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Previews

Disruptive Events in the Life of Prostate Cancer

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Two recent reports in *Nature* provide evidence for increasingly complex "disruptive" molecular alterations that occur during prostate cancer progression. They shed light on the intricacy of genetic changes that modulate PTEN's control over the phosphoinositide 3-kinase pathway and prostate cancer progression, and identify new potential biomarkers and therapeutic targets.

The number of genomic changes observed in cancer is rapidly expanding, due to the emergence of enabling technologies. In prostate cancer, approximately half of all tumors harbor rearrangements, which frequently render a gene from the *ETS* family of transcription factors under the control of androgen-regulated promoter elements (Tomlins et al., 2005) (Figure 1). Another well-established set of molecular alterations in this disease are mutations in the tumor suppressor gene *PTEN*, which lead to activation of phosphoinositide 3-kinase (PI3K)/AKT pathways (Li et al., 1997) and cooperate with *ETS* fusions in prostate carcinogenesis (Carver et al., 2009; King et al., 2009). While many prostate cancers can be characterized by *ETS* and/or *PTEN* status, additional "disruptive" events —genomic events with promalignant consequences—are being identified in smaller subsets of disease that exemplify the enormous genomic complexity of prostate cancer.

With the goal of identifying novel somatic events in prostate cancer, Berger et al.(2011) recently completed whole genome sequencing of seven primary prostate cancers (three harboring *ETS* rearrangements) and their matched normal controls. This led to the identification (and in some cases reconfirmation) of mutations in several genes, including *SPTA1*, *SPOP*, *ZNF407*, *CHD1, CHD5, HDAC9, DICER* and *PTEN*. As is often the case with genomic changes that drive cancer progression, it is common to find functionally recurrent mutations that disrupt multiple genes in a pathway. Specifically, rearrangements disrupting both *PTEN* and its interacting protein *MAGI2* were identified. Knockdown experiments may further confirm that the loss of MAGI2 expression drives AKT phosphorylation, suggesting that susceptibility pathways can be mutated at different points and expanding the number of mutations known to disrupt PTEN signaling in prostate cancer.

Since these data reveal that multiple disruptive genomic events can alter PI3K signaling, it is not surprising that genetically engineered mouse models with *PTEN* and *ETS* lesions do not fully recapitulate the disease phenotypes of human prostate cancer. In fact, mice with either prostate-specific overexpression of *TMPRSS2-ERG* (the predominant ETS fusion) or *PTEN* loss of heterozygosity only develop precursor-like lesions of prostate cancer, called prostate intraepithelial neoplasia (PIN), which in the case of complete *PTEN* inactivation can progress to high-grade adenocarcinoma after long latency (Chen et al., 2005). When *ERG* is overexpressed in a *PTEN* heterozygous background, mice develop invasive prostate cancer more rapidly than control mice (Carver et al., 2009; King et al., 2009), but without a reported propensity for distant metastasis. These models suggested that either a fundamental difference between mice and men exists—especially considering that wild-type mice do not develop prostate cancer—or that we do not yet have a complete understanding of all of the disruptive events that occur prior to metastatic progression.

Following the latter postulation that additional unknown barriers are preventing metastatic progression, Ding et al. (2011) recently compared the gene expression profiles of *PTEN* deletion-induced PIN to wild-type prostate epithelium. This led to the identification of a difference in expression of genes in the TGFβ signaling pathway. Subsequent prioritization of targets in this pathway led to the identification of SMAD4 as a key regulator of TGFβ signaling that is downregulated in human prostate cancer metastasis as compared with localized prostate cancer. Importantly, prostate-specific deletion of both *SMAD4* and *PTEN* led to faster occurring prostate cancer with a high propensity for metastasis, while *SMAD4* deletion alone had no effect. This suggested that before *PTEN*-impaired prostate tumors become metastatic, they must first develop mechanisms to disrupt the tumor suppressive effects of SMAD4-mediated canonical TGFβ signaling. It will be interesting to see if genomic sequencing of metastatic prostate cancer reveals evidence of TGFβ pathway disruption.

