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Review Article

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Clinical Significance of 21q22.2 Genomic Rearrangement in Prostate Cancer

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Abstract

Prostate cancer (PCa) is a heterogeneous disease characterized by highly recurrent molecular alterations. Among them, the 21q22-23 intrachromosomal rearrangement leading to TMPRSS2-ERG gene fusion is unquestionably the most common. De novo expression of the N-terminal truncated form of ERG (ERGMet40) provides PCa cells with aggressiveness and metastatic potential. Pre-clinical evidence defines ERG expression as a vulnerable condition for synthetic lethality approaches. However, clinical trials failed in demonstrating greater efficacy of PARP inhibitors in ERG tumors, leaving many questions unanswered. Organoid technology and artificial intelligence may help find the solutions.

Keywords: *Prostate cancer; ERG; Organoids; Synthetic lethality*

Introduction

Occurring in more than 50% of cases, rearrangements of members of the ETS-gene family are the most common genetic alterations in prostate cancer (PCa) [1]. Among them, the predominant is the 21q22.2-3 that involves the Transmembrane Protease Serine 2 (TMPRSS2) and ETS-related gene (ERG). Detectable in almost 50% of prostate cancer biopsies from Caucasians, TMPRRS2-ERG genes fusion is less frequent in African-American and Asian men (27-31%) [2]. Moreover, the rearrangement is commonly identified in 5-30% of high-grade PIN (HGPIN) lesions, which classifies the lesion as an early event during prostate carcinogenesis [3-5]. TMPRSS2-ERG rearrangement characterizes as well other prostatic histotypes -such as small cell carcinoma of the prostate (pure or mixed with acinar carcinoma)- where it's found in about 45% of cases and where its presence underscores the prostatic origin of the malignancy in the differential diagnosis of a metastatic small cell carcinoma of unknown primary origin [6,7]. Functionally, ERG expression has been associated to tumor aggressiveness by promoting local invasion and metastatic progression of the disease through the transcriptional control of targeted genes in PCa cells [8-10]. Less clear is the role of ERG in the early stage of prostate tumorigenesis since *in vitro* and *in vivo* studies demonstrate that ERG is not sufficient to trigger the malignant transformation of the prostate epithelium [9-14].

Leveraging organoid technology to investigate ERG functions

Prostate organoids (PrOs) are cell culture models constituted by proliferating wild type adult prostate progenitors that self-assemble to reconstitute the correct basal-luminal architecture surrounding the lumen of adult prostate epithelium. Notably, PrOs are characterized by a very stable genome and dependence on testosterone for luminal lineage differentiation and lumenogenesis [15]. Doxycycline inducible expression of exogenous ERGMet40 in mouse prostate organoids (mPrOs) determines the expansion of the luminal compartment and contraction of the basal layer, closely resembling the histologic appearance of HGPIN. However, ERG+ organoids grow slowly compared to control lines and they are likely to get lost after a few passages if kept in full medium. Surprisingly, in sharp contrast to wild-type prostate organoids that are dependent on exogenous epidermal growth factor (EGF, 0.5 ng/mL) to survive, ERG+mPrOs grow in the absence of EGF [16], supporting the thesis that ERG+HGPIN cells could escape the quiescence that largely characterizes adult prostate tissue homeostasis and proliferate in the absence of physiologic stimuli. HGPIN is not the only intraductal proliferative lesion of the prostate. Intraductal carcinoma (IDC) is a clinically aggressive form of prostatic carcinoma characterized by a lumen-spanning proliferation of neoplastic prostate epithelium

within a preserved basal layer and it is associated with a high Gleason score (>7), large tumor volume, extra prostatic extension, positive lymph node status, and increased recurrence risk [17-19]. Most (about 75%) IDC lesions have the TMPRSS2-ERG rearrangement [20] and a similar percentage is found in atypical intraductal cribriform proliferations (AIP) that histologically appear more ominous than HGPIN, but do not fulfil the criteria of classic IDC [21] (Figure 1).

