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Review

The hunt for a selective 17,20 lyase inhibitor; learning lessons from nature

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ABSTRACT

Given prostate cancer is driven, in part, by its responsiveness to androgens, treatments historically employ methods for their removal from circulation. Approaches as crude as castration, and more recently blockade of androgen synthesis or receptor binding, are still of limited use long term, since other steroids of adrenal origin or tumor origin can supersede that role as the 'castration resistant' tumor re-emerges. Broader inhibition of steroidogenesis using relatively nonselective P450 inhibitors such as ketoconazole is not an alternative since a general disruption of steroid biosynthesis is neither safe nor effective. The recent emergence of drugs more selectively targeting CYP17 have been more effective, and yet extension of life has been on the scale of months rather than years. It is now becoming clear this shortcoming arises from the adaptive capabilities of many tumors to initiate local steroid synthesis and/or become responsive to novel early pathway adrenal steroids that are synthesized when lyase activity is not selectively blocked, and ACTH rises in the face of declining cortisol feedback. Abiraterone has been described as a lyase selective inhibitor, yet its use still requires co-administration of prednisone to suppress such a rise of ACTH and fall in cortisol. So is creation of a selective lyase inhibitor even possible? Can C19 steroid production be achieved without a prominent decline in cortisol and corresponding rise in ACTH? Decades of scientific study of CYP17 in humans and nonhuman primates, as well as nature's own experiments of gene mutations in humans, reveal 'true' or 'isolated' 17,20 lyase deficiency does quite selectively prevent C19 steroid biosynthesis whereas simple 17 hydroxylase deficiency also suppresses cortisol. We propose these known outcomes of natural mutations should be used to guide analysis of clinical trials and long term outcomes of CYP17 targeted drugs. In this review, we use that framework to re-evaluate the basic and clinical outcomes of many compounds being used or in development for treatment of castration resistant prostate cancer. Specifically, we include the nonselective drug ketoconazole, and then the CYP17 targeted drugs abiraterone, orteronel (TAK-700), galaterone (TOK-001), and seviteronel (VT-464). Using this framework, we can fully discriminate the clinical outcomes for ketoconazole, a drug with broad specificity, yet clinically ineffective, from that of abiraterone, the first CYP17 targeted therapy that is limited by its need for prednisone co-therapy. We also can identify potential next generation CYP17 targeted drugs now emerging that show signs of being far more 17,20 lyase selective. We conclude that a future for improved therapy without substantial cortisol decline, thus avoiding prednisone co-administration, seems possible at long last.

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1. The problem

One area of modern medicine that continues to evade us is the treatment of prostate cancer. Like breast cancer, prostate cancer is commonly referred to as an 'endocrine' cancer due to the fact initial growth is driven by naturally occurring C19 bioactive steroids, including testosterone and its respective metabolites [1]. Two recent approaches towards treatment of both of these steroid hormone-driven malignancies involve blockade of steroid binding to, or downregulation of androgen receptors (AR) [2] or estrogen receptors (ER) [3], respectively, or by inhibition of steroidogenic enzymes late in the steroidogenic pathway, particularly from the use of CYP19 (aromatase) inhibitors [4]. Steroid receptor blockade strategies, however, can fail due to treatment-induced removal of negative feedback regulation on hypothalamic gonadotropin releasing-hormone (GnRH) and pituitary gonadotropins, resulting in overdrive of endogenous steroid biosynthesis and so requiring accompanying GnRH analog therapy to ensure inhibition of pituitary gonadotropin release [5]. While steroid receptor antagonists may prove to be of future use, a more effective contemporary method is needed for controlling steroid biosynthesis in order to prevent induction of natural or drug-derived steroid ligands capable of driving tumor resurgence.