Although Berger et al. did not identify events disrupting TGFβ signaling, their study provides insight into the mechanism of how gene fusions are formed. For example, many of the rearrangements occurred in a balanced manner such that reciprocal genomic rearrangements are generated, creating a series of many different gene fusions in which no DNA copy number changes were identified (Berger et al., 2011). This study also found that a single gene could be disrupted by

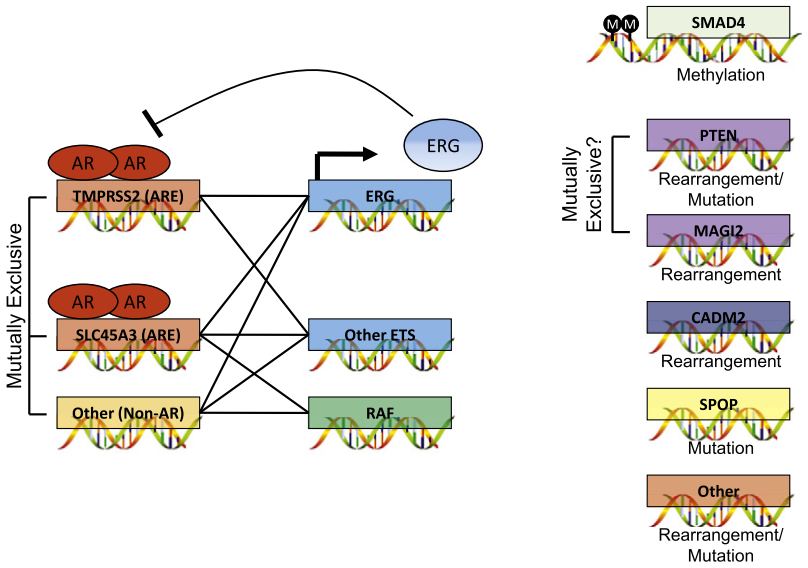

Figure 1. Disruptive Events Found in Primary Prostate Cancer

Rearrangements and base substitution mutations disrupting several pathways have been identified in localized prostate cancer, including rearrangements driving ETS transcription factor overexpression, rearrangements causing constitutive RAF kinase activation, epigenetic changes to the *SMAD4* locus blocking TGFβ signaling (Ding et al., 2011), and rearrangements/mutations disrupting PI3K signaling (such as PTEN and MAGI2) (Berger et al., 2011). Likewise, mutations in an E3-ubiquitin ligase gene (*SPOP*) have been reported to occur in a subset of human prostate cancer (Berger et al., 2011). While rearrangements of ETS and RAF genes appear to be mutually exclusive, it is still unknown whether the other disruptive mutations will collaborate.

a different mechanism of rearrangement in each tumor. For example, they identified rearrangements that occur in approximately 6% of prostate cancers in a cell adhesion gene called *CADM2*, and each rearrangement occurred by a different combination of genomic deletions, duplications, and inversions. This suggests that while the type of rearrangement may be different, a conserved mechanism must be responsible for creating a rearrangement "hotspot."

By overlapping the breakpoint locations with available genome-wide location analyses for androgen receptor (AR), ERG, and histone marks (Yu et al., 2010), Berger et al. demonstrated that the breakpoints correlated with open chromatin marks as well as AR binding in tumors with ETS rearrangements. This is surprising, as the most common ETS gene fusion product, ERG, functions to disrupt AR signaling (Yu et al., 2010).It will be interesting to see if other genomic events correlated with *ETS* status, such as chromosome 3p14 deletion, are also correlated with enrichment of these factors (Taylor et al., 2010). Nonetheless, this observation supports recent mechanistic data suggesting that activated AR facilitates genomic rearrangements by bringing linearly distant genomic loci together in a process termed induced-proximity (multiple studies reviewed in Mani and Chinnaiyan, 2010). The fact that androgen receptor was enriched at genomic breakpoints also suggests that these "hotspots" may be tissue type specific.

In addition to addressing how rearrangement breakpoints are selected, the data also gave insight into the repair mechanism that fuses the DNA ends after breaks occur. For example, nonhomologous end joining frequently utilizes regions of microhomology to facilitate the ligation of otherwise noncompatible DNA ends. Interestingly, most of the called rearrangements were precise joins without overlapping or intervening sequence at the junction. In contrast, analysis of sequence data used to analyze breakpoints in breast cancer demonstrated that most fusion junctions had 2-3bp of microhomology (Stephens et al., 2009). It is tempting to speculate that the DNA ends may be rejoined in the two cancers by different repair processes whose activities are cell cycle dependent.