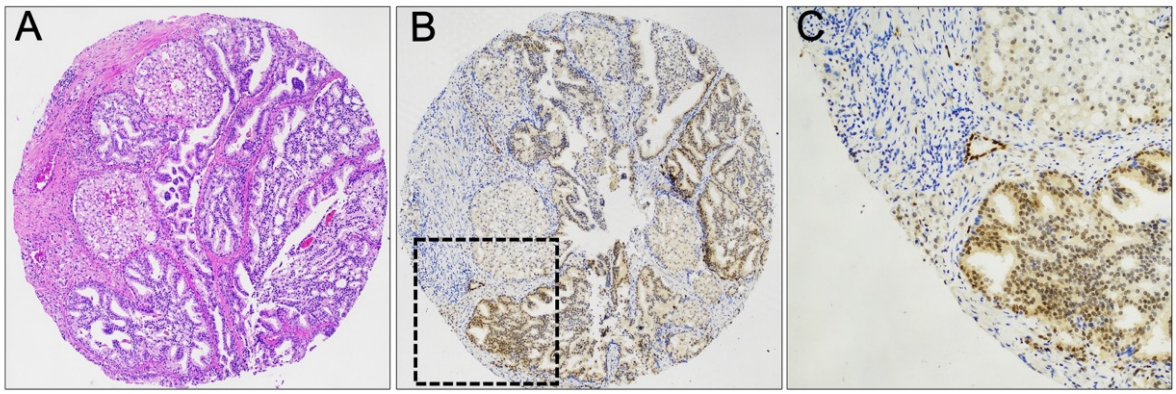

Figure 1: Atypical intraductal proliferation (AIP) intermingled with intraductal carcinoma (IDC), both with dense cribriform pattern (A, H&E x10). Low (B, x10) and high (C, x40) magnification of ERG immunohistochemistry showing diffuse nuclear positivity.

Recent studies have shown that prostate cancer with coexistent IDC and/or invasive cribriform carcinoma is associated with a higher percentage of genomic alterations than prostate cancer without these patterns [22,23], and that such genomic events cluster in specific chromosomal regions associated with aggressive disease such as deletions of 8p, with the involvement of the NKX3.1 gene [22]. In addition to its role as a transcription factor, NKX3.1 protein contributes to genome stability by favoring DNA damage repair in prostate epithelium [24-28] while ERG is known to promotes DNA double strand breaks (DSBs) [29-31]. In prostate progenitors, we demonstrated that ERG pose a major threat to genomic stability by promoting the proteasome degradation of NKX3.1 protein and the consequent accumulation of ERG-induced DNA damage, which remains sub-lethal [16]. These findings could reasonably help explain, at least in part, the increased rate of genomic alterations and highly malignant behavior of IDC and invasive cribriform carcinoma characterized by TMPRSS2-ERG rearrangement and NKX3.1 loss.

Clinical relevance of ETS genes expression

As ERG expression in prostate cancer cells leads to DNA DSB [30,31], synthetic lethality strategies of therapeutic intervention should be considered in patients with tumors harboring ETS related gene rearrangement [32]. sTOPARP-B trial showed anti-tumor activity of the PARP-inhibitor olaparib in patients with specific DNA repair gene defects (DRDs) [33]. Similar conclusions have been obtained by the PROFOUND trial for patients having somatic or germinal DRDs [34,35]. GALAHAD (a phase II trial) demonstrated a significant response rate of mCRPC patient with BRCA mutations treated with niraparib [36]. Finally, again in patients presenting with DRDs, promising results have been obtained by TRITON2 and TALAPRO-1 trials with the use of rucaparib and talazoparib, respectively [37-39]. As shown by Brenner JC, et al. (2011) treatment of ERG overexpressing cells with the PARP inhibitor olaparib not only decreased ERG-mediated cell invasion and intravasation, but also inhibited growth in mouse xenograft models [30]. Further *in vitro* work showed resistance to radiation of cells overexpressing ERG, which was reverted by inhibition of PARP [31,40]. However, clinical trials failed to identify differences in the response rate of ETS (mainly ERG) positive and negative mCRPC treated with PARP inhibitor veliparib and the androgen biosynthesis inhibitor abiraterone [41]. Similarly, ERG fusion status was not prognostic in patients with intermediate risk prostate cancer treated with radiation [42], although the presence of ERG rearrangement and PTEN loss was independently associated with recurrence-free survival in patients undergoing brachytherapy [43]. Future studies might clarify the potential role of ERG in selecting patients who could benefit more from a PARP inhibitor therapy, alone or in combination with other therapies. Along with PARPi, in the last few years immunotherapy has become increasingly important in the therapeutic plan of oncological patients, in particular the use of immune checkpoint-inhibitors (ICIs). Programmed death-1 (PD-1) and its ligand PD-L1 are transmembrane glycoproteins expressed by different types of immune cells, and, mostly PD-L1, by tumor cells including those of prostate cancer [44]. The PD-1/PD-L1 pathway leads to the inactivation of PD-1 expressing cells, mainly CD8+ cytotoxic T cells, thus favoring tumor immune escape [44]. Accordingly, increasing attention has been dedicated to immunohistochemical evaluation of PD-1/PD-L1 proteins as predictor factors of ICIs efficacy. Therapeutic strategy based on

ICIs proved to be effective for various cancer types including non-small-cell lung cancer [45], renal cell carcinoma [46,47], urothelial cancer [48,49], colorectal cancer [50], breast cancer [51,52] and melanoma [53,54], upon accurate stratification of patients. Contrariwise, ICIs resulted poorly effective in prostate cancer patients, likely dependent by the strong immunosuppressive tumor microenvironment (TME), the lower infiltration of T-cells and the reduced tumor mutation burden (TMB) [55]. Recent clinical trials, however, have demonstrated excellent responses to ICIs and/or their combinations with other agents of prostate cancer characterized by the biallelic loss of CDK12, high tumor mutation burden, high microsatellite instability (MSI-h) and mismatch repair-deficient (dMMR) [55,56]. ERG expression can also contribute to increase genome instability and tumor mutation burden in PCa cells [16]. In this scenario, it is interesting to note that a concordant IHC status of ERG with a "nodular" pattern of PDL1 has been described [44,57].

