

## ACTIVIN A UPREGULATES ENDOMETRIAL METALLOPROTEASES: POTENTIAL MECHANISMS FOR PROMOTION OF DECIDUALISATION AND IMPLANTATION

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Activin and inhibin subunits are co-expressed by human endometrial epithelial and decidualised stromal cells. Activin A is a potent stimulator of decidualisation in vitro, but the mechanisms are unknown. Matrix metalloproteases (MMPs) are known to be important during decidualisation, as administration of a broad spectrum MMP inhibitor in the rat results in reduced decidualisation. Transforming Growth Factor(TGF)- $\beta$ s are closely related to activins and inhibit MMP production in endometrial epithelial cells. We hypothesised that activins regulate MMP production during decidualisation and/or trophoblast invasion. Epithelial and stromal cells were isolated from human endometrium and treated for 24 h with activin, inhibin, activin/inhibin, and follistatin. Media were collected and subjected to gelatin and caesin zymography. In epithelial cells, activin A stimulated the expression of latent forms of MMPs-1, -2, -7 and -9, and increased formation of active forms of MMPs-2 and -7. Cotreatment with inhibin prevented this stimulation, whilst inhibin alone completely inhibited MMP production. Treatment with follistatin treatment reduced MMP levels. Similar regulation was seen in stromal cells for MMPs-1, -2 and -9. These data show that activin stimulates the production and activation of MMPs in both endometrial cells, and that inhibin is a potent inhibitor. It is interesting that activin is acting in an opposing manner to TGF- $\beta$ , indicating that these two closely related proteins have divergent signalling pathways in endometrial cells. Further, this is the first demonstration of a role for inhibin in regulating MMPs and indeed for inhibin action in the endometrium. These findings are of potential importance in understanding regulation of MMPs in the peri-implantation endometrium. Activin is the predominant dimer produced by decidual and epithelial cells, where it may be promoting decidualisation though enhancing MMP production and activation. Furthermore, activin secretion by invasive cytotrophoblasts may stimulate focal decidual MMP production promoting their invasion during embryo implantation.