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Genomic Rearrangements in Prostate Cancer

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Abstract

Purpose of review—Genomic instability is a fundamental feature of human cancer, leading to the activation of oncogenes and inactivation of tumor suppressors. In prostate cancer, structural genomic rearrangements, resulting in gene fusions, amplifications and deletions, are a critical mechanism effecting these alterations. Here we review recent literature regarding the importance of genomic rearrangements in the pathogenesis of prostate cancer and the potential impact on patient care.

Recent findings—Next generation sequencing has revealed a striking abundance, complexity, and heterogeneity of genomic rearrangements in prostate cancer. These recent studies have nominated a number of processes in predisposing prostate cancer to genomic rearrangements, including androgen-induced transcription.

Summary—Structural rearrangements are the critical mechanism resulting in the characteristic genomic changes associated with prostate cancer pathogenesis and progression. Future studies will determine if the impact of these events on tumor phenotypes can be translated to clinical utility for patient prognosis and choices of management strategies.

Keywords

rearrangement; fusion; copy number aberrations; genome sequencing

INTRODUCTION

Cancer is a genetic disease, characterized by the activation of oncogenes and inactivation of tumor suppressors. These changes can be driven by a variety of genomic mechanisms, including protein altering point mutations, copy number alterations, and promoter

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CONFLICTS OF INTEREST

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hypermethylation. In prostate cancer (PCA), structural genomic rearrangements represent the most common mechanisms that effect the genetic changes leading to oncogenic events. Genomic rearrangements result in cardinal genetic alterations in PCA such as amplification of oncogenes like *MYC*, *AR*, and *PIK3CA*, and deletion of tumor suppressors such as *PTEN*, *TP53*, and *NKX3-1*. Oncogenic gene fusions also result from genomic rearrangements in PCA; fusion of the androgen-driven *TMPRSS2* gene with the oncogenic transcription factor *ERG* occurs in nearly 50% of PCA (1, 2). The fact that these events represent the most common genomic abnormalities in PCA reinforces the central role of structural genomic rearrangements in the inactivation of tumor suppressors and activation of oncogenic signaling pathways and their critical importance to the pathogenesis of PCA.

In this review, we examine recently reported data regarding genomic rearrangements in PCA, associations with underlying molecular features, and implications for patient prognosis and clinical decision-making.

Discovery of recurrent ETS gene fusions: A paradigm shift in cancer research

The report of recurrent gene fusions in PCA in 2005 represents a paradigm shift regarding genomic rearrangements in cancer (2). Prior to this discovery, genomic rearrangements, and particularly translocations, were thought to be largely restricted to hematologic malignancies and sarcomas, playing a minimal role in solid epithelial tumors. We now know that gene fusions between androgen regulated genes and ETS genes are common, recurrent, and act as drivers of prostate tumorigenesis. In addition, rare fusion events, such as recurrent rearrangements of *BRAF* (3, 4) and *KRAS* (5), can also act as oncogenic drivers in PCA.

ETS family gene fusions

ETS family fusions are present in about 50% of PCA. In general, these rearrangement events are characterized by the presence of an androgen regulated gene as the 5' fusion partner, with an oncogenic transcription factor of the ETS family as the 3' partner, thus driving overexpression of an oncogenic factor with a tissue specific promoter. The archetype of this class of genomic rearrangements is the *TMPRSS2-ERG* fusion, the most common genomic abnormality in PCA. As shown in a recent meta-analysis of over 10,000 men, *TMPRSS2-ERG* is present in 47% of PCA (6), and resulting aberrant *ERG* expression acts as a driver of prostate tumorigenesis in a number of model systems (7-11).

Since the initial description of fusion genes involving ETS family transcription factors in PCA, studies have revealed additional fusion events following this paradigm (12). Androgen driven 5' partners include *SLC45A3* (13, 14), *HERPUD1* (15), and *NDRG1* (16), while additional ETS family members acting as downstream 3' partners include *ETV1*, *ETV4*, *ETV5*, *ELK4*, and *FLI1* (2, 17-19). This repertoire of fusions is analogous to hematopoietic malignancies and sarcomas, where typically there is one highly recurrent translocation (e.g., *TMPRSS2-ERG*) and a large number of rare variants of the theme, thus confirming the biologically significant role of ETS transcription factors in PCA carcinogenesis.

