and whether these interactions are in turn influenced by PAR formation.

With these new findings, a comprehensive and satisfying picture has emerged to account for the biphasic pattern of BRCA1 assembly at DSBs (Figure 1). In this scenario, the BRCA1/BARD1 heterodimer is rapidly recruited to DSB ends in an H2AX-independent manner by virtue of the interaction of its BARD1 BRCT domain with PAR. Subsequently, the heterodimer associates in a more durable fashion with the flanking DSB chromatin through the well-defined γH2AX pathway upon interaction of its BRCA1 BRCT domain with phosphorylated Abraxas. It is important to note that the vast majority of BRCA1 and BARD1 mutations associated with hereditary breast cancer are either (1) truncating or missense mutations that ablate BRCT phospho-recognition or (2) missense mutations that abolish BRCA1/BARD1 heterodimerization. Thus, a common denominator of most tumor-predisposing defects is disruption of either the early and/or late pathways of BRCA1/BARD1 recruitment. A key objective of future studies will be to determine the specific functions of BRCA1/BARD1 within each of the two DSB subcompartments and to ascertain whether these functions are relevant for tumor suppression.

The exquisite sensitivity of BRCA1- and BRCA2-defective tumors to PARP inhibitors was originally thought to reflect a synthetic lethal effect whereby BRCA1/2 mutant cells, which are intrinsically defective for DSB repair, are rendered inviable by simultaneous inactivation of single-strand DNA break repair, which is normally dependent on PARP1 (Rouleau et al., 2010). However, recent studies suggest that this model is incomplete and that other actions of PARP may also be relevant (Helleday, 2011). As noted by Li and Yu (2013), most BRCA1-deficient tumors have lesions of the BRCA1 BRCT domains that would disrupt the late γH2AX-dependent, but not the early PAR-dependent, pathway of BRCA1/BARD1 recruitment. Thus, the heightened sensitivity of these cells to PARP inhibition might reflect the fact that both modes of BRCA1/BARD1 recruitment are ablated simultaneously. As such, this work may have important clinical implications for the anti-cancer activity of PARP inhibitors.

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Chromoplexy: A New Category of Complex Rearrangements in the Cancer Genome

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Widespread structural alterations of cancer genomes are increasingly observed in a broad spectrum of tumors. In a recent issue of *Cell*, Baca and colleagues describe large chains of rearrangements that coordinately affect multiple chromosomes in prostate cancer. This phenomenon of chromoplexy may define cancer subtypes and drive punctuated tumor evolution.

The application of next-generation sequencing technologies has resulted in systematic efforts to characterize the mutational spectrum, genomic alterations, and clonal evolution of a wide range of tumors. In particular, whole-genome sequencing approaches can reveal extensive structural rearrangements throughout the tumor genome, which can be difficult to detect using more limited exome sequencing approaches. The whole-genome sequencing

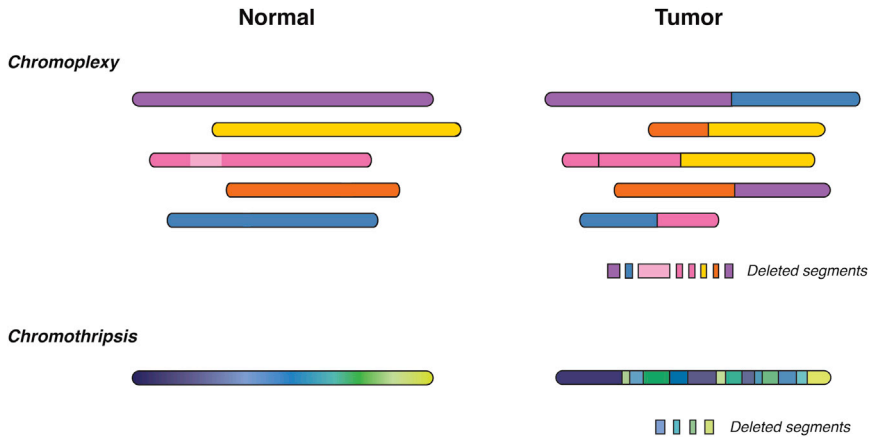

Figure 1. Comparison of Chromoplexy and Chromothripsis
Schematic representations show chromosomal rearrangements that occur in tumor genomes as a consequence of chromoplexy (top) or chromothripsis (bottom).

analysis of prostate tumors by Baca et al. (2013) represents the most comprehensive analysis to date for one of the most common human malignancies, resulting in a surprising new insight into cancer genomes.

Prostate cancer was the first solid tumor shown to have frequent large-scale chromosomal rearrangements, as originally demonstrated by the discovery of the *TMPRSS2-ERG* fusion (Tomlins et al., 2005). Subsequent studies have shown that chromosomal rearrangements and extensive copy number alterations are prevalent in prostate cancer, whereas point mutations are relatively infrequent, suggesting that structural alterations in tumor genomes represent the primary drivers of prostate cancer progression (Barbieri et al., 2012; Rubin et al., 2011; Taylor et al., 2010). Furthermore, previous whole-genome sequencing of seven prostate tumors showed frequent occurrence of complex chains of balanced rearrangements, involving both intrachromosomal and interchromosomal events (Berger et al., 2011).

In the current study, Baca et al. (2013) performed whole-genome sequencing analysis of 57 prostate tumors and identified 5,596 somatic rearrangements. Notably, almost 40% of the detected rearrangements were components of complex and lengthy series of rearrangements, often occurring as closed chains. Such chained rearrangements could display precise or nearly precise joins at their breakpoints or alternatively were associated with large DNA deletions at their junctions, corresponding to "deletion bridges." The number of rearrangements within a chain was highly variable, ranging from 3 to over 40, with six or more chromosomes possibly involved. Nearly 90% of the tumors contained chains with five or more rearrangements, and more than 60% of the tumors contained more than one such chain. Importantly, statistical analyses indicated that such rearrangements are unlikely to arise independently, and instead may form in a coordinated and simultaneous fashion. Thus, Baca et al. (2013) coin the term "chromoplexy" to describe this phenomenon of intricately weaved genomic rearrangements occurring in concert (Figure 1).

