The expression of tumor endothelial marker 8 in mammary gland tumor, and the effects of endotrophin on neoplastic cells

Abstract of Doctoral Thesis

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Tumor endothelial marker 8 (TEM8) is highly expressed in vascular endothelial cells within tumors and involved in tumor angiogenesis. In this study, to clarify the expression and biological significance of TEM8 in canine mammary gland tumors (MGTs), we investigated the histological localization of TEM8 and expression of TEM8-isoforms in canine normal tissues, developmental alterations of TEM8 expression in normal mammary gland (MG) epithelium, and the phenotypical characteristics of TEM8 expressing MGT cells in canine MGT cases and canine MGT cell lines. Furthermore, we also examined the effects of endotrophin (ETP) on the MGT cells. In the mammogenesis, TEM8 expression in MG epithelial cells was increased along with the development of luminal structures and related to the expressions of Notch-1 and c-MET. Previous studies demonstrated that Notch-1 induced the differentiation of luminal cells, and c-MET promoted the luminal structure formation during development of MG epithelial cells, indicating that TEM8 contributes to regulation of the luminal cell differentiation and maturation. In canine MGTs, TEM8 expression was detected in luminal-like (CK19/p63/αSMA; +/-/-) but not in basal-like neoplastic cells (CK19/p63/αSMA; -/+/-). Almost TEM8 (+) MGT cells showed the luminal formation and expressed Notch-1 and c-MET as in the normal MG. In addition, TEM8 (+) MTG cells also showed expression of collagen Ⅵ α3 C5-domain, a source of ETP. Furthermore, ETP-stimulation significantly increased proliferation, cell migration and expressions of *CD44* and *CD49b* mRNA, and significantly decreased expressions of *EpCAM* and *CD133* mRNA in MGT cells. These results indicated that ETP/ TEM8 autocrine signaling might maintain the MGT cells at luminal progenitor stages with high proliferation ability by induction of differentiation from MGT stem cells to the

luminal progenitor and suppression of maturation to luminal cells. This study indicated that TEM8 had involved in the expression of the pathological characteristics related to the kinetic of MGT neoplastic cells, and might be an important indicator for estimating the clinical and biological behaviors in canine MGT cases.