学 位 論 文 の 要 約

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主論文の題名

Castration-induced stromal remodeling disrupts the reconstituted prostate epithelial structure

（去勢誘導性間質リモデリングは再構築前立腺上皮構造を崩壊させる）

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主論文の要約

Introduction

The stroma of the normal adult prostate is composed of abundant smooth muscle cells. Androgen acts on smooth muscle cells to maintain a fully differentiated prostate epithelial structure, which is composed of an outer layer of basal cells with basement membrane (BM) and an inner layer of luminal cells. The BM regulates the organization of epithelial cells such as growth/quiescence, functional differentiation, and polarity of epithelial cells. Thus, prostatic smooth muscle cells play an important role in maintaining the normal adult prostate epithelial structure.

Background

The histopathological features of benign prostatic hyperplasia (BPH) are nodular hyperplasia and/or chronic inflammation, whereas those of prostate cancer (PCa) are atypical glands called Gleason patterns. There are structural differences in the epithelium between BPH and PCa; however, the stromal structures of BPH and PCa are quite similar. Structural alterations of the stroma in both BPH and PCa are referred to as stromal remodeling (i.e., replacement of smooth muscle cells with fibroblasts or myofibroblasts). Fibroblasts and myofibroblasts secrete cytokines and extracellular matrix proteins. Thus, active stimuli from fibroblasts and

myofibroblasts can be associated with the abnormalities in prostate epithelial structure.

Objectives

We elucidated the role of stromal remodeling in prostate epithelial structure, which might provide us critical insights into the role of prostate stromal structure in prostate proliferative diseases such as BPH and PCa.

Methods

We performed *in vivo* experiments using the human prostate epithelial cell line BPH-1 and fetal rat urogenital sinus mesenchyme to generate heterotypic tissue recombinants that form human prostate-like epithelial structure. Host mice were castrated at 12 weeks post-transplantation (castration) and implanted with a dihydrotestosterone pellet at 14 days post-castration (androgen replacement treatment; ART). Co-culture experiments of BPH-1 cells with fibroblasts were performed using cell culture inserts *in vitro*.

Results

In the castration group *in vivo*, the percentages of fibrotic area and disrupted prostate epithelial structure without the BM increased proportionally in a time-dependent manner, but were suppressed by ART. In the castration group, tenascin-C (TNC)-positive fibroblasts were abundant in the stroma surrounding disrupted prostate epithelial structure without the BM. TGF-ß1 secretion from BPH-1 cells was increased by co-culturing with fibroblasts *in vitro*. Additionally, TNC mRNA expression was increased in fibroblasts co-culturing with BPH-1 cells and was suppressed by treatment with a TGF-ß RI kinase inhibitor. Finally, in the castration group, the percentage of p-Smad2-positive cells was significantly higher in the stroma surrounding disrupted prostate epithelial structure without the BM.

Conclusions

We demonstrated that castration-induced stromal remodeling disrupted the reconstituted human prostate-like epithelial structure and induced the appearance of TNC-positive fibroblasts accompanied by activation of TGF-ß signaling. The alteration of prostate stromal structure may be responsible for loss of the BM and epithelial cell polarity.