Editorial

Fibroblast growth factor signaling as a bypass mechanism of the androgen receptor pathway: new perspectives for castration-resistant prostate cancer

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Till now, prostate cancer (PC) appears among the most critical public health concerns in men in developed as well as developing countries. Androgens operating through androgen receptor (AR) nourish the development and function of normal prostate and may pathologically contribute to PC in case of any deformation or deregulation (1). Based on this, inhibiting the production of androgens by castration or their effects by using anti-AR agents is employed as a treatment of advanced PC disease. However, in most instances, upon therapy, cancer will develop in a form called castrate-resistant prostate cancer (CRPC). Reactivation of AR expression and activity is often noticed in this disease stage (2,3). Treatment with more potent anti-AR agents can be useful in this setting but their efficacy can be limited in time, while high therapeutic pressure will select for aggressive and highly adaptable cancer variants leading to therapeutic impasse.

Emerging observations provide relevant clues to how PC cells adapt to their microenvironment including drug treatment. They also underline the importance of heterogeneity of the tumor hosting subclonal cancer cell populations that may take advantage of the treatment selection pressure to promote tumor evolution. In particular, the studies of Himisha Beltran and other investigators previously suggested that neuroendocrine CRPC aggressive variants (CRPC-NE) might arise from CRPC variants characterized as prostate adenocarcinomas (CRPC-Adeno), and that enables tumor adaptation in response to AR-directed therapy. Indeed, CRPC-NE tumors display neuroendocrine features and an "AR-indifferent" cell state, thus hijacking the AR pathway. *In vitro*, *in vivo*, and *in situ* data highlighted the cellular and molecular complexity of these events and proposed numerous ways through which a prostate carcinoma cell characterized by an epithelial phenotype, can lose its epithelial "AR-driven" state while acquiring a neuroendocrine "AR-indifferent" state in a transdifferentiation process called neuroendocrine transdifferentiation (4-6). The data also suggest a spectrum of differentiation states from AR-dependent to AR-indifferent states, which echoes other types of transdifferentiation programs including epithelial-mesenchymal transition (EMT) (7). Thus, there may be CRPC diseases on the way to AR independence with no or moderate neuroendocrine differentiation that have not fully transited towards a neuroendocrine phenotype (4,8,9). The relevance of such CRPC remains an enigma, as well as the mechanisms driving their progression in the context of therapy resistance.

In *Cancer Cell*, Bluemn *et al.* (10) present an advance in our understanding of molecular mechanisms underlying AR-independence.

In their work, the authors have investigated a small subset of CRPC characterized by AR-null/NE-null phenotype (at least null for a panel of advanced neuroendocrine markers).

Importantly, such phenotype seems to be enriched in the contemporary era in which PC patients are heavily treated with AR pathway antagonists such as Enzalutamide and Abiraterone in addition to more standard castration therapies.

Since the EMT pathway came out in this analysis as highly enriched in these tumors, the double negative (AR-null/NE-null) phenotype may also highlight changes in the EMT status of CRPC escaping the AR pathway dependence. Given the small number of patient samples classified in the double negative category, it will be important to analyze additional series to further study the potential contributions of other specific EMT-related mechanisms and to deliver novel therapeutic options for this patient group. It will also be critical to the efforts to develop better biomarkers of EMT and neuroendocrine states that enable to discriminate early states from late states of differentiation. It will also be important to enlarge the number of patient samples analyzed to definitely prove that potent AR–targeted agents such as Enzalutamide and Abiraterone, rather than other therapies, promote the emergence the double negative (AR-null/NE-null) phenotype. Interestingly, through the involvement of overlapping alterations, or the expression of common driver genes, there are evidence for intimate connections among NE phenotype, EMT, epithelial plasticity and stemness properties (4,8,11-13). As discussed by Bluemn *et al.*, it is tempting to speculate a continuum of progression from AR dependent epithelial to EMT/stemness to NE "AR independent" phenotypes, but such sequence of events is yet to be investigated. Here again, the development of more pertinent markers and tools could help statute on this aspect.

