Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Defining The Role Of Androgens In Hernia Associated Skeletal Muscle Fibrosis

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Introduction: Inguinal hernia is a highly prevalent condition occurring in 27% of adult men in their lifetime. The recurrence rate of hernia is 5-20%, resulting in a substantial cost burden in surgical repair procedures. Until recently, the mechanisms leading to the lower abdominal muscle (LAM) weakening characteristic of hernia were unknown. Our group developed the first mouse model of inguinal hernia through expression of the human aromatase enzyme in male mice (Arom<sup>Hum</sup>). Aromatase converts androgens to estrogens, and is expressed in the skeletal muscle in humans, but not mice. We found that locally formed estrogen from aromatase activity in LAM and decreased circulating testosterone levels are associated with muscle atrophy and fibrosis resulting in hernia. However, it is unclear how decreasing androgen levels might affect muscle fibrosis, and defining this potential mechanism could impact hernia treatment. We hypothesized that low androgen levels promote muscle fibroblast proliferation and fibrosis, and that androgen treatment would prevent hernia progression in Arom<sup>Hum</sup> mice.

Methods: Arom<sup>Hum</sup> mice (3 weeks old) were treated with high-dose dihydrotestosterone (DHT) via injection for 7.5 weeks with hernia volume continuously recorded (n=5/group). Primary fibroblasts were isolated from LAM from WT and Arom<sup>Hum</sup> mice (n=5/genotype). Cells were treated for 24 hours with increasing doses (0.001, 0.01, 0.1, 1, 5, 10 and 100 nM) of R1881, a synthetic androgen, and compared to untreated cells by western blot.

Results: Hernia volume was significantly decreased in Arom<sup>Hum</sup> mice treated with DHT compared to vehicle-treated mice, and volume remained consistently suppressed after DHT treatment (p < 0.005). In both primary fibroblast lines, R1881 treatment increased AR levels in a dose dependent manner, indicating that the treatment was effective. Preliminary data indicated that low doses of R1881 (0.001 and 0.01 nM) increased PCNA levels in LAM WT and LAM Arom<sup>Hum</sup> fibroblasts. Densitometry normalized to GAPDH showed 80% and 60% increases for 0.001 nM and 0.01 nM respectively in LAM WT fibroblasts, and 20% and 30% increases at these doses in LAM Arom<sup>Hum</sup> fibroblasts. Higher doses of R1881 decreased PCNA levels in LAM Arom<sup>Hum</sup> fibroblasts by 40% (10 nM) and 30% (100 nM), whereas a 25% decrease was detected in LAM WT fibroblasts at 100 nM.

Conclusion: These data suggest that low androgen doses increase LAM fibroblast proliferation, which possibly contributes to hernia formation. Androgen treatment at higher doses can partially block the progression of hernia in vivo. However, it is unclear whether and how androgen deficiency in combination with excess estrogen affects fibroblast proliferation and hernia formation. Additional research is required to determine if androgen supplementation in sufficient doses is a potential therapeutic for inguinal hernia and other muscle weakness diseases.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Phenotype of Patients Carrying the c.709(-7-2)del PRKAR1A Mutation in a Large Cohort of 41 Patients

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Objective: The Carney Complex (CNC) is a multiple endocrine and non endocrine neoplasia, mostly due to PRKAR1A mutations. The PRKAR1A mutation c.709(-7-2)del located in the intron 7 is one of the three known hot spot. The objective of this study is to described the CNC manifestations presented by patients harboring the c.709(-7-2)del. Methods: This study is a multicenter retrospective longitudinal study. Patients data have been collected from medical files. Multicenter retrospective study. Age at the diagnosis or at the screening of the different CNC manifestations is described by mean +/- standard deviation or median (interquartile) according to the distribution. Results: 41 patients [14 index cases and 37 relatives, 29 females, 43.6 ±14.3 years old (yo)] from 15 families have been included. 58% of the cohort including the 14 index cases presented with a primary pigmented adrenal disease (PPNAD) at 24-yo (18-40). For the remaining 17 patients, only 3 patients had normal glucocorticoid biological evaluation while others presented with subclinical hypercortisolism diagnosed at 35-yo (22-50). 7% of the cohort had an abnormal IGF1 and/or GH after oral glucose tolerance test while other patients had normal evaluation with a last test performed at 41 ±15yo. 22% of patients presented with lentigines diagnosed at 43yo (24-51) while others had no dermatological lesions at the last examination performed at 37 ±14yo. 13% of patients had thyroid nodules or papillary carcinoma diagnosed at 46 ±15yo (normal ultrasound for others at 37 ±15yo). At the last cardiac ultrasound, pituitary magnetic resonance imaging (MRI), spine MRI, testicular ultrasound, mammography performed at 40±15yo, 37.9±14.3yo, 46±12yo, 35±13yo and 48±12yo, no patient had cardiac myxoma, pituitary adenoma, schwannoma, testicular calcifying tumor or breast myxoma. Overall, 52% of the relatives did not have any manifestations of the disease. Penetration of the disease is 65%. Conclusion: The phenotype of patients carrying the c.709(-7-2)del PRKAR1A mutation is restricted to PPNAD, lentigines, fluctuating somatotroph anomalies and thyroid tumors. Follow-up of these patients should also be individualized from other CNC patients. Imaging, especially repeated cardiac ultrasound may not be needed to follow these patients The results of this real life study will be useful to elaborate further recommendation for follow-up of CNC patients.