HHS Public Access

Author manuscript

Trends Mol Med. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Trends Mol Med. 2023 August ; 29(8): 586–588. doi:10.1016/j.molmed.2023.06.002.

ELAC2 is a functional prostate cancer risk allele

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Abstract

Stentenbach and colleagues unveil a functional role of a common human germline mutation found in the RNase Z enzyme, *ELAC2,* in prostate cancer. Here, we discuss the importance of these findings in enhancing our understanding of how risk variants enable prostate cancer progression and post-transcriptional mechanisms underlying oncogenesis.

Keywords

ELAC2; translation control; tRNA; prostate cancer

Germline genetic variants and polygenic risk in prostate cancer

Prostate cancer is the most common occurring cancer in men and has a strong genetic basis. The carrier frequency of rare germline pathogenic mutations in DNA-repair genes among men with metastatic prostate cancer is ~11–12%, which is significantly higher than in men with localized prostate cancer [1]. Polygenic risk scores (PRS) demonstrate the strong contributions of common risk variants across diverse populations, with men in the highest PRS risk category (the top decile, 90–100%) having 3–5-fold increased risk of prostate cancer compared to men in the average PRS risk category (40–60%) [2]. The effect of rare pathogenic variants differs by PRS, with men of European ancestry carrying a variant in *HOXB13*, *BRCA2*, *ATM* or *CHEK2* having a lifetime absolute risk of prostate cancer that ranged from 9% to 56% in the lowest and highest PRS deciles, respectively [3]. How germline variants functionally impact the normal or diseased prostate remains a major question in the field.

In recent findings published in *EMBO Molecular Medicine*, Stentenbach and colleagues functionally characterized a potential prostate cancer susceptibility gene *ELAC2* [4]. The authors found that introducing a human-based missense variant via CRISPR-Cas9 editing

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Conceptualization and writing S.B., R.M., and A.C.H.; Funding Acquisition S.B., R.M., and A.C.H.

was well tolerated in mice and resulted in enlargement and inflammation of the murine prostate, but no tumor formation. In the presence of a “second hit,” using the transgenic carcinoma of the mouse prostate (TRAMP) model, they showed that the *ELAC2* mutant or knockout exacerbated prostate cancer initiation and progression.

Post-transcriptional processes in prostate cancer

While there has been abundant work characterizing prostate cancer from hormone sensitive to castration resistant disease, most of these studies have focused on mechanisms related to transcription regulation involving the androgen receptor (AR) and co-related factors. Much less attention has been paid to post-transcriptional processes such as mRNA translation. Over a decade ago, Furic et al., were the first to demonstrate the critical role of the translation initiation factor (eIF) eIF4E in regulated prostate tumorigenesis [5]. This was followed by a study that revealed the critical importance of mRNA-specific translation in dictating prostate cancer phenotypes including metastasis [6]. Subsequent studies showed translation initiation as critical driver for AR-deficient prostate cancer, an intractable form the disease that is currently on the rise. Here, it was discovered that AR functions as a negative regulator of protein synthesis by inhibiting translation initiation through transcriptional control of eIF4E binding protein 1 (4EBP1), which limited eIF4F translation initiation complex formation and the proliferative capacity of cells *in vivo* [7]. Loss of AR increased eIF4F assembly to drive the translation of a network of proproliferation mRNAs that share a conserved and functional guanine-rich motif, which was required for enhanced tumor growth in the setting of low AR. Pharmacologic and genetic disruption of the eIF4F complex decreased tumor growth and improved survival *in vivo*, thus serving as an intriguing therapeutic target downstream of AR [7].

The integrated stress response (ISR) is an adaptive response to cells under conditions of stress. Phosphorylation of the alpha subunit of eIF2 is a critical linchpin of the ISR. This triggers reduction of global protein synthesis, thereby conserving energy and inducing adaptive changes in gene expression. Cordova et al., showed that the ISR regulator GCN2, which is an eIF2 kinase (EIF2KA4), is activated in prostate cancer following histidine depletion and accumulation of $tRNA^{His}$. Activated GCN2 increased expression of amino acid transporters and maintained a free pool of amino acids. Targeting GCN2 resulted in decreased tumor progression in AR sensitive and castrate resistant *in vivo* models by limiting expression of amino acid transporters such as SLC3A2.

Transfer RNAs in malignancy

Translation control is critical for maintaining cellular homeostasis with much attention given to regulation of protein synthesis by eIFs. Subsequent processes in elongation and termination have long been thought to be static, essential machinery for mRNA translation within cells. However, tRNA modulation is emerging as a dynamic regulator of expression of specific transcripts that promote cell fate decisions and disease progression. In breast cancer, Goodarzi et al., demonstrated that two tRNAs promote metastasis through modulation of ribosome occupancy and stability of transcripts enriched for their cognate codons [9]. Degeneracy of the genetic code has also been shown to be co-opted in advanced

breast cancer, where two isoacceptor tRNAs, that decode synonymous codons, modulate metastasis in opposing directions [10].

Linking a prostate cancer risk variant with mRNA translation and disease

Stentenbach *et al.*, describe a novel role of ELAC2 in modulating tRNA processing in the mitochondria and the nucleus [4]. Impaired RNA metabolism in the mitochondria resulted in increased tumor growth via activation of immune and metabolic pathways. Whereas impaired processing of nuclear pre-tRNAs altered the pool of miRNAs that target transcripts involved in immune and innate stress responses, thereby potentiating oncogenesis in the TRAMP background (Figure 1).

