Progesterone receptor-mediated effects on apoptosis in periovulatory granulosa cells

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Göteborgs universitet kommer att försvaras offentligt i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 15 september 2006, kl. 09.00

av

Emilia Rung

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Professor Alex Tsafriri
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Avhandlingen baseras på följande arbeten:

I **Progesterone receptor-mediated inhibition of apoptosis in granulosa cells isolated from rats treated with human Chorionic Gonadotropin.**
Svensson ECh, Markström E, Andersson M and Billig H.
Biology of Reproduction (2000) 63: 1457-64

II **Progesterone receptor antagonists Org 31710 and RU 486 increase apoptosis in human periovulatory granulosa cells.**
Svensson ECh, Markström E, Shao R, Andersson M and Billig H.
Fertility and Sterility (2001) 76: 1225-31

III **Progesterone receptor antagonists and statins decrease de novo cholesterol synthesis and increase apoptosis in rat and human periovulatory granulosa cells in vitro.**
Rung E, Friberg PA, Shao R, Larsson DGJ, Nielsen ECh, Svensson PA, Carlsson B, Carlsson LMS and Billig H.
Biology of Reproduction (2005) 72: 538-45

IV **Depletion of substrates for protein prenylation increases apoptosis in human periovulatory granulosa cells.**
Rung E, Friberg PA, Bergh C and Billig H.
Molecular Reproduction and Development (2006) 73: 1277-83

Progesterone receptor-mediated effects on apoptosis in periovulatory granulosa cells

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ABSTRACT

The most common fate of developing ovarian follicles is demise due to a process known as atresia. Regulation of atresia is dependent on the developmental stage of the follicles, resulting in a continuous reduction of the number of follicles as they differentiate and grow towards ovulation. The mechanism behind atresia of growing follicles is apoptosis of the granulosa cells. This thesis focuses on progesterone receptor (PR)-mediated regulation of granulosa cell apoptosis during the final phase of follicular development, the periovulatory interval.

By using two PR antagonists (RU 486 and the more specific Org 31710) we have shown that PR stimulation is important for the survival of periovulatory rat and human granulosa cells in vitro. PR regulated gene expression in rat periovulatory granulosa was characterised by microarray analysis, comparing the expression profiles after incubation in vitro with or without the addition of 10 μM Org 31710. Close to 100 genes were found to be transcriptionally regulated in the presence of Org 31710. This included downregulation of several genes involved in cholesterol synthesis, and a decreased rate of cholesterol synthesis was verified by measuring the incorporation of ^{14}C-acetate into cholesterol, cholesterol ester and progesterone. Based on this we investigated the granulosa cell dependence on cholesterol synthesis and in particular the branch-point reactions supplying cells with prenylation substrates for post-translational lipid modification of proteins. Blocking the cholesterol synthesis with statins increased apoptosis, as did inhibitors of prenyl transferases. The increase in apoptosis after treatment with statins or PR antagonists was partially reversed by the addition of substrates for prenylation.

In conclusion, PR stimulation is important for the survival of periovulatory granulosa cells in both rats and humans. PR stimulation regulates the transcription of several groups of genes including cholesterol synthesis. The cholesterol synthesis also provides the cells with substrates for protein prenylation, which may be one of the factors regulating granulosa cell survival in periovulatory follicles.

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