were castrated, which led to a dramatic reduction in AR protein level in each of the four lobes of the murine prostate. The functional impact of castration on AR activity was confirmed by analyzing RNA sequencing data. ChIP-seq data from *Pten*$^{LoxP/LoxP}$ mice showed that AR binds to the first intron of *4ebp*. Subsequently the AR regulated protein synthesis was studied *in vivo*. Proximity ligation assay data showed an increase of an interaction between eIF4E – eIF4G whereas the eIF4E – 4E-BP1 interaction decreased in castrated mice compared to non-castrated mice. In conclusion, *in vivo* mouse model experiments demonstrate that forming the eIF4F-complex is necessary for initiation and maintenance the proliferative potential of AR-low PCa.

One important question that may arise is whether AR regulates global mRNA translation initiation or exhibits some specificity towards a subset of mRNAs. Interestingly, Liu *et al*. (1) highlight that increasing eIF4F-assembly impact particular those mRNAs that are more sensitive to modifications during translation initiation dynamics. Ribosome profiling of tumors from both intact and castrated *Pten*$^{LoxP/LoxP}$ mice identified differentially translated mRNAs. Interestingly, the translationally upregulated mRNAs contain a higher GC-content in the 5' untranslated region (UTR) and are more stable compared to control without significant difference of the length of the 5' UTR (1). This implies that eIF4F sensitive mRNAs have a cis-regulatory element located within the 5' UTR. Nevertheless, not all sequences that are enriched for guanines are responsive to changes in eIF4F activity. Provided data suggest that the sequence around the GC-rich region may also play a role in eIF4F hypersensitivity (1). Future studies shall verify or disprove this hypothesis.

Taken together, AR decreases protein synthesis by regulating the excess of the translation initiation inhibitor 4E-BP1 and eIF4F complex formation. The application of effective inhibitors of AR or androgen biosynthesis over the last two decades has flowed into in a 2.5-fold augmentation of highly treatment-resistant PCa, which are also characterized by AR-low or AR deficiency (25). This observation is important and suggests that reduced AR mediated inhibition of translation is associated with PCa aggressiveness.

Currently, inhibitors of translation initiation are in clinical trials for PCa patients (10). Thus, in addition to preclinical models, the analysis of clinical specimens from patients will complement our view on translational control by androgens and may result in benefit for those PCa patients with de-repressed translation initiation, especially in AR-low setting cancers.

In summary, the contribution by Liu *et al*. (1) provides a new principium for a translational function of the AR being promising for a novel therapeutic target. Therefore, patient stratification and development of novel therapies that target the translation initiation machinery in PCa could be useful.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.02.31). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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