This finding presents an intriguing idea that defects in intra-organellar processing of tRNAs can activate stress-induced cell behaviors contributing to tumorigenesis. A potential underlying mechanism for this is through ELAC2 interaction with SFPQ and NONO, AR co-regulators and RNA binding proteins, with roles in telomere stability and intron splicing. Defects in RNA metabolism can also elicit stress responses through PERK-mediated unfolded protein response and NIK/NF-kB signaling mediated inflammation.

Further investigation is needed to understand the mechanism of how impaired mitochondrial and nuclear tRNA processing leads to prostate progression and whether this functionally impacts mRNA translation (Figure 1). Importantly, the murine models were full body knockouts or knockins, thus one cannot rule out a non-cell autonomous role for *ELAC2* in prostate cancer. In summary, germline variants are not simply bystander mutations associated with prostate cancer, but rather have a causal role in the natural history of the disease and therefore, might represent therapeutic targets once their mechanism of action are deciphered. Moreover, the findings in this work raise the broader question of if and how other germline variants hardwired into the human genome cause prostate cancer.

ACKNOWLEDGEMENTS

We thank Dr. Burcu Darst for her thoughtful comments on this work. This work was supported by NIH grants R01 CA276308, R37 CA230617, R01 GM135362 to A.C.H. S.B. is supported by NIH T32 CA009515.

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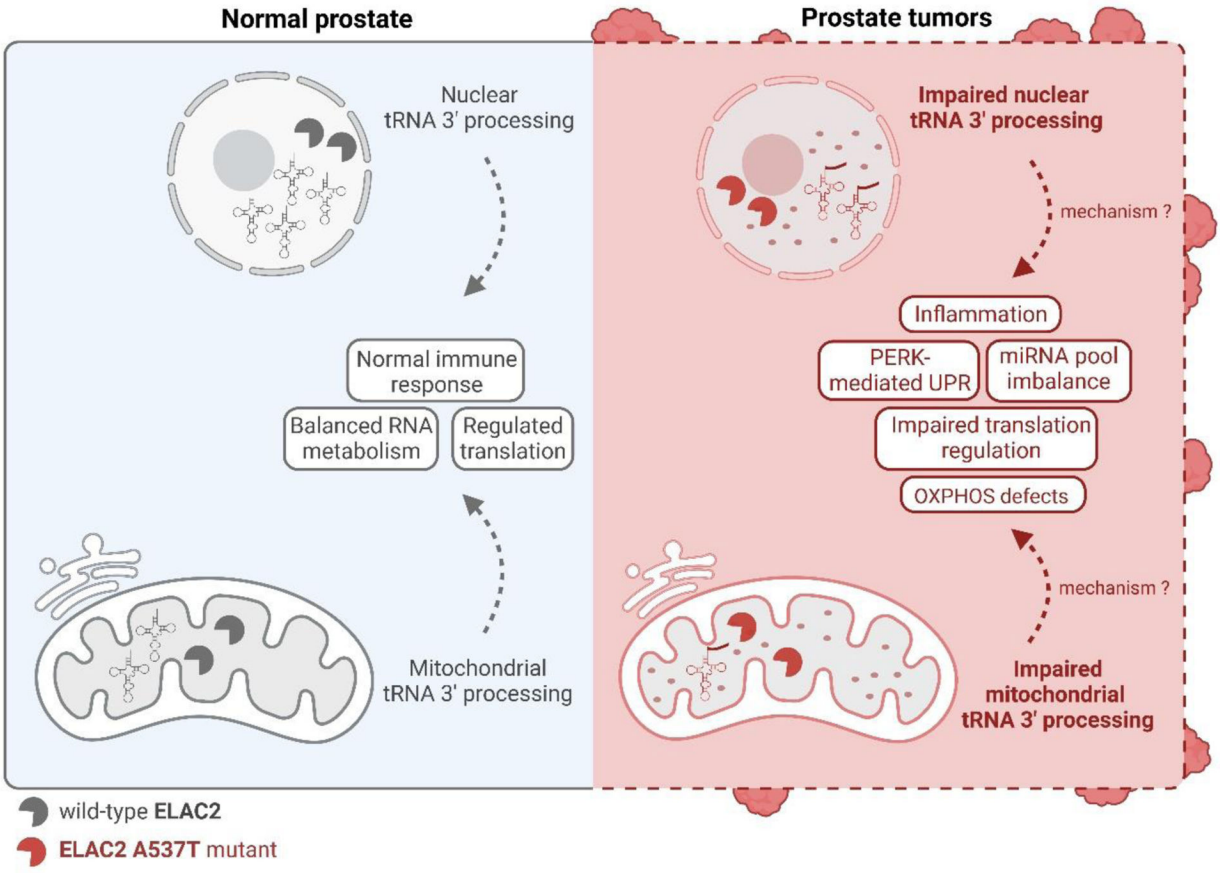

Figure 1.

ELAC2 A537T variant predisposes to prostate cancer progression, as published by Stentenbach *et al.* [4]. The blue section on the left of the figure illustrates a wild-type ELAC2 (grey circle) in normal prostate maintaining cellular homeostasis. The red section on the right displays a mutant variant, ELAC2 A537T (red circle) in prostate that potentiates cancer pathogenesis. The ELAC2 mutant impairs nuclear and mitochondrial tRNA processing and dysregulates RNA metabolism, translation, stress response and immune function. This figure was created using BioRender.