Chromoplexy can account for many of the known genomic alterations found in prostate cancer by generation of oncogenic fusion genes as well as by disruption or deletion of genes located near rearrangement breakpoints (Baca et al., 2013). Although no novel recurrent rearrangements were discovered in this analysis, the *TMPRSS2-ERG* fusion was often found as part of chromoplectic rearrangement chains. Moreover, putative oncogenic fusions involving *BRAF* and *MAPK1* were uniquely identified in individual tumors, while loss-of-function alterations due to chromoplexy for the putative tumor suppressor genes *PTEN*, *NKX3.1*, *TP53*, and *CDKN1B* were observed in multiple tumors. In particular, several tumors contained evidence for multiple loss- and gain-of-function alterations occurring in the context of a single chromoplectic event.

The coordinated structural rearrangements characteristic of chromoplexy exhibit features similar to but distinct from the phenomenon of chromothripsis that has been observed in a diverse range of malignancies (Figure 1) (Forment et al., 2012; Jones and Jallepalli, 2012). Both chromothripsis and chromoplexy display random breakage and fusion of genomic segments with low copy number states, most likely mediated by non-homologous end-joining. However, the genomic breakpoints associated with chromothripsis typically number in the hundreds and are locally clustered within one or two chromosomes, whereas the chained rearrangements characteristic of chromoplexy are unclustered, usually number in the tens, and include multiple chromosomes. Furthermore, chromothripsis appears to occur as a single clonal event early in tumor progression, while chromoplexy can occur more than once in prostate cancer evolution, with sequential events detected at clonal or subclonal frequencies. Finally, chromothripsis represents a relatively infrequent event for all tumor types analyzed to date, whereas chromoplexy is a common event in prostate cancer. Nonetheless, the distinction between chromothripsis and chromoplexy is not well defined, and it is conceivable that some coordinated structural rearrangements may have intermediate properties.

Distinct molecular mechanisms are likely to underlie chromothripsis versus chromoplexy. Although several models have been advanced to explain the mechanistic basis for chromothripsis, major causes are likely to be replication stress and mitotic errors, perhaps in association with the formation of micronuclei and premature chromosome compaction (Forment et al., 2012; Jones and Jallepalli, 2012). Notably, micronucleus formation is a characteristic feature of genomic instability, and loss of p53 appears to result in increased frequency of chromothripsis. In contrast, the mechanistic basis of chromoplexy is less well understood at present, but may be causally related to DNA damage induced by transcription factor binding. Previous studies have shown that formation of the *TMPRSS2-ERG* fusion in tumor cell lines is mediated by double-strand breaks induced by binding of androgen receptor (AR), and can be facilitated by genotoxic stress

(Haffner et al., 2010; Rubin et al., 2011). Consistent with such a model, chromoplectic rearrangement breakpoints are associated with active transcription and open chromatin configurations (Baca et al., 2013).

The study by Baca et al. (2013) also sheds light on potential molecular subtypes of prostate adenocarcinoma. Despite the existence of categories of prostate cancer patients with markedly different survival outcomes, previous attempts to discern distinct histopathological or molecular subtypes of prostate cancer have met with limited success (Shen and Abate-Shen, 2010). Baca et al. (2013) now suggest the existence of at least two distinct molecular subtypes defined by the presence or absence of the *TMPRSS2-ERG* fusion (ETS^+) and by the mutational status of *CHD1*, which encodes a chromodomain helicase involved in chromatin remodeling. Whereas rearrangements occurring in ETS^+ $CHD1^{WT}$ tumors are predominantly interchromosomal and display features of chromoplexy, ETS^- $CHD1^{del}$ tumors display a higher frequency of intrachromosomal rearrangements, which more closely resemble chromothripsis. Moreover, the rearrangement breakpoints in ETS^+ $CHD1^{WT}$ tumors tend to occur near highly expressed loci, consistent with a transcription-associated mechanism for chromoplexy, but the ETS^- $CHD1^{del}$ tumors instead contain rearrangements that are often associated with heterochromatin. Whether these molecularly distinct groups correspond to distinct patient outcomes and/or treatment responses will undoubtedly represent a major issue for future studies.

Although chromoplexy appears to be a cardinal feature of many prostate tumor genomes, it is currently unclear whether it plays a key role in other cancer types. Interestingly, Baca et al. (2013) detect chained rearrangements in a significant proportion of non-small cell lung cancers, head and neck cancers, and melanomas, suggesting that chromoplexy can also occur in a broad spectrum of tumors. Given the apparent central role of AR and possibly ETS transcription factors in promoting chromoplexy in prostate tumors, it will be interesting to determine whether the chromoplectic events found in other cancers are qualitatively similar or distinct.

Overall, chromoplexy and chromothripsis undoubtedly represent key drivers of tumor evolution. In contrast to traditional "gradualist" views of sequential accumulation of cancer-promoting mutations, the large-scale structural alterations of both chromoplexy and chromothripsis are likely to promote discontinuous tumor evolution in a form of "punctuated equilibrium" (Baca et al., 2013). Moreover, further discrete steps in tumor evolution can potentially arise through the sequential occurrence of chromothripsis followed by chromoplexy or by successive rounds of chromoplexy. Modeling the causes and consequences of such genomic alterations will be a serious issue for cancer biologists, while their impact on treatment response and resistance will pose significant clinical challenges.

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