MATRIX METALLOPROTEINASES IN THE MOUSE MODEL OF MENSTRUATION: EFFECT OF DOXYCYCLINE INHIBITION

J. Shen[2], J. Zhang[2], T. J. Kaitu'u[1,2], M. Brasted[2], L. A. Salamonsen[2]

[1]Obstetrics and Gynecology, Monash University, Clayton, VIC, Australia; [2]Prince Henry's Institute of Medical Research, Clayton, VIC, Australia

Strong correlative evidence supports a role for matrix metalloproteinases (MMP) in the tissue breakdown at menstruation. Because menstruation occurs only in women and a few old-world primates, it has not been possible to examine the functional significance of potentially key mediators of this process. To this end, we developed a mouse model for menstruation (1), in which ovariectomised mice are subjected to a decidualising stimulus: injection of oil into the uterine lumen following appropriate hormone-priming. During the 24 h following withdrawal of progesterone (P), the decidualised tissue progressively breaks down, in a manner that morphologically resembles that of human endometrium at menstruation. The aims of the present study were to examine the pattern of MMP expression during the time from progesterone withdrawal until complete tissue breakdown, and to determine whether administration of doxycycline, (a known MMP modulator), 3 h prior to P withdrawal, affected the expression or activity of the MMPs or restrained the tissue destruction. MMP-3 was present at foci in the decidual zone: these were initially associated with the restructuring at decidualisation and subsequently with the tissue destruction. MMP-7 was detected both in epithelium and in leukocytes, predominantly neutrophils. These were first apparent in the basal zone during the earliest stages of tissue instability, and dramatically increased in numbers as breakdown progressed. MMP-9 was found only in leukocytes, predominantly neutrophils and some macrophages, with greatly increased numbers with time. Zymography revealed a dramatic increase in both latent and active MMP-9 as tissue breakdown proceeded. Doxycycline reduced immunoreactive MMP-3 but not MMP-7 or MMP-9 in the tissue, and also decreased gelatinase activity. However, no apparent effect on tissue breakdown was observed. Further studies with a more potent MMP inhibitor are required to fully establish the importance of MMPs in these processes.

(1) Brasted *et al*. (2003) *Biol. Reprod*. **69**, 1273.

10.1071/SRB04Ab265