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RESEARCH HIGHLIGHT

Chromoplexy: a new paradigm in genome remodeling and evolution

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Early massively-parallel sequencing studies have revealed the mutational landscape of protein-coding genes in prostate cancer. However, most of these studies have not explored the extensive influence of genomic rearrangement in prostate cancer. In a recent *Cell* article, Baca and colleagues used whole-genome sequencing to tackle this issue, comprehensively surveying the abundance of genomic rearrangements present in a large cohort of 57 prostate cancers. They characterized a wide-spread phenomenon termed 'chromoplexy', which may drive cancer evolution through the phenomena of punctuated equilibrium by concurrently dysregulating numerous cancer genes across multiple chromosomes. While the causes of this event still require elucidation, this defining discovery undoubtedly offers an important glimpse into the evolutionary process of prostate cancer.

Genomic rearrangements are highly prevalent in prostate cancer, have a profound impact on tumor development and progression (reviewed in Ref. [1]), and may serve as promising prognostic biomarkers.[2,3] For example, numerous recurrently gained or lost regions are linked to poor clinical outcome, such as *MYC* amplifications at 8q24 and *PTEN* deletions at 10q23.[4] Also, gene fusions involving ETS-family transcription factors (e.g., *TMPRSS2–ERG*) are considered an early carcinogenic event and are present in up to 70% of Western prostate cancers.[5] Whereas microarray-based studies were largely limited to the analysis of copy number aberrations, in prostate cancer, massively-parallel sequencing-based technologies allow investigation of far more complex structural variants.

The first whole-genome studies reported complex genomic rearrangements involving multiple genes.[6–8] These complex rearrangements can produce 'poly-gene fusions' disrupting multiple genes simultaneously, or form 'closed-chains of breakage and rejoining', which are analogous to the breaking, shuffling and rejoining of many regions in a closed chain rearrangement. The involvement of the *TMPRSS2–ERG* gene fusion in several of these complex events suggested their relevance to prostate cancer initiation,[6] and laid the foundation for the significant follow-up study carried out by Baca *et al.* Surprisingly, they revealed these complex genomic events to be a wide-spread phenomenon in prostate cancer and termed the phenomenon 'chromoplexy' to reflect the complex weaving or restructuring of the genome.[9]

Baca *et al.* expanded on prior observations of chained rearrangements[6] and developed a computational method to systematically detect chromoplexy events. Surprisingly, almost 90% of the 57 malignant tumors analyzed contained a chain consisting of five or more rearrangements and over 60% of tumors contained two or more of these chains. These chromoplexy events collectively involved almost 40% of total genomic rearrangements, suggesting a fundamental link to the etiology of genomic rearrangements in prostate cancer. Moreover, additional computational simulations revealed that these complex events most likely arise through a single, coordinated process, rather than independently through multiple, sequential steps.

Interestingly, Baca *et al.* observed a difference in the chromoplexy distribution across different molecular subtypes of prostate cancer defined by ETS fusion status and *CHD1* mutation status. Tumors with the oncogenic ETS fusions ($ETS^+/CHD1^{wt}$) harbored greater number of interchromosomal rearrangements, involving up to seven chromosomes in a single chain. A majority of ETS^+ tumors had chromoplexy events that involved *ERG* fusions, which suggests chromoplexy may arise from the same transcriptional process driven by the androgen receptor (AR) that yields *TMPRSS2–ERG* fusions.[10] This possibility was additionally supported by the enrichment of breakpoints from these chains in highly expressed genomic regions.

In contrast, the *CHD1*-deleted subset of ETS^- tumors ($ETS^-/CHD1^{del}$) featured more intrachromosomal rearrangements. In these tumors, where chained rearrangements were typically localized across only one or two chromosomes, there were more rearrangements overall (up to seven times the average number of rearrangements). The phenotypic differences between these two tumor subtypes may be related to the role of *CHD1* as a chromatin-modifying tumor suppressor whose inactivation can suppress AR-transcriptional activity and prevent *ERG*-fusion formation.[11] The enrichment of breakpoints in late-replicating DNA and heterochromatin regions with lower gene expression also supports an alternative cause of chromoplexy in ETS^- tumors. Recently, *SPOP* has been implicated as a tumor suppressor gene recurrently mutated in 13% of prostate cancers and in mutually exclusivity to ETS family rearrangements.[12] Since *SPOP* mutations and *CHD1* deletions collectively define a large fraction of ETS^- tumors, it remains to be seen if they can cooperate in shifting chromoplexy formation away from an AR-driven transcriptional mechanism.

The characteristics of chromoplexy are reminiscent of chromothripsis, another emerging phenomenon in cancer evolution. Whereas the classical view of cancer progression follows the gradual accumulation of

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mutations that promote cell survival and invasion,[13] both chromoplexy and chromothripsis are large-scale genomic rearrangement events that can disrupt numerous essential cell processes in a single step. As such, these catastrophic events are predicted to be retained only by inducing oncogenic alterations that compensate the cell with strong selective advantages.

At the same time, chromoplexy differs from chromothripsis in a number of fundamental aspects. Chromoplexy affects fewer rearranged regions, numbering in the tens rather than hundreds, scattered across many chromosomes rather than localized in one or two chromosomes.[14] Furthermore, chromoplexy appears to be a frequent phenomenon in prostate cancer, whereas the frequency of chromothripsis ranges between 2% and 3% in different cancers.[14] Although the mechanisms of both phenomenon still need to be clearly understood, chromoplexy in prostate cancer may be caused by a number of processes including a transcriptional-related mechanism in ETS^+ tumors, whereas converging evidences suggest genome instability and micronuclei formation as a leading cause of chromothripsis.[15]

In the wake of this study, we eagerly anticipate follow-up to a number of important questions. Although features of chromoplexy in ETS^+ prostate tumors strongly suggests DNA damage induced by AR-driven transcription as a probable mechanism, observations of these complex genomic rearrangements in an androgen-stimulated *in vitro* model will be necessary to validate this hypothesis. Similarly, examining chromoplexy in other cancer systems removed from AR influence (e.g., breast cancer, small-cell lung cancer) may facilitate an understanding for this phenomenon in ETS^- tumors. Interestingly, like genome instability generally, the occurrence of chromoplexy appears to support a punctuated equilibrium model of evolution that proposes long periods of relative stability punctuated by sudden, rapid periods of radical change. Since the progression of prostate cancer may largely depend on multiple rounds of chromoplexy, elucidating the triggers for these periods of punctuated change can hold the key to locking prostate cancer in evolutionary stasis. Moreover, confirmation of punctuated equilibrium as a mechanism for cancer evolution will ultimately have profound implications for evolutionary biology as a whole.

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