We should consider that some cancer cells are more prone than others to undergo EMT and this may favor intratumoral heterogeneity. In our previous published work, we investigated the role of CRIPTO in PC (14). CRIPTO is the founding member of the EGF-CFC (Cripto, FRL-1, Cryptic) protein superfamily. This gene is implicated in embryogenesis, oncogenesis, as well as in stemness maintenance and its expression is markedly increased in many cancer types. CRIPTO expression in these tumors was associated with poor outcomes and with EMT in *in vitro* models (14). In PC tumors, we demonstrated the existence of a population of CRIPTO expressing carcinoma cells exhibiting mesenchymal characteristics within the primary tumor, while other carcinoma cells expressing CRIPTO remained with more epithelial features (14). This highlights the pleiotropic nature of certain factors driving various effects in carcinoma clones and generating phenotypic diversity/intratumoral heterogeneity. The work of Bluemn and his colleagues supports the intratumoral heterogeneity notion in prostate tumors where different cellular clones with different cellular differentiation states may exist, cooperate, communicate and influence the progression of tumor. For instance, their cellular model (LNCaP double negative clones) was obtained after drastic selective pressure combining androgen deprivation and AR knock-out conditions.

Analysis of patient specimens and model systems developed by Bluemn *et al.* led to the identification of elevated fibroblast growth factor (FGF) and downstream mitogen-activated protein kinase (MAPK) pathway activity as the main mechanism driving the bypass of AR dependence in this setting. FGF signaling was enough to evade AR signaling pathway as they did indicate that absence or depletion of AR activity can be compensated by hyperactive FGF and MAPK pathways to maintain proliferation and survival. Meanwhile, when these two latter pathways are switched off, no growth of double negative PC cells *in vitro* and *in vivo* was observed. This finding may provide novel therapeutic opportunities. FGF/MAPK hyperactivity in certain CRPC tumors could be exploited therapeutically with fibroblast growth factor receptor (FGFR) inhibitors, and preclinical data presented by the authors are very promising in this regard.

Interestingly, FGFR1 signaling can also promote EMT program (15). Previous work also suggested the FGF/FGFR1 axis as an important element in PC initiation and progression in association with aggressiveness (15-17). In a recent study, we showed that CRIPTO overexpression mediates EMT in the CRPC model 22Rv1 cells, while this effect appeared to be promoted through parallel actions of FGFR1/MAPK and AKT signaling pathways (14). It is noteworthy that activation of FGFR1/MAPK signaling leading to EMT as a consequence of CRIPTO expression was accompanied by a marked reduction of the AR signaling (unpublished data). Interestingly, the mesenchymal-like PC cells derived in our study conserved their tumorigenic capacity in nude mice (unpublished data). These observations are in accordance with those of Bluemn *et al.* where elevated activity of FGF signaling is correlated with tumor progression in an AR-indifferent manner.

It is also important to consider the potential impact of interclonal cooperation and communications that might occur among the distinct clones driving intratumoral

heterogeneity. In line with this hypothesis, we recently assessed the effects of the extracellular vesicles (EVs) released by mesenchymal PC cells on recipient androgen-dependent epithelial PC cells. EVs occupied wide attention among scientific community during the last years as an extracellular component impacting the intratumoral heterogeneity and interclonal communication. We showed that mesenchymal like PC derived vesicles promoted mesenchymal features in the recipient epithelial-like PC cells (18). This transformation was accompanied by reduced AR signaling and activation of TGFβ signaling pathway. Moreover, recipient cells acquiring mesenchymal traits displayed enhanced migratory and invasive properties as well as increased resistance to the AR antagonist, enzalutamide (18). It will be interesting to see if the double negative model of PC developed in the study of Bluemn and colleagues may similarly influence the behavior and function of neighboring cells in the tumor microenvironment via secretion of vesicles or FGF species.

Overall, the study by Bluemn provides an innovative advancement of our understanding of the cellular and molecular determinants underlying escape of AR-directed therapy in CRPC. Additional studies are required to define the prevalence of these events, and their connections with cancer cell plasticity, EMT and NE phenotypes. Bluemn's study opens new perspectives towards finding a therapeutic approach that may target and treat CRPC patients that have gained resistance to AR-directed therapy with the emergence of cancer cell clones that are null for both AR/NE features.

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Footnote

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