Further studies are needed to investigate the role of ERG fusions with regards to PD-L1/PD-1 expression, immune infiltration, and ICIs response.

Conclusion

One critical aspect may be the criteria adopted for ERG stratification. Rather than "positive" or "negative", a quantitative biparametric assessment by IHC of the different levels of ETS protein expression and the relative percentage of positive cells might help to better interpret the response of ETS-positive tumors to specific clinical protocol [58]. Artificial intelligence is fueling the field of computational quantitative pathology, which will contribute substantially to solving issues like this. Machine learning-based approaches will improve the accuracy and reproducibility of histopathological analyses, while also making them faster and, overall, quantitative [59]. Further clinical studies will be needed to understand the complex relationship between the expression of ETS genes and the clinical relevance of agents acting on the DNA damage response and immune activity. In the meantime, the goal of preclinical research will be to increasingly define the molecular mechanisms that undermine susceptibility to PARP and IC inhibitors, with the aim of discovering new therapeutic strategies and expanding the potential spectrum of treatable patients (Figure 2).

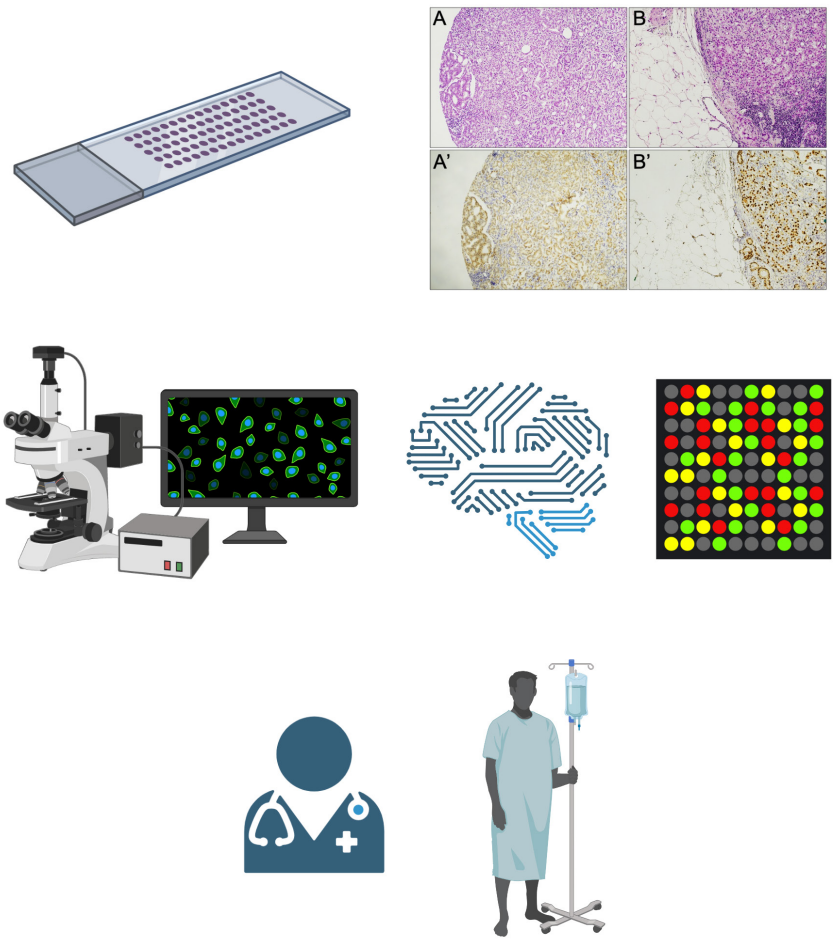

Figure 2: *Prostate carcinoma* (A, H&E x20) and lymph node metastasis (B, H&E x20) positive for ERG (A', B'; IHC x20). Note that ERG shows different degrees of expression within the same specimen and between distinct specimens (created with BioRender.com).

Author Contributions

Conceptualization: AL, FGC. MB. Data curation: FGC. Formal analysis: FGC, MB, AL. Funding acquisition: AL. Visualization: FGC, AL. Writing – original draft: FGC. Writing – review & editing: AL, FGC, MB.

Conflict of Interest

The authors declare no conflicts of interest.

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