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2

Expression of steroidogenic enzymes and sex-steroid receptors in human prostate

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Identification of the cell types expressing the steroidogenic enzymes and sex steroid receptors in the human prostate has recently been performed using immunocytochemistry and in-situ hybridization. The enzymes 3β-hydroxysteroid dehydrogenase (3β-HSD), which converts dehydroepiandrosterone (DHEA) into androstenedione, and type 5 17β-HSD, which catalyzes the reduction of androstenedione to testosterone, have been localized in basal cells of alveoli as well as in stromal cells and endothelial cells of blood vessels. On the other hand, type-2 5α-reductase, which converts testosterone into the most potent androgen dihydrotestosterone (DHT), has been mostly observed in the luminal cells in alveoli. Aromatase, which converts testosterone into estradiol, has also been found to be expressed in the luminal cells of the alveoli as well as in stromal cells. Androgen receptor (AR) has been localized in luminal cell nuclei of alveoli and a large number of stromal cells, while estrogen receptor β has been detected in both basal and luminal cells in alveoli and also in stromal cells.

Key words: steroidogenic enzymes; sex steroid receptors; prostate; androgens; estrogens; immunocytochemistry, in-situ hybridization.

LOCALIZATION OF ENZYMES INVOLVED IN THE BIOSYNTHESIS AND METABOLISM OF SEX STEROIDS IN THE HUMAN PROSTATE

The human prostate is composed mainly of alveoli and stroma. The stratified epithelium lining the alveoli is divided into two layers: the basal layer, made of low cuboidal cells which are separated from the stroma by a basement membrane, and the layer of columnar secretory cells (luminal cells). The secretory cells possess luminal microvilli, well-developed rough endoplasmic reticulum and numerous large secretory granules. The basal cells are devoid of any secretory granules.

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The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD), which converts dehydroepiandrosterone (DHEA) into androstenedione, has been observed almost exclusively in the basal cells of alveoli (Figure 1A).[1–3] Immunolabelling of the two enzymes was also detected in the fibroblasts of stroma as well as in the endothelial cells and fibroblasts of blood vessels. We also performed ultrastructural studies using immunogold labelling. In all the positive cell types, the intracellular distribution of gold particles was rather diffuse throughout the cytoplasm.[3] No obvious association with organelles was detected, except bundles of microfilaments which occasionally appeared to be more labelled than the other intracellular components.

The localization of 17β-HSD type 5, which catalyzes the reduction of androstenedione to testosterone, has been studied by both in-situ hybridization and immunocytochemistry.[1–3] The results were very similar to those obtained for 3β-HSD. In the glandular epithelium, basal cells highly expressed the mRNA and the protein (Figure 1B). Type-5 17β-HSD was also shown to be expressed in the fibroblasts (stroma and blood vessels) and the endothelial cells lining the blood vessels. At the electron microscopic, 17β-HSD type 5 immunoreactivity was diffusely distributed throughout the cytoplasm in the reactive cell types.[3]

Testosterone can be converted into the most potent natural androgen, namely dihydrotestosterone (DHT), by the steroidogenic enzyme steroid 5α-reductase. Type-2 5α-reductase, which has been shown to be highly expressed in human prostate, has been detected by in-situ hybridization mostly in the luminal cells of the alveoli (Figure 2)[4] as well as in stroma cells. Similar results have been obtained in the mouse prostate, [5]where the basal cells are much less numerous than in the human.[6]

The histological data thus strongly suggest that DHEA originating from the general circulation is transformed in the basal cells of the glandular epithelium into androstenedione by 3β-HSD and then into testosterone by type 5 17β-HSD, whereas DHT is synthesized in the luminal cells by 5α-reductase type 2. DHT could then activate AR, which is highly expressed in the luminal cells (see below) (Figure 3).

The enzymes involved in estrogen biosynthesis and metabolism are also expressed in the human prostate.[7,8] Aromatase, which converts testosterone into estradiol (E_2) and androstenedione into the weak estrogen estrone (E_1), has been detected by both in-situ hybridization and immunocytochemistry in the cytoplasm of luminal cells of the alveoli as well as in stromal cells (Figure 4).

Two enzymes involved in the glucuronidation of androgens, namely uridine diphosphate-glucuronosyltransferases (UGTs) 2B15 and 2B17, have been localized in the

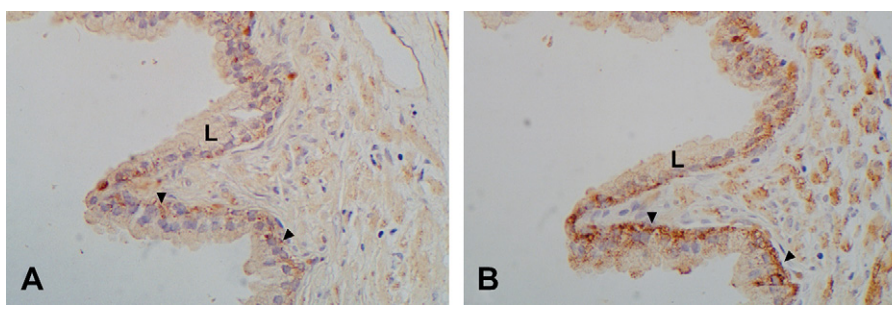

Figure 1. Immunocytochemical localization of 3β-HSD (A) and type-5 17β-HSD (B) in consecutive sections of human prostate. The two enzymes are mainly detected in basal cells (arrowheads). L: luminal cells. X 675.