FGF Signaling in Prostate Tumorigenesis—New Insights into Epithelial-Stromal Interactions

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DOI 10.1016/j.ccr.2007.11.021

Members of the fibroblast growth factor (FGF) family are believed to play critical roles during organogenesis and carcinogenesis via signaling between epithelial and stromal compartments. Two new studies in this issue of *Cancer Cell* underscore the importance of FGF signaling in mediating epithelial-stromal interactions during prostate carcinogenesis. These papers show that deregulated FGF signaling in mouse models of prostate cancer leads to cancer progression and promotes an epithelial-mesenchymal transition, suggesting that FGF receptor inhibitors may have therapeutic value for prostate cancer treatment.

Long before it was fashionable to talk about the role of the tumor microenvironment in cancer development, the pioneering studies of Gerald Cunha and others identified the importance of epithelial-stromal interactions for formation and tumorigenesis of the prostate gland (Cunha et al., 1987). These investigators showed that the prostate is highly amenable for investigating the role of paracrine growth factor signaling between epithelial and stromal compartments, particularly since these signaling interactions can be recapitulated in vitro as well as in male *nude* mice hosts. In particular, Cunha and colleagues used tissue recombinations of isolated epithelium and mesenchyme (stroma) to define the tissue and cellular requirements for prostate formation, elucidate the roles of growth factor and androgen signaling, and demonstrate the contribution of the stromal compartment to prostate carcinogenesis (Cunha et al., 1987; Hayward et al., 2001). In particular, this work identified specific members of the FGF family as having central roles in mediating epithelial-mesenchymal interactions in the prostate.

FGFs are encoded by a highly conserved family of 22 mammalian genes, which can promote a range of biological effects, including mitogenesis and cellular differentiation, as well as increased cellular motility and invasiveness in specific contexts (Kwabi-Addo et al., 2004; Ornitz and Itoh, 2001). FGF ligands signal through four cognate high-affinity tyrosine kinase receptors, designated FGFR-1 to -4, leading to downstream activation of multiple signal transduction pathways, including the Erk, MAPK, and PI3K-Akt pathways. During prostate organogenesis, FGF10 expression in the mesenchyme is essential for prostate induction, acting independently of the androgen receptor (AR) signaling pathway (Thomson and Cunha, 1999). Conversely, epithelial expression of the FGFR2 IIIb isoform (FGFR2b), which specifically binds FGF10, as well as FGF7 and FGF22, is essential for normal prostate organogenesis in an AR-independent manner (Lin et al., 2007).

Several previous studies have shown that multiple FGF ligands display elevated expression in prostate cancer and can potentially act as either paracrine or autocrine factors (Kwabi-Addo et al., 2004). In addition, prostate cancer progression has been associated with altered expression of specific FGF receptor isoforms; notably, epithelial FGFR2b is downregulated and has been proposed to have tumor suppressor activity (Kwabi-Addo et al., 2004). However, the underlying mechanisms by which deregulated FGF signaling may promote prostate tumorigenesis are poorly understood, and the functional consequences of pathway activation have not been investigated.

In this issue of *Cancer Cell*, two manuscripts provide new insights into the role of epithelial-stromal interactions in prostate tumorigenesis, through studies of the consequences of FGF10 overexpression in the prostate stroma (Memarzadeh et al., 2007), or of FGFR1 in the prostate epithelium (Acevedo et al., 2007). In the first paper, Witte and colleagues have adapted a tissue recombination approach to investigate the molecular factors involved in prostate formation and cancer (Memarzadeh et al., 2007). Using lentiviral delivery to manipulate gene expression in the stromal compartment, they have shown that stromal overexpression of FGF10 results in epithelial hyperproliferation that is correlated with upregulation of AR expression. Furthermore, recombination of stroma overexpressing FGF10 with epithelium expressing activated

