

LEUKOCYTE MATRIX METALLOPROTEINASE EXPRESSION IS REGULATED IN RESPONSE TO SELECTED CHEMOKINES: IMPLICATIONS FOR BREAK-THROUGH BLEEDING

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Break-through bleeding is a problem common to many women using long-acting progestin-only contraceptives such as Implanon, and is the main reason many women discontinue using them. Our previous studies (1) identified a number of chemokines (chemoattractive cytokines) that are highly expressed during the menstrual cycle with the capacity to selectively attract the leukocyte subsets present in each phase. Leukocytes produce factors thought to be critical for endometrial breakdown and remodelling, including matrix metalloproteinases (MMPs). We hypothesised that progestins act on endometrial epithelial cells to activate chemokine expression. The chemokines attract leukocytes into the tissue and stimulate their production of MMPs, contributing to tissue breakdown and break-through bleeding. The present study investigated the role of appropriately selected chemokines on leukocyte MMP production. The eosinophilic cell line EOL-1 and the mast cell line HMC1 were treated with four chemokines (fractalkine, HCC-1, MCP-3 and IL-8) at a range of concentrations. MMP production and activation were analysed by gelatin and casein zymography of culture medium. No response was observed from the mast cells under any of the treatments. However, there was a significant increase in latent MMP-9 production by eosinophils in response to increasing concentrations of IL-8 and MCP-3. Results show a greater than 2-fold increase in the amount of latent MMP-9 in response to IL-8 or MCP-3 (300 ng/mL and 80 ng/mL respectively) compared to non-treated controls. These chemokines had no significant effect on levels of active MMP-9 or latent and active forms of MMP-2. HCC-1 and fractalkine had little effect on either MMP-9 or MMP-2 production by these cells. These data support the hypothesis that MMP production by leukocytes is regulated, at least in part, by selective chemokines expressed during menstruation. Future studies will expand the leukocyte subtypes tested and investigate the role of synthetic progestins in chemokine expression from endometrial epithelial cells.

(1) Jones R. L. *et al.* (2003) Proceedings 34th Annual Conference of Society for Reproductive Biology. *Reprod. Fertil. Dev.* **15** (suppl.), A85.