Given the enormous complexity of disruptive events in a prostate cancer genome, an important question is: how can this information be used clinically? Recognizing the apparent mechanistic importance of PTEN and SMAD4 signaling to prostate cancer progression, Ding et al. (2011) identified two key effectors of the TGFβ signaling pathway, the invasion-associated gene product SPP1 and the cell cycle regulator CyclinD1, to help develop a test to predict for aggressive disease. Subsequent expression analysis of these four genes—*PTEN*, *SMAD4*, *CCND1*, and *SPP1*—was able to predict lethal metastasis in prostate cancer better than Gleason score alone (Ding et al., 2011). In light of the ever-expanding number of recurrent mutations in prostate cancer and the fact that other events disrupting PI3K signaling were not analyzed, this observation is all the more remarkable.

In conclusion, the recent reports by Berger, Ding, and colleagues highlight the complex nature of disruptive events in the life of prostate cancer. As advanced sequencing approaches become more widely implemented, it is certain that additional genetic alterations along key progression pathways will be identified. Understanding the genesis and effect of these events, relative to existing lesions such as *PTEN* inactivation and *ETS* fusions, will be critical to the efforts to develop better biomarker-based predictors of progression and to identify potential targets for prostate cancer therapy. While the discovery of key genetic alterations, such as *PTEN* inactivation, *ETS* and *RAF* fusions, *SPOP* mutations, *MAGI2* rearrangements, and *SMAD4* silencing have represented significant strides toward a better understanding of prostate cancer progression, it is clear that we are seeing just the tip of the iceberg of cancer-defining disruptive lesions, but are also at the beginning of an exciting period of discovery.

REFERENCES

Berger, M.F., Lawrence, M.S., Demichelis, F., Drier, Y., Cibulskis, K., Sivachenko, A.Y., Sboner, A., Esgueva, R., Pflueger, D., Sougnez, C., et al. (2011). Nature *470*, 214–220.

Carver, B.S., Tran, J., Chen, Z., Carracedo-Perez, A., Alimonti, A., Nardella, C., Gopalan, A., Scardino, P.T., Cordon-Cardo, C., Gerald, W., and Pandolfi, P.P. (2009). Nat. Genet. *41*, 619–624.

Chen, Z., Trotman, L.C., Shaffer, D., Lin, H.K., Dotan, Z.A., Niki, M., Koutcher, J.A., Scher, H.I., Ludwig, T., Gerald, W., et al. (2005). Nature *436*, 725–730.

Ding, Z., Wu, C.J., Chu, G.C., Xiao, Y., Ho, D., Zhang, J., Perry, S.R., Labrot, E.S., Wu, X., Lis, R., et al. (2011). Nature *470*, 269–273.

King, J.C., Xu, J., Wongvipat, J., Hieronymus, H., Carver, B.S., Leung, D.H., Taylor, B.S., Sander, C., Cardiff, R.D., Couto, S.S., et al. (2009). Nat. Genet. *41*, 524–526.

Li, J., Yen, C., Liaw, D., Podsypanina, K., Bose, S., Wang, S.I., Puc, J., Miliaresis, C., Rodgers, L., McCombie, R., et al. (1997). Science *275*, 1943–1947.

Mani, R.S., and Chinnaiyan, A.M. (2010). Nat. Rev. Genet. *11*, 819–829.

Stephens, P.J., McBride, D.J., Lin, M.L., Varela, I., Pleasance, E.D., Simpson, J.T., Stebbings, L.A., Leroy, C., Edkins, S., Mudie, L.J., et al. (2009). Nature *462*, 1005–1010.

Taylor, B.S., Schultz, N., Hieronymus, H., Gopalan, A., Xiao, Y., Carver, B.S., Arora, V.K., Kaushik, P., Cerami, E., Reva, B., et al. (2010). Cancer Cell *18*, 11–22.

Tomlins, S.A., Rhodes, D.R., Perner, S., Dhanasekaran, S.M., Mehra, R., Sun, X.W., Varambally, S., Cao, X., Tchinda, J., Kuefer, R., et al. (2005). Science *310*, 644–648.

Yu, J., Yu, J., Mani, R.S., Cao, Q., Brenner, C.J., Cao, X., Wang, X., Wu, L., Li, J., Hu, M., et al. (2010). Cancer Cell *17*, 443–454.