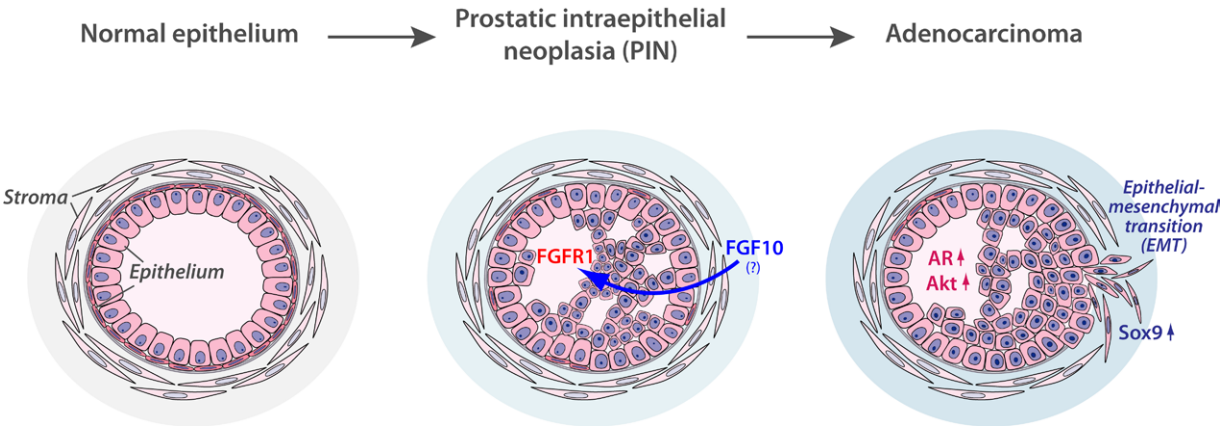

Figure 1. Model for FGF-Mediated Stromal-Epithelial Interactions during Prostate Carcinogenesis
Stromal expression of FGF10 (or perhaps another FGF) leads to activation of FGFR1 in the epithelium, resulting in hyperplasia and PIN. Further stimulation of the FGFR signaling pathway, together with additional transforming events, leads to increased expression of androgen receptor (AR) and activation of Akt, as well as upregulation of Sox9 and an epithelial-mesenchymal transition (EMT).

Akt (myristoylated AKT1) results in cooperative effects on tumorigenesis. These findings are consistent with the synergy between AR and Akt in the prostate epithelium (Xin et al., 2006), as well as the cooperativity of FGF8 overexpression and *Pten* inactivation in mouse prostate tumorigenesis (Zhong et al., 2006).

Taken at face value, these results support a model in which stromal FGF10 drives tumorigenesis by upregulating AR signaling in the epithelium, which in turn cooperates with Akt (Figure 1). Such a model fits with a growing body of evidence demonstrating the critical roles of AR and the PI3K-Akt pathway in human prostate carcinogenesis. One caveat is that FGF10 is not expressed in human prostate cancer samples (Ropiquet et al., 2000), so the significance of these mouse studies for human cancer is presently uncertain. Nonetheless, it is conceivable that another member of the FGF family may be relevant in vivo, such as FGF7 or FGF22, which have similar receptor-binding specificities to FGF10.

In a complementary study, Spencer and colleagues (Acevedo et al., 2007) describe a complex set of phenotypic consequences following FGF pathway activation in the prostate epithelium, although they do not address the potential role of AR signaling. These investigators have utilized a novel strategy for conditional and reversible activation of the FGFR1 cytoplasmic signaling domain mediated by a chemical inducer of receptor heterodimerization. Transgenic mice that conditionally activate FGFR1 in the prostate epithelium using this methodology develop hyperplasia and prostatic intraepithelial neoplasia (PIN), a prostate cancer precursor, by 12 weeks of age (Freeman et al., 2003).

In their new study, Spencer and colleagues report that FGFR1-activated mice up to 1 year of age can develop a spectrum of prostate malignancies, including adenocarcinoma as well as a low frequency of metastases to lymph nodes and liver (Acevedo et al., 2007). Interestingly, histological analyses showed that these mice developed a greater incidence of a transitional sarcomatoid carcinoma with increasing age, consistent with the appearance of an epithelial-mesenchymal transition (EMT). The occurrence of EMT is supported by expression profiling studies that demonstrate elevated expression of Sox9, a known downstream target of FGF signaling, in both prostate tumors and metastases. Since Sox9 is expressed in human prostate cancer, it will be important to determine whether the expression of this putative transcriptional regulator of EMT is correlated with elevated FGF signaling in human cancer, and whether expression of either Sox9 or FGFR1 is relevant for prostate cancer metastases. Taken together, these findings may be consistent with a direct causal role for FGF signaling in prostate cancer, as suggested by the authors. However, the long latency of tumorigenesis and the FGFR1 independence of the more advanced tumors imply the necessity of other cooperating events for prostate tumorigenesis, which will be important to identify in future studies.

Given the apparent complementarity of these two new papers, can we conclude that the effects of FGF10 are mediated by FGFR1 in vivo? Here, the data are less clear. Witte and colleagues show that the transforming effects of stromal FGF10 can be blocked by epithelial expression of a truncated FGFR1 receptor that acts as a dominant-negative, but only partially by a dominant-negative FGFR2. This result suggests that FGF10 signaling is indeed mediated by FGFR1, although the interpretation of such dominant-negative experiments can potentially be complicated by receptor heterodimerization. Moreover, FGFR2 is unlikely to be a candidate receptor for stromal FGF10, since inducible overexpression of FGFR2 in the prostate epithelium does not lead to a hyperplastic phenotype, indicating that FGFR1 and FGFR2 are not equivalent in their functional consequences (Freeman et al., 2003). In contrast, however, previous studies have indicated that FGF10 activity

is mediated by the FGFR2b receptor isoform in vivo and only signals weakly through the FGFR1b isoform (Ornitz and Itoh, 2001; Zhang et al., 2006). One possible explanation is that high levels of FGF10 may be sufficient to activate FGFR1 in vivo—further analyses of FGF10 signaling in the prostate will undoubtedly shed additional light on this issue.

