Androgen receptor signaling mechanisms in bone

Akademisk avhandling

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av Jianyao Wu

Fakultetsopponent:
Professor Ola Nilsson
Örebro universitet

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Androgen receptor signaling mechanisms in bone

Jianyao Wu

Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Osteoporosis is a common age-related disease that increases the risk of fractures. Androgens are crucial for bone health in males. Although a substantial part of the effects of androgens on the skeleton is mediated via conversion of testosterone to estradiol, direct effects of androgens on the androgen receptor (AR) also contribute to male bone homeostasis. The aim of this thesis is to increase the knowledge about the significance of the AR for bone metabolism to potentially identify bone-specific AR signaling pathways.

The thesis is based on studies using several different mouse models with altered AR signaling. In Paper I, we demonstrated that inactivation of the AR in immature osteoblast-lineage cells reduces trabecular but not cortical bone mass. Since antiandrogens are frequently used in the treatment of men with prostate cancer, we investigated the possible skeletal side effects of the recently approved antiandrogen drug enzalutamide (Paper II). Although this drug effectively reduced the weights of androgen-sensitive reproductive tissues, bone mass was reduced moderately and only in the axial skeleton. To determine the importance of the AR for pubertal and adult bone metabolism, avoiding confounding developmental effects, we inactivated the AR in pre-pubertal as well as in young adult male mice (Paper III). We demonstrated that adult AR expression is crucial for trabecular and cortical bone mass maintenance while pubertal AR expression is crucial for normal fat mass homeostasis in adult male mice. The AR activity is regulated by post-translational modifications, including AR SUMOylation. In Paper IV, we demonstrated that AR SUMOylation regulates bone mass but not the weights of androgen-responsive reproductive tissues, suggesting that therapies targeting AR SUMOylation might result in bone-specific anabolic effects with minimal adverse effects in other tissues.

The findings in this thesis contribute with important knowledge for the development of new treatment options for men with osteoporosis and safer endocrine treatments, with minimal skeletal side effects, for men with prostate cancer.

Keywords: Androgen receptor, bone, osteoporosis, mouse