An alternative approach to this problem would be to inhibit the biosynthesis of dehydroepiandrostenedione (DHEA), which in humans and nonhuman primates is an obligatory intermediate in all C19 steroid biosynthesis from CYP17A1 [6]. There has indeed been a great deal of excitement in the oncology field over recent success in going beyond the initial use of general steroid biosynthesis inhibitors, such as ketoconazole [7], and testing of newer CYP17A1 inhibitors, such as abiraterone [8–10] to limit DHEA biosynthesis. Recent trials have suggested that the CYP17A1 inhibition strategy is indeed successful, with ~5 months of additional overall survival accruing to subjects receiving abiraterone who had already developed castration resistant prostate cancer [11–15]. There is, nevertheless, a major problem that remains to be overcome; while tumor cells develop steroid producing ability of their own, as in the case of prostate cancer [10,13–15], they are not the major biosynthetic source of steroid hormones in the body. That title is clearly claimed by the adrenal, which dwarfs steroidogenic output by testes, ovaries or other organs, including adipose and the brain. There is also the specific problem that the CYP17 enzyme which creates DHEA and all subsequent C19 steroid metabolites, is also the same enzyme necessary for cortisol biosynthesis. Complete and absolute inhibition of CYP17 in itself creates major problems that we will

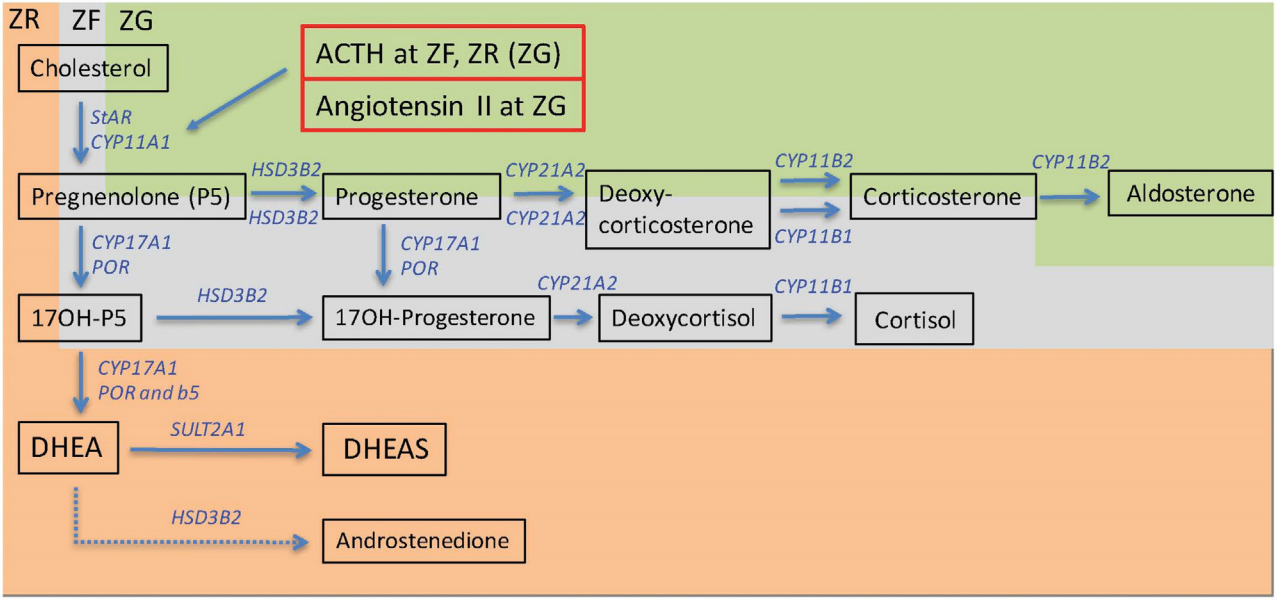

Fig. 1. ACTH-dependent, specialized steroidogenic pathways of the adrenal cortex. In the zona glomerulosa (ZR, green shading), an absence of CYP17A1 leads to aldosterone as the major hormone released, while in the zona fasciculata (ZF, grey shading), expression of CYP17A1 without CytB5 leads to predominant 17-hydroxylase activity and cortisol as the major hormone released. In the zona reticularis (ZR, orange-pink shading), expression of CYP17A1 together with CytB5 now enhances 17,20 lyase activity. Coexpression of sulfotransferase, but diminished expression of 3beta-hydroxysteroid dehydrogenase, within the ZR leads to DHEA and DHEAS as the major products released post adrenarche, and androstenedione as a minor product (dashed arrow). Under physiological conditions, ACTH stimulated ZF and ZR steroidogenic function is regulated by cortisol negative feedback alone, while angiotensin II (and circulating K+) predominantly regulate ZG steroidogenic function.

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