Other fusion events

Non-ETS fusion events are also observed in PCA. Some, like rearrangements of genes in the RAF pathway (3, 4) and the oncogene KRAS (5), are classic drivers of carcinogenesis, although rearrangements in this category are rare (1-2% of cancers). Interestingly, recurrent alterations in the Ras/Raf pathways appear to be restricted to ETS-negative cancers, possibly suggesting an overlap in oncogenic mechanisms. Others, such as rare rearrangements involving CDKN1A, CD9, PIGU, RSRC2, and IKBKB, have less known about their functional importance in PCA, although these genes exhibit biological roles in other cell types (20).

Types of genomic rearrangements in prostate cancer

Structural alterations to the genome can occur at several different scales with a variety of subtypes. Large scale alterations at the level of entire chromosomes or chromosome arms (often referred to as chromosomal instability, CIN) can result in aneuploidy and gross karyotypic abnormalities. Smaller scale events result from imperfect repair of double strand DNA breaks (DSB) and can manifest as interchromosomal rearrangements, in which different chromosomes exchange material with minimal loss of genetic material, or intrachromosomal rearrangements, occurring within a single chromosome but often resulting in DNA deletions (Figure 1A-C). Broadly speaking, these general processes result in the translocations, genomic deletions, and amplifications that activate oncogenes and inactivate tumor suppressors in cancer.

In addition to these basic components, complex patterns of genomic rearrangements have been described and observed specifically in PCA. Chromoplexy, comprised of complex, coordinated chains of balanced, copy number neutral rearrangements, was described by Baca et al. in 2013 (Figure 1D) (21). While evidence of these chained rearrangements can be found in other tumor types, it appears that this phenomenon is highly prominent in PCA, possibly indicating a tissue specific mechanism for formation of these events. Furthermore, chained rearrangements are particularly associated with ERG fusion positive PCAs, again implicating prostate-specific mechanisms. Finally, other complex genomic rearrangements in cancer are associated with a phenomenon known as chromothripsis, a striking pattern of hundreds of clustered rearrangements thought to arise through the shattering and inaccurate reassembly of a single chromosome (22). Chromothripsis-like patterns have been reported in PCA, particularly in ETS-negative classes (21, 23). However, true chromothripsis generates clonal alterations from a single catastrophic event (24). It remains to be established if the chromothripsis-like complex rearrangements observed in PCA occur as a single event or through a progressive, stepwise mechanism.

Factors predisposed to rearrangements

A variety of mechanisms have been proposed to associate with genomic rearrangements and possibly have a causative relationship. Several studies have noted a relationship of the position of genomic rearrangements with a pattern of localized hypermutation involving highly localized substitution mutations. This hypermutation phenomenon, known as *kataegis* (from the Greek for “thunder”), is characterized primarily by C>T and C>G point mutations,

and it has been proposed to be associated with activity of the APOBEC family of cytidine deaminases and subsequent base excision repair activity. While multiple reports have shown the spatial relationship between regions of kataegis and genomic rearrangements (25-28), the biological underpinnings of this phenomenon, and whether the point mutations have a causative relationship with observed genomic rearrangements, remains unclear.

Telomere dysfunction and genomic instability

Telomeres, and their associated proteins, are specialized structures located at the ends of chromosomes, and they serve to distinguish chromosome ends from DNA breaks, preventing inappropriate activation of the DNA damage response. Genomic instability, through fused chromosome ends, results when the protective function of telomeres is compromised (reviewed in (29)). In the absence of appropriate cell cycle control, fused chromosomes break randomly during cell division, resulting in unequal distribution of genetic material. This phenomenon, described as “fusion–breakage–bridge cycles,” will continue to propagate with further cell division and will result in multiple genomic aberrations.

