ABSTRACTS

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INVESTIGATION OF THE LOCAL EXPRESSION OF THE RELAXIN-SYSTEM IN CANINE MAMMARY TUMORS

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Introduction - New functions for the peptide hormone relaxin-2 (RLX-2) have been described in terms of remodeling the connective tissue, suggesting RLX-2 as an important factor for tumor cell invasion, while there is a local increase of RLX-2 expression in human neoplastic breast tissue (3). RLX-2 can enhance the in-vitro invasiveness of human breast cancer cell lines and higher RLX-2 levels in plasma are associated with metastatic disease as well as shorter overall survival in women (1). Furthermore, RLX-2 induces matrix metalloproteinases (MMPs) as potent modulators of the intercellular matrix, which also seem to play a role in canine mammary tumors (2).

Objectives - Therefore, the aim of the present study was to investigate the expression of the RLX-2-system (RLX-2 and RLX-2 receptor (RXFP-1)) in tumors of the mammary gland of bitches with extreme plasma RLX-2-levels related to clinical parameters and local expression of three MMPs.

Materials and methods - Bitches with mammary tumors were selected due to their extremely high (group 1) or low (group 2) levels of plasma RLX-2 at their first surgical therapy. Collected tumor tissue was divided and stored in paraformaldehyde for histology as well as liquid nitrogen for molecular biology. 15 tissue samples within group 1 (RLX-2 levels ranging from 2.703 to 38.054 ng/ml plasma) were analyzed while group 2 (RLX-2 levels ranging from 0.000 to 0.190 ng/ml plasma) contributed 16 tissue samples. Specimens for molecular biology examination were analyzed for local expression of RLX-2, RXFP-1 and MMP2, 9 and 13 by Real-time-PCR. First strand cDNA synthesis was performed under identical conditions for all samples. Acquired values from Real-time-PCR were normalized for the 18S content of every specimen before statistical revision.

Results - Expression analysis demonstrated strong expression of RLX-2, RXFP-1 and MMP2, 9 and 13 in all samples in both groups. Statistical investigation of each parameter revealed no difference between the two groups. The comparative investigation of both groups according to one-year-survival, recidivation (6 months after first surgical treatment), radiologically detectable lung metastases (6 months after first surgical treatment) or histologically assessed dignity did show one significant difference among the investigated parameters RLX-2, RXFP-1 and MMP2, 9 and 13: In group 1 bitches with lung metastases (n=5) had a higher expression of MMP9 than bitches without (n=8) (p=0.045). Within group 2 there were significant positive correlations between the local expression of RLX-2 and RXFP-1 (p=0.001), between RLX-2 and MMP2 (p=0.041) as well as between RXFP-1 and MMP2 (p=0.006) in the tumor tissue. There was also a significant positive correlation between plasma RLX-2 and RXFP-1 (p=0.028). Whereas in group 1 there was only one significant correlation between MMP9 and MMP13 expression (p=0.038).

In summary, the genes of the analyzed factors, which are supposed to be involved in tissue remodulation, are expressed in canine mammary tumors. So far the plasma RLX-2 has no direct influence on the absolute level of expression among the observed parameters. However,
the correlation between MMP 9 and 13 expression under the influence of high plasma RLX-2 versus the correlation between MMP2 expression and the RLX-2-system in the low plasma RLX-2 group suggests different stages of tumor development (e.g. early stage of cancer development, tumor differentiation), which needs to be clarified by further histological analysis of tumor differentiation and invasion.

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