Abstract

Endometriosis is a gynecological disease, where endometrium-like lesions develop outside uterus. This inflammatory disease affects ~10% of reproductive women worldwide, resulting in severe pelvic pain and infertility. The etiology of endometriosis remains unknown. In the present study, we looked into the involvement of a group of zinc-dependent endopeptidases, known as matrix metalloproteinase (MMP) in the pathogenesis of endometriosis. In one chapter, the role of MMP-2 on endometriosis was studied. We report that ovarian endometriosis progression is associated with angiogenesis, alongwith elevated MMP-2 activity and reduced tissue inhibitor of metalloproteinses (TIMP)-2 expressions. When investigated in human endothelial cells, we found the upregulated MMP-2 activities and increased endothelial tube formation were regulated by prostaglandinE2 (PGE2) through COX-2/PGE2/pAKT axis. Inhibition of specific MMP-2 activity attenuated tube formation in endothelial cells and angiogenesis in chick chorioallantoic membrane assay. In another chapter, involvement MMP-1 was studied in ovarian endometriosis and found to be elevated with disease progression, while expressions for TIMP-3 downregulated. Treatments with interleukin-1β or PGE2 elevated MMP-1 expressions in endometriotic cell line (HS-832). Moreover, PGE2 and IL1β together elevated MMP-1 expressions as well as cellular invasiveness in a synergistic manner. Studies with inhibitors for specific mitogen activated protein kinase (MAPK) pathways proved that MMP-1 expression is regulated by cJUN N-terminal kinase (JNK)-activator protein (AP)-1 pathway. Furthermore, SiRNA-mediated silencing of cJUN confirmed JNK-pcJUN mediated regulation for MMP-1 expressions, as well as cellular invasiveness. In the next chapter, we utilized mouse model of endometriosis to look into disease pathogenesis and therapeutic efficacy of curcumin. Day dependent study of endometriosis showed functional endometriosis-like gland development within mouse peritoneum, with elevated MMP-1,-2,-9,-3 and -14 responses. Treatment with curcumin significantly downregulated the reported MMP expressions, except MMP-1. Curcumin regressed *in vivo* endometriotic lesions and glands by inducing severe mitochondria-mediated apoptosis, alongwith elevated caspases, p21, p53 and p38 responses. In summary, the present thesis explored the involvement of MMP-1 and MMP-2 in pathogenesis of ovarian endometriosis in clinical and *in vitro* studies, and efficacy of curcumin as an anti-endometriotic agent for *in vivo* model of endometriosis.

Aberrant regulation of matrix metalloproteinases (MMPs) may be the primary cause of endometrial lesion formation in a group of predisposed women. Prospect for the genuine origin of endometriosis is ongoing, since retrograde menstruation leads to presence of endometrial debris in peritoneal cavity of many women, which do not experience endometriosis. Tissue remodeling is regulated precisely by a balance of MMPs and their inhibitors.Â Moreover, endometriosisâ€‘induced changes in the matrix balance leads to adhesion formation, ovulatory dysfunction and fertility impairment. Endometriosis, a benign gynecologic disorder, occurs in about 10% of women in reproductive age and in up to 50% of women with infertility. The basic etiologic factors causing this disease are unknown as yet. Matrix metalloproteinases (MMP) are involv.Â Matrix metalloproteinases (MMP) are involved in degradation of the extracellular matrix (ECM). Their proteolytic activity is regulated by tissue inhibitors of metalloproteinases (TIMPs). Tumor necrosis factor-alpha converting enzyme (TACE) is a membrane-bound disintegrin metalloproteinase that processes the membrane-associated cytokine proTNF-alpha to its mature soluble form. TNF-alpha induces the secretion of several MMPs. Matrix metalloproteinases (MMPs) activity is thought to be particularly essential in the early phases of endometriosis development. Any changes in the equilibrium between MMPs activity and their tissue inhibitors (TIMPs) could be potentially harmful, promoting endometriosis development. The aim of this study was to investigate whether the MMP-2, MMP-9, TIMP-1 or TGF-B2 expression in eutopic endometrium from women with early endometriosis differ when compared with healthy subjects. The results were referred to the serum progesterone levels. [b]Materials and method.[/b] Endometrial biopsy was ta