# Organization of hyaluronan in the matrix surrounding ovulated oocytes: impact on female fertility

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EDUCATION/EMPLOYMENT:

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| July 1976, Ph.D. (with honors), University of Rome "La Sapienza", Rome | |
| 1976-1977 | Research Fellow, University of Rome "La Sapienza" |
| 1978-1984 | Assistant Professor of Histology and Embryology, School of Medicine, University of L'Aquila |
| 1984-1986 | Assistant Professor of Histology and Embryology, School of Medicine, University of Rome "Tor Vergata" |
| 1986-2001 | Associate Professor of Embryology, School of Medicine, University of Rome "Tor Vergata" |
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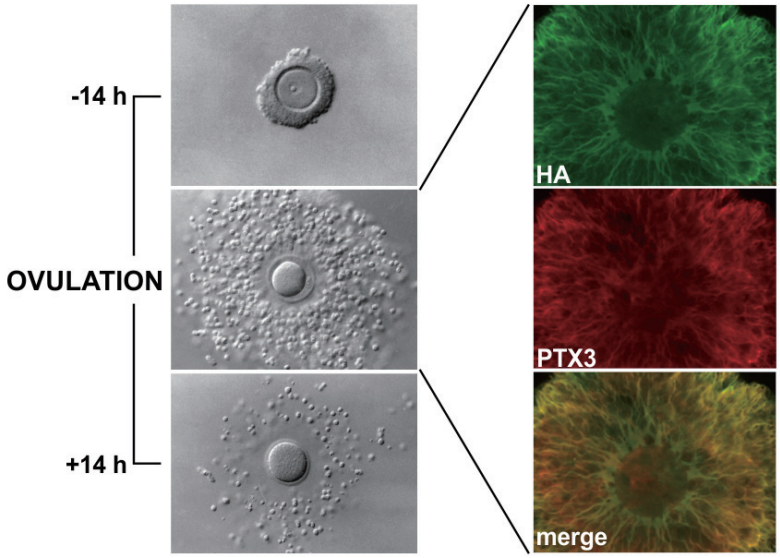
MAIN RESEARCH FIELDS:
She worked in identifying endocrine and paracrine factors involved in extracellular matrix deposition by cumulus cells surrounding the oocyte. These studies provided the first evidence that oocyte soluble factors influence somatic cell response to gonadotropin stimuli playing a critical role in ovarian function. She also contributed to identify components of the cumulus matrix essential for in vivo oocyte fertilization. Recently, she has been involved in studying the role of anti-inflammatory molecules in female mouse fertility.

Extensive production of extracellular matrix (ECM) by cumulus cells surrounding the oocyte occurs before ovulation, a process referred to as cumulus expansion. We have shown that oocytes actively participate in the regulation of this process by producing growth factors able to dramatically up regulate Has2 expression by cumulus cells in response to endocrine and paracrine factors [1)2)]. The activation of Has2 gene expression leads to the production of long hyaluronan (HA) molecules (more than 2000 kDa) that are organized into a mesh-like network. Serum-derived I-alpha-I and at least two proteins synthesized in parallel by cumulus cells, TSG6 and PTX3, are essential for HA organization and stability of cumulus matrix. Female mice with targeted disruption of genes relative to these proteins ovulate oocytes surrounded by unstable and disorganized cumuli [3)-5)] . How these proteins influence and integrate their action in assembling the cumulus matrix is not fully understood.

It has been well established that, during cumulus matrix formation, the heavy chains of I-α-I are covalently linked to HA and that this process is mediated by TSG6 [6)]. We found that heavy chains of I-alpha-I bind to PTX3 and that this interaction is necessary for cumulus matrix assembly [7)]. PTX3 is a multimeric protein formed by eight identical protomers and we proposed that this molecule can function as a node in cross-linking HA by binding several heavy chains of I-alpha-I. In agreement with this model, we have recently shown that PTX3 mutants with reduced multimeric status have decreased capacity to support matrix assembly in Ptx3 $^{-/-}$ cumuli induced to expand *in vitro* [8)]. Interestingly, TSG6 has the ability to bind to both HA and PTX3, but it does not seem to be directly involved in cross-linking HA. In fact, displacement of




**Timing of formation and degradation of hyaluronan rich-extracellular matrix by the cumulus cell-oocyte complex. At the ovulation hyaluronan is organized in the matrix by interactions with proteins, including PTX3. Note HA and PTX3 co-localization**

TSG6 from the expanded matrix by the antibody against the HA binding region of TSG6 (A38 antibody) as well as by HA oligos (HA14) caused neither HA and/or PTX3 release nor cumulus disaggregation (our unpublished results). Defective cumulus expansion in female mice null for any of these three genes is associated to sterility due to oocyte fertilization failure. However, we demonstrated that oocytes ovulated from Ptx3 mice can be successful fertilized *in vitro*. All together these findings strongly suggest that cumulus matrix plays a crucial role for the recruitment and activation of sperm *in vivo*, a condition likely circumvented under *in vitro* fertilization settings. This idea is supported by recent reports showing that, in physiological circumstances, the acrosome reaction, required for successful fertilization, occurs during sperm passage through the expanded cumulus [9]. Interestingly, we also found that, shortly after ovulation, cumulus matrix disassembly parallels changes of the enclosed oocytes that make them more likely to produce abnormal embryos when fertilized. We now show that experimental maintenance of cumulus integrity after ovulation increases the fertilization rate of the enclosed oocytes without to improve their developmental capacity (unpublished results). Thus, it is likely that timing of both the formation and disassembly of the cumulus matrix is functional to facilitate fertilization of newly ovulated oocytes and to prevent that of aged oocytes.

## References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