STUDIES ON THE ROLE OF MATRIX METALLOPROTEINASES AND THEIR INHIBITORS IN THE PATHOGENESIS OF ENDOMETRIOSIS

Submitted by: Sayantan Jana

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. Herein, we looked into the involvement of a group of zinc-dependent endopeptidases, known as matrix metalloproteinase (MMP) in the pathogenesis of endometriosis. The role of MMP-2 on endometriosis was studied in the 2nd chapter of the thesis. We report that ovarian endometriosis progression is associated with angiogenesis, along with elevated MMP-2 activity and reduced tissue inhibitor of metalloproteinases (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 used 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 MMP expressions, except MMP-1. Curcumin regressed in vivo endometriotic lesions and glands by inducing severe mitochondria-mediated apoptosis, along with 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 inhibitory actions of curcumin against endometriosis in in vivo model.

Sayantan Jana
14th June 2016