28. LOCALIZATION OF ADAMTS-1 AND PROTEOLYTIC CLEAVAGE OF VERSICAN DURING CUMULUS MATRIX EXPANSION AND OVULATION

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Prior to ovulation a specialized matrix is assembled around the oocyte and accompanying cumulus cells. Hyaluronan (HA) and a group of HA binding proteins are major components of this matrix and we recently found that the hyalectan versican is selectively incorporated, most likely acting as a crosslinking matrix organizer. The protease ADAMTS-1 (a disintegrin and metalloprotease with thrombospondin motifs-1) is a member of the ADAM family of metalloproteases that cleave members of the hyalectan family of proteoglycans including versican. ADAMTS-1 is rapidly induced in the periovulatory follicle and female progesterone receptor knockout (PRKO) mice have impaired periovulatory induction of ADAMTS-1 mRNA. PRKO as well as ADAMTS-1 null mice display anovulatory infertility due primarily to impaired ovulation. We therefore investigated the protein localization and function of ADAMTS-1 in ovulating ovaries. Specific antibodies against the pro-domain of ADAMTS-1 identified the 110 kDa pro-protein in mural granulosa cells that appeared localized to cytoplasmic secretory vesicles. An antibody against the metalloprotease domain detected the 85 kDa mature (pro-domain truncated) form secreted from cells and selectively bound to the extracellular matrix of the ovulating cumulus oocyte complex (COC). Versican in the ovulating COC matrix was found to be cleaved yielding a 70 kDa N-terminal fragment immunopositive for the neoepitope DPEAAE generated by hyalectanase mediated cleavage. This extracellular processing of versican was reduced in ADAMTS-1 deficient PRKO mouse ovaries, suggesting that ADAMTS-1 is at least partially responsible for this process. Cleavage of versican may alter the matrix structure, adhesive or viscoelastic properties of ovulating COC. These observations indicate that one function of ADAMTS-1 in ovulation is to cleave versican in the expanded COC matrix and suggest that the anovulatory phenotype of PRKO mice is at least partially due to loss of this function.

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