In PCA, telomere shortening has been correlated with some of the most common genomic rearrangements in the disease, specifically, abnormalities on chromosome 8, including deletions of 8p and amplification of 8q (30). In addition, reactivation of telomerase following telomere dysfunction was shown to promote tumor metastasis in a non-metastatic mouse model of PCA (31). Notably, telomere length has been proposed as a potential marker associated with metastasis and death from PCA (32). Many questions regarding the relationship between telomere dysfunction, genomic rearrangements, and PCA outcomes remain to be answered.

Transcriptional activity and genomic rearrangements

It is well established that highly accurate DNA replication and repair processes are critical for genome maintenance. However, transcriptional activity has also emerged as a potential predisposing factor for genomic rearrangements, particularly in PCA. Transcribing DNA to RNA is a highly regulated and complex process involving the coordination of multiple levels of cellular events, including transcription factors and binding sites on the DNA template, alteration of the DNA template, remodeling of the DNA template with topoisomerases, local chromatin remodeling, and processing of the RNA product. Furthermore, the transcriptional and replication machinery are required to share the same DNA template, requiring coordination between these processes to avoid collisions of RNA and DNA polymerases. With errors in these events, transcription therefore has the potential to generate diverse types of genomic rearrangements.

In PCA, accumulating evidence supports transcription as a source of genomic instability predisposed to structural rearrangements. The closed chain pattern of rearrangements frequently observed in whole genome sequencing of PCA is consistent with the idea that the genomic loci involved in these rearrangements are spatially co-localized prior to the actual translocation events. “Transcription factories” refer to discrete sites in the nucleus where active RNA polymerases co-localize to coordinate gene expression from multiple loci (33,

34). Consistent with this concept, rearrangement breakpoints from PCA whole genome sequencing data spatially correlated with chromatin marks of active transcription – interestingly, however, this phenomenon may be restricted to ERG-fusion positive tumors (35). Furthermore, interchromosomal, chained rearrangements are significantly more pronounced in tumors harboring ETS fusions, and ERG fusions frequently arise in this context (21). Finally, using a genome-wide chromosome conformation capture approach, ERG itself has been shown to affect global changes in the topology of chromosome organization, inducing new patterns of spatial associations between genomic loci (36). Therefore, the temporal dependency of transcriptional activity, ETS fusions, and genomic rearrangements is still unclear. There is evidence for both the hypothesis that ETS fusions *cause* genomic rearrangements and the hypothesis that they represent *consequences* of transcriptional-induced rearrangements. The true mechanisms underlying these phenomena may represent a complex combination of these concepts.

Androgen stimulated transcription has received particular attention as a potential mechanism for the induction of genomic rearrangements in PCA. Androgen signaling induces proximity of the *TMPRSS2* and *ERG* genomic loci (as well as other AR targets), predisposing to the formation of the *TMPRSS2-ERG* gene fusion (37-39). In addition, early onset-PCAs (< age 50), which are enriched for ETS fusions (40-42) have been reported to exhibit rearrangement break points spatially localized near AR binding sites (40). These findings suggest that androgen driven transcription preferentially induces specific types of interchromosomal rearrangements, leading to a cascade of oncogenic molecular events such as recurrent ETS rearrangements.

Taken together, these concepts paint a mechanistic picture of the critical nature of androgen-stimulated transcription in the formation of genomic rearrangements in PCA. Potentially, androgen receptor and its cofactors promote formation of highly active transcriptional centers, bringing together “transcriptional hubs,” comprised of genomic loci widely separated in linear chromosomal space and across different chromosomes, and in doing so form a conducive environment for structural rearrangements.

In contrast ETS-negative PCAs have their own, distinct patterns of genomic rearrangements. In general, these prostate tumors are more heavily enriched in intrachromosomal rearrangements, leading to copy number losses, and have specific patterns of SCNAs (21, 43, 44). The importance of these rearrangement patterns, the mechanisms responsible for their differences among different molecular classes of PCA, and how they reflect the underlying biology of these tumors are all areas of active investigation.

