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TITLE

PROGESTERONE RECEPTOR-MEDIATED ADAMTS AND MMP3/10 EXPRESSION IN HUMAN GRANULOSA CELLS: THE DIFFERENTIAL ROLE OF HIF1A

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ABSTRACT

Progesterone Receptor (PR) mediates the expression of several matrix metalloproteinases (MMPs) including metalloproteinases 3 and 10 (MMP3/10) and members of the desintegrin and metalloproteinase with thrombospondin motifs family (ADAMTS). However, in the human there are scarce data available regarding gonadotropin-activated (LH, hCG and FSH) PR expression and signaling pathways involved in MMPs expression presumably linked to the rupture of the dominant follicle. Our hypothesis is LH/hCG and FSH increase PR expression in human GC through different signaling pathways, leading to an increased expression of ADAMTS and MMP3/10 that may mediate follicular rupture through the transcription factor, HIF1A. Human GCs were isolated from follicular aspirates obtained from twenty-two healthy women participating in our IVF program for treatment of male factor infertility. PR and HIF1A protein expression was assessed by immunofluorescence, and PKA, PKC, PI3K and ERK, ADAMTS and MMP3/10 protein expression by WB in pre-ovulatory GC and in cultured human luteinizing GC. Our results show that hCG, LH and FSH regulated PR protein expression and activated PKA, PKC, PI3K and ERK signaling pathways in human GC but PR expression is only mediated by PKA, PKC and ERK pathways. Furthermore, hCG, FSH and LH regulated ADAMTS and MMP3/10 expression via PR. Moreover, hCG-PR-dependent HIF1A expression stimulated MMP3/10 expression but not that of ADAMTS. These results suggest differential downstream PR signaling, since PR regulates MMP3/10 expression via the transcription factor HIF1A, which is not involved in ADAMTS expression. This study enhances the understanding of the molecular regulatory mechanisms involved in human ovulation.

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