Nature Reviews Endocrinology | Published online 09 Feb 2018; doi:10.1038/nrendo.2018.14

BONE

A novel androgen–vitamin D link

Androgen deficiency in men, which can result from normal ageing or prostate cancer therapy, is associated with reduced levels of vitamin D_3 and an increased risk of osteoporosis. Now, new research has uncovered a novel link between vitamin D_3 metabolism and sex hormone levels, a finding that could be exploited therapeutically to treat vitamin D deficiency.

Eui-Ju Hong and colleagues first assessed whether endogenous androgens altered androgen-responsive gene expression in the kidney, a known androgen target organ. Dihydrotestosterone (DHT) treatment markedly decreased renal *Esr1* (encoding oestrogen receptor α, ERα) and *Pgr* (encoding progesterone receptor, PR) expression in orchidectomized mice; these observations were corroborated in human cell lines.

Next, the effect of PR loss on vitamin D-related gene expression was investigated. In mouse proximal convoluted tubule (PCT) cells, *Pgr*-targeted small interfering RNA (siRNA) reduced levels of *Cyp24a1* (encoding 24-hydroxylase), a vitamin D_3-inactivating enzyme, whereas human PGR overexpression increased *Cyp24a1* expression. Subsequent ChIP-sequencing showed that progesterone treatment increased PR recruitment to the *Cyp24a1* promoter, inferring a transcriptional mechanism for DHT-dependent *Cyp24a1* suppression.

Consistently, DHT markedly reduced renal *Cyp24a1* mRNA and protein expression in orchidectomized mice, suggesting that androgen stimulation decreases 24-hydroxylase-dependent vitamin D_3 inactivation. Indeed, DHT increased serum levels of vitamin D_3 in these mice, confirming the link between androgens and vitamin D homeostasis.

"Using modulators of PR, we want to further investigate the role of PR in the metabolism of vitamin D," explains Hong. "We also wish to investigate the biosynthesis and metabolism of vitamin D in renal tissue during pregnancy, during which the expression of sex steroid hormones and their receptors is increased."

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ORIGINAL ARTICLE Lee, S. R. et al. 5α-dihydrotestosterone reduces renal *Cyp24a1* expression via suppression of progesterone receptor. *J. Mol. Endocrinol.* **60,** 159–170 (2018)