Study on the expression and function of MMP-3 in bovine endometrium

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(ウシ子宮内膜における MMP3 の発現および機能に関する研究)

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Thesis Summary

Tissue remodeling in the uterus is considered important from fertilization through placentation, and the ECM-degrading enzyme MMP plays significant roles in the process. Although there are many reports on gelatinases, MMP2 and 9, the expression and functions of stromelysin MMP3 have not been clarified in bovine endometrium. The aim of the present study is to analyze the expressional regulation of MMP3 as well as its possible functions in bovine endometrium.

Expression of *MMP3* in bovine endometrial tissue at follicular, luteal and implantation stage was analyzed by qPCR. Bovine endometrial stroma (BES) and epithelial (BEE) cells were cultured in DMEM/F12 containing 10%FBS. E2 (100nM), P4 (1μM) and IFNα (50IU) were applied to observe the gene and protein expression of MMP3 by qPCR and casein zymography, respectively. Inhibitors for MMP3 and EGFR (AG1478) were used to clarify the involvement of the factors. Cell proliferation was measured by automated cell counting machine after 6 days in culture. To detect the release of HB-EGF in BES, supernatant and cell lysate were analyzed by western blotting.

The expression of *MMP3* in bovine endometrial tissue was significantly high at follicle stage compared to luteal and implantation stage. E2 increased the gene expression and clearance of MMP3 in BES in vitro, but P4 and IFNα decreased the expression. E2 also increased the

cell proliferation of BES, but MMP3 inhibitor and AG1478 significantly suppressed the proliferation induced by E2. Furthermore, E2 significantly increase the release of HB-EGF in BES but MMP3 inhibitor suppressed this release. There was no direct effect of E2 on MMP3 expression and cell proliferation of BEE. However, the condition medium (CM) of BES treated with E2 significantly increased the BEE proliferation but was inhibited by AG1478.

The present study demonstrated high expression of *MMP3* at follicular stage and E2 increased MMP3 expression in BES. These results indicated the physiological roll of MMP3 at follicular stage. Since it was reported the proliferation activity of endometrial cells increase at follicular stage, the present study was conducted assuming that MMP3 is involved in the proliferation of endometrial cells. The results of analysis using specific inhibitors indicated the involvement of MMP3 and EGF family members in cellular proliferation. Several studies suggested that HB-EGF is processed by the MMP3. The present study also supported the reports and demonstrated that MMP3 induce the release of HB-EGF in BES. It was suggested that MMP3 involved in the regulation of the endometrial cell proliferation. The CM increased the cell proliferation of BEE suggested that rather than E2, BES released HB-EGF affects BEE cell proliferation in paracrine manner.

In summary, E2 increase the expression of *MMP3* in BES. Since MMP3 induced the release of HB-EGF from BES, it was suggested that function of MMP3 involved in the proliferation mechanism of endometrial cells during follicular stage.