ABSTRACTS
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Molecular genetics and biology of progesterone signaling in mammary neoplasia

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As in other species progesterone plays an important role in reproductive processes in dogs and cats. The signal transduction cascades involved in progesterone signaling start with binding of progesterone to specific receptors. The two well-known nuclear progesterone receptors (PR) are transcribed from a single gene but - through use of different promoters - two different PR isoforms are synthesized. The shorter form, PRA, contains the hormone binding domain, a hinge region and a DNA binding domain but lacks an amino-terminal sequence which is unique for the longer PRB receptor. This B-upstream segment (BUS) contains an activation domain, AF3, which results overall in a much higher transactivation potential of the PRB in relation to PRA (1). PRA is mainly found in nuclei whereas PRB has both nuclear and cytoplasmic localizations. Progesterone plays a central role in the regulation of stem and progenitor cells within the mammary gland (2). Cells expressing the PR act as sensors and upon progesterone binding they stimulate the stem cell compartment to proliferate and differentiate (3).

In the cat, endogenous progesterone and synthetic progestins may induce fibroadenomatous hyperplasia (FAH) of the mammary gland. In such FAH tissues we demonstrated both PR isoforms PRA (80-86 kDa) and PRB (116-120 kDa) using Western blots. In FAH examined by immunohistochemistry we found predominant staining for PR in ductal epithelium with both nuclear and cytoplasmic localization. In stromal cells also cytoplasmic staining was observed. Compared to feline mammary carcinoma PR expression as measured by Q-PCR was greatly elevated in FAH with a concomitant increased expression of growth hormone (GH), GHR and IGF-I mRNA. Cats with FAH can be treated successfully with the PR antagonist Aglepristone (4).

In the dog exposure to endogenous progesterone or to synthetic medroxyprogesterone acetate (MPA) may result in acromegalic changes and mammary hyperplasia (5). Expression analysis revealed induction by MPA of the expression of GH and IGF-I mRNA in the mammary gland (6), whereas GHR and PR expression were down-regulated (7). Gene-profiling studies showed induction of the Wnt-pathway with remarkable increased expression of Wnt4, but also of genes involved in cell proliferation such as PCNA, NPY, RAN and alterations in expression of transcription factors and cell adhesion molecules (8).

We have cloned and sequenced the canine PR. Immunohistochemical analysis revealed definite nuclear staining in canine uterus and mammary epithelium. Staining for PR was positive in epithelial cells in proliferative zones of the mammary gland whereas in differentiated mammary tissue PR-positive cells were low. No staining was found in stromal or myoepithelial cells. In mammary tumors marked heterogeneous staining was found including perinuclear staining of tumorous cells and cytoplasmic staining in spindle cells. In addition, all GH-producing cells were positive for PR emphasizing the relation between progesterone exposure and local mammary GH expression (9). Nevertheless, using GH-promoter luciferase constructs transfected to canine mammary cells, no direct effect of progesterone on GH gene activation could be shown (10).

Finally we measured the transactivation potential of the canine PRA and PRB isoforms. Human and canine PRA had a comparable transactivation potential, but in vitro studies revealed a lower and limited transactivation potential of canine PRB in comparison to human PRB (unpublished). These differences may underlie the relative high risk of dogs to develop mammary hyperplasia and carcinomas and shed new light on the role of PRB in reproduction of the dog.