In summary, the two new manuscripts in this issue of *Cancer Cell* indicate that paracrine actions of FGF signaling between stromal and epithelial compartments may be critical for prostate tumorigenesis, as has long been proposed in the literature. These provocative studies open new avenues for further research, particularly to determine how FGFR pathway activation can drive EMT and promote metastasis. Notably, the interactions between FGFR signaling and the AR and Akt pathways during prostate tumorigenesis suggest that potentially valuable therapeutic strategies may exist for targeting FGF receptors in conjunction with Akt or related pathway inhibitors.

REFERENCES

Acevedo, V.D., Gangula, R.D., Freeman, K.W., Li, R., Zhang, Y., Wang, F., Ayala, G.E., Peterson, L.E., Ittmann, M., and Spencer, D.M. (2007). Cancer Cell, this issue.

Cunha, G.R., Donjacour, A.A., Cooke, P.S., Mee, S., Bigsby, R.M., Higgins, S.J., and Sugimura, Y. (1987). Endocr. Rev. *8*, 338–362.

Freeman, K.W., Welm, B.E., Gangula, R.D., Rosen, J.M., Ittmann, M., Greenberg, N.M., and Spencer, D.M. (2003). Cancer Res. *63*, 8256–8263.

Hayward, S.W., Wang, Y., Cao, M., Hom, Y.K., Zhang, B., Grossfeld, G.D., Sudilovsky, D., and Cunha, G.R. (2001). Cancer Res. *61*, 8135–8142.

Kwabi-Addo, B., Ozen, M., and Ittmann, M. (2004). Endocr. Relat. Cancer *11*, 709–724.

Lin, Y., Liu, G., Zhang, Y., Hu, Y.P., Yu, K., Lin, C., McKeehan, K., Xuan, J.W., Ornitz, D.M., Shen, M.M., et al. (2007). Development *134*, 723–734.

Memarzadeh, S., Xin, L., Mulholland, D.J., Mansukhani, A., Wu, H., Teitell, M.A., and Witte, O.N. (2007). Cancer Cell, this issue.

Ornitz, D.M., and Itoh, N. (2001). Genome Biol. *2*, REVIEWS3005.

Ropiquet, F., Giri, D., Kwabi-Addo, B., Schmidt, K., and Ittmann, M. (2000). Prostate *44*, 334–338.

Thomson, A.A., and Cunha, G.R. (1999). Development *126*, 3693–3701.

Xin, L., Teitell, M.A., Lawson, D.A., Kwon, A., Mellinghoff, I.K., and Witte, O.N. (2006). Proc. Natl. Acad. Sci. USA *103*, 7789–7794.

Zhang, X., Ibrahimi, O.A., Olsen, S.K., Umemori, H., Mohammadi, M., and Ornitz, D.M. (2006). J. Biol. Chem. *281*, 15694–15700.

Zhong, C., Saribekyan, G., Liao, C.P., Cohen, M.B., and Roy-Burman, P. (2006). Cancer Res. *66*, 2188–2194.

New Breast Cancer Genes—Discovery at the Intersection of Complex Data Sets

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The identification of genes that contribute to the oncogenic process, including those that determine risk of cancer onset, holds the key not only in understanding mechanisms of oncogenesis but also in the identification of new targets for therapeutic development. Traditional methods of genetics and molecular biology have been successful but are slow and laborious. The advent of genome technologies, leading to the generation of large data sets describing various properties of genes and proteins relevant to cancer phenotypes, has afforded a new opportunity for discovery. M. Vidal and colleagues have made use of this data, and in particular the integration of various forms of genome-scale data, to identify new genes involved in breast cancer.

The development of technologies that facilitate genome-scale analyses of gene expression, DNA sequence variation, protein accumulation, protein interactions, DNA copy number, and more has had a transforming effect on biology and medicine. This is perhaps best seen in cancer, where complex data sets have been coupled with powerful analytical methods to extract a level of detail of the underlying biology not achievable with the once powerful methods of molecular biology. As an example, the use of large-scale gene expression data has dissected cancer into a variety of subtypes that begin to address the full complexity of the disease, recognizing that lymphoma, breast cancer, and others are not single diseases, or even two or three diseases, but rather a vast array of complex diseases defined by a variety of genetic alterations (Alizadeh et al., 2000; Golub et