RELATIONSHIP OF REARRANGEMENTS TO PROGNOSIS: *TMPRSS-ERG* and association with clinical outcome

Numerous studies have examined the effect of *TMPRSS2-ERG* on clinical outcome in PCA. No definitive conclusion has been forthcoming due to conflicting data. ERG rearrangement is reported as associated with both more aggressive and more indolent PCA, which may represent differences in patient cohorts and management strategies, the impact of sampling, PCA multifocality molecular heterogeneity, and differences in specific choices of outcomes.

This has been reviewed in detail by others (45). In brief, population-based studies focused on patients diagnosed by TURP (non PSA-screened) and managed with watchful waiting have shown a significant association between *ERG* status and adverse pathology, metastases, or death from PCA (46, 47). TMPRSS2-*ERG* is reported to be associated with adverse pathologic features (tumor volume and Gleason grade) in an active surveillance population (48). The impact of ETS rearrangement on adverse pathologic features or clinical outcome following radical prostatectomy is less clear with several studies reporting association between ETS status and features of aggressive PCA (including increased Gleason grade, stage, or BCR) while others report no associations or even association with indolent features (lower Gleason grade or improved recurrence-free survival). Finally, a recent study of patients undergoing treatment with brachytherapy showed that *concurrent* *ERG* rearrangement and PTEN deletion, rather than *ERG* fusion alone, was predictive of poorer recurrence free-survival (49).

In summary, population-based studies of watchful waiting cohorts have shown ETS fusions associated with poorer outcomes, while retrospective radical prostatectomy series have conflicting results regarding prognosis. A unifying conclusion across studies is made difficult by the variation in techniques to detect *ERG* rearrangement, variation in patient populations, and lack of PSA screening in some cohorts.

Total burden of genomic rearrangements and clinical outcome

Several studies have reported the ability to classify of PCA based on patterns of SCNAs and have attempted to correlate these findings with patient outcome (44, 50, 51). Most recently, the total burden of SCNAs—defined as the percent of the genome altered by copy number changes, rather than specific deletions or amplifications—was reported to be associated with clinical outcomes. In over 250 clinically localized PCA cases, Hieronymus and colleagues showed that increasing numbers of SCNAs was an independent predictor of biochemical recurrence and metastasis after radical prostatectomy, adding predictive information to standard clinicopathologic parameters, including Gleason grade (51). This finding implies that the total number of genomic rearrangements, and by inference the degree of genomic instability, may be a factor highly predictive of PCA aggressiveness. This concept has been established in other cancer types (breast, ovarian) where the degree of genomic instability, and particularly chromosomal instability, correlates with aggressive features.

CONCLUSION

Structural genomic rearrangements play a critical role in the pathogenesis of PCA, resulting in activation of oncogenes, inactivation of tumor suppressors, and production of oncogenic gene fusions. The mechanisms responsible for the predilection of PCA towards these genome changes and the biology underlying the difference in structural rearrangements between molecular classes of PCA represent exciting areas of active investigation. Establishing the clinical significance of these events will require large cohorts, well annotated for both clinical and molecular characteristics, with long-term follow up.

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KEY POINTS

- Structural genomic rearrangements are the most common mechanism of altering the genome in PCA
- Genomic rearrangements result in amplification of oncogenes, deletion of tumor suppressors, and production of oncogenic gene fusions
- Multiple mechanisms lead to distinct patterns of rearrangements in different molecular classes of PCA – the biological and clinical significance of this is still poorly defined

Figure 1. Generation of distinct types of genomic rearrangements

(A) Double strand breaks in DNA can be repaired by joining different chromosome, without significant DNA loss, or by rejoining the same chromosome after loss of genetic material.

(B, C) Circos plots of rearrangement chains in representative tumors, showing primarily interchromosomal rearrangements (B) and primarily intrachromosomal events leading to copy number alterations (C). Rearrangements in the same chain are depicted in one color. Rearrangements in gray were not assigned to a chain. The inner ring shows copy number gain and loss in red and blue, respectively. (D) Graphical representation of genomic breakpoints linked in chains in chromoplexy. Adapted from Baca et al, *Cell* 2013.