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European Association of Urology

Letter to the Editor

Re: Abraham Morgentaler, Abdulmaged M. Traish. Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth. Eur Urol 2009;55:310–21

The Saturation Model presented by Morgentaler and Traish [1] is a great improvement over the previous model of prostate cancer (PCa) growth being dependent on serum testosterone (T) levels. For any biological model, however, to be an accurate representation of reality, it must be consistent with all known experimental results.

Human PCa cell line LNCaP xenografts were transplanted into nude castrated mice to study the effects of T and finasteride (F) [2], a drug that prevents the conversion of T to dihydrotestosterone (DHT). Continuous androgen ablation (CAA) followed by the addition of F resulted in a 91% increase in tumor volume, CAA resulted in a 114% increase in tumor volume, and intermittent androgen ablation followed by continuous exposure to T resulted in a 128% increase in tumor volume. These findings are all consistent with the Saturation Model, with decreasing agonism of the intracellular androgen receptor (iAR) corresponding to decreased tumor volume. Intermittent androgen ablation followed by continuous exposure to T plus F, however, resulted in only a 23% increase in tumor volume. This finding is inconsistent with the Saturation Model, which would predict that T plus F should end up with a tumor volume somewhere between that of T alone and of F alone, since the agonism of iAR by T plus F is between what it is by T alone and by F alone.

There is a straightforward explanation for the above results that does not involve the Saturation Model. The membrane androgen receptor (mAR) and the iAR tend to act in opposition to each other, with mAR upregulating proapoptotic proteins such as Fas and iAR downregulating these proteins [3]. By creating an imbalance in which there is much more agonism of mAR than of iAR, therefore, it is possible to reach a threshold level of proapoptotic proteins that significantly increases the rate of apoptosis. Ordinarily, there is little or no upregulation of proapoptotic proteins by mAR when the agonism of mAR and iAR is roughly in balance. When both T and F are present, however, the agonism to iAR is reduced approximately 5-fold, since DHT binds to iAR five times more strongly than T does [4], while both T and DHT bind equally strongly to mAR [5].

If the above explanation is correct, then increasing the imbalance by using T bound to albumin (T-BSA) in LNCaP cells transplanted into nude mice should be even more effective than T plus F, since T-BSA only binds to mAR. In fact, when T-BSA serum levels of 10^{-7} M were obtained, there was a 60% reduction in tumor size after 1 mo [5]. Additionally, it would be expected that T alone should be able to kill PCa cells in the absence of iAR, and this ability was demonstrated in the iAR-negative DU145 PCa cell line [5].

To accurately model the effects of T on PCa, it is essential that the properties of iAR and mAR be taken into account with the effect of aromatase on converting T to estradiol.

Conflicts of interest: The author has nothing to disclose.

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March 24, 2009
Published online on 1 April 2009

DOI of original article: 10.1016/j.eururo.2008.09.024
 doi:10.1016/j.eururo.2009.03.068