IGF2 revs the steroidogenesis engine

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Abstract

Molecular understanding of how prostate cancers evade hormone therapy greatly increased over the last several years, and the realization that *de novo* steroidogenesis plays a significant role in tumor progression and therapeutic bypass has led to development of promising new therapeutics. In the April 2013 issue of *Endocrine-Related Cancer*, Lubik *et al.* revealed a new molecular pathway by which the IGF2 can ignite the *de novo* steroidogenesis engine and promote molecular events associated with tumor progression.

Key Words

- steroidogenesis
- IGF2

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To date, prostate cancer remains the most frequently diagnosed non-cutaneous malignancy and second leading cause of male cancer death in most Western countries. Organ-confined disease can be successfully managed through radiation and/or surgical methodologies; however, cures for patients with non-organ-confined disease remains elusive (Omlin & de Bono 2012). For reasons not yet fully understood, prostate cancers are largely resistant to most cytotoxic agents and standard chemotherapies. However, it is well accepted that the strong dependence of prostatic adenocarcinoma cells on androgen and androgen receptor (AR) signaling for survival and proliferation provides an important therapeutic opportunity (Knudsen & Penning 2010). Given the reliance of this tumor type on AR function, first-line therapeutic intervention for all patients with disseminated disease aims is geared toward suppressing AR activity, as achieved through pharmacological ligand (androgen) deprivation used frequently in combination with direct AR antagonists (such as bicalutamide or enzalutamide) (Mukherji *et al.* 2012). Such therapies are effective in the vast majority of patients, as observed through tumor reduction accompanied by suppression of detectable serum levels of prostate-specific antigen (PSA). Monitoring of PSA is an important metric for assessing the efficacy of

hormone therapy and the state of AR signaling, as PSA is encoded by *KLK3*, a gene under direct AR regulation (Chen *et al.* 2008). Consistent with the conclusion that tumor progression is largely driven by resurgent AR activity, hormone therapy ‘failure’ is typically first detected by a rise in PSA despite the maintenance of ligand depletion and AR-directed therapeutic regimens, indicating that AR has been reactivated. This stage of disease, quite appropriately referred to as ‘castration-resistant prostate cancer’ or CRPC, is thought to occur through multiple mechanisms that restore AR activity under conditions of sustained first-line hormone therapy.

A litany of molecular investigations and clinical analyses brought forth the understanding that a substantial fraction of CRPC tumors shows evidence of intracrine androgen restoration, wherein the tumors themselves harbor androgen levels sufficient to induce AR activity, even in a patient whose serum testosterone levels remain in the castrate range (Stanbrough *et al.* 2006, Locke *et al.* 2008, Montgomery *et al.* 2008, Green *et al.* 2012). Further investigation confirmed that a series of defined molecular switches induce intracrine androgen synthesis, including upregulation of enzymes that convert weak adrenal androgens to testosterone, such as CYP17A1. These remarkable discoveries provided the foundation for

utilization of CYP17A1 inhibitors for treatment of CRPC, and the CYP17A1 inhibitor abiraterone acetate was recently approved as second-line hormone therapy for patients with advanced disease (Omlin & de Bono 2012). Thus, a thorough understanding of the molecular basis for intracrine androgen synthesis is imperative for predicting the means by which tumor cells can restore AR activity and evade hormone therapy and for designing successful new therapeutics for advanced prostate cancer.

In the new study by Lubik *et al.* (2013), published in the April 2013 issue of *Endocrine-Related Cancer*, IGF2 was unexpectedly identified as a key factor able to induce *de novo* steroidogenesis in prostate cancer cells. Notably, high levels of IGF2 have been implicated with increased risk for development of a variety of solid malignancies, including cancers of the breast, lung, bladder, endometrium, and prostate (Bergman *et al.* 2012). Further, a strong relationship between IGF2 and unchecked growth is classically associated with Beckwith–Wiedemann syndrome, an overgrowth disorder that is associated with increased tumor development. Beckwith–Wiedemann syndrome patients can develop Wilms' tumors and may also exhibit rhabdomyosarcomas, adrenocortical carcinomas, and hepatoblastomas. While the underlying mechanisms by which IGF2 can regulate cell proliferation, growth, differentiation, and survival are varied and show cell type specificity, interaction with key receptors (including IGF type 2 and type 1 receptors) are important for IGF to function. In the new study, interest in IGF2 arose from the knowledge that increased expression of IGF2 as well as associated receptors has been observed in advanced prostate cancers. Moreover, it was recently reported that insulin, which can increase in response to hormone therapy, promotes expression of enzymes that increase intracellular androgens in human cancer cells (Lubik *et al.* 2011). Similarities in function of insulin and IGF2 led the investigators to more rigorously assess IGF2 activity in the context of prostate cancer.

The importance of IGF2 in human disease was validated through analysis of clinical samples from patients who underwent neoadjuvant hormone therapy prior to surgery, wherein it was observed that IGF2 expression was significantly elevated after 5–6 months of treatment; elevated IGF2 levels were sustained in tumors from patients that received treatment longer than 6 months, and in the transition to castration-resistant disease. Moreover, enhanced immunoreactivity of selected IGF2 receptors (IGFR1 and INSR) was also observed in tumors from patients receiving neoadjuvant hormone

therapy. These findings provided a logical basis for further modeling and molecular analysis. Subsequently, using models systems of AR-positive early-stage (hormone therapy responsive) or CRPCs, the investigators interrogated the role of IGF2 on the *de novo* steroidogenesis pathway and downstream AR signaling. In both tumor-type models, IGF2 enhanced expression of steroidogenesis enzymes. It was interesting to note that higher absolute levels of many steroidogenic enzymes were detected in tumor cells that along with full-length receptor also express 'short-form' variants of AR that are consecutively active and are thought to be major contributors to disease progression. The relative contribution of such enhanced steroidogenic enzyme expression and IGF2 for the castration-resistant phenotype in CRPC cells that express both full-length and short-form receptors would be important to explore. As would be expected based on the increased expression of these enzymes, IGF2 was observed to enhance both intracellular and secreted steroids in the model examined and to promote enhanced PSA expression. These findings are consistent with the concept that IGF2 promotes androgen levels sufficient to invoke molecular changes associated with the transition to castration resistance. Finally, experimental strategies to pinpoint which receptors are important for the IGF2 affect were performed using pharmacological inhibitors. Interestingly, these studies revealed that IGF2 and insulin can utilize multiple receptors to promote steroidogenesis.

On balance, these exciting findings reveal an unexpected link between IGF2 and steroid production in prostate cancer cells, and establish the growth factor as sufficient to enhance the levels of obligatory enzymes required for *de novo* steroid synthesis, and to increase the total level of steroids to a threshold sufficient for activation of AR. These findings add to previous studies demonstrating the multiple mechanisms by which intracrine androgen synthesis is achieved in response to hormone deprivation and highlight the importance of understanding the molecular underpinnings of these events. It will be of interest to determine whether these IGF2-mediated effects are sufficient to drive the transition to castration resistant both with regard to tumor cell growth and progression. These findings also raise interest in the possibility of combining IGF2 receptor inhibitors with CYP17A1 inhibitors (e.g. abiraterone acetate) to putatively achieve improved/enhanced suppression of intracrine androgen synthesis and AR activation. Taken together, the exciting findings reported in Lubik *et al.* (2013) have identified IGF2 as a potential therapeutic target for advanced prostate cancer.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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