Revisiting the ovarian stroma: More than a holding zone for the follicle

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Outline

Organs, organoids, and ovaries-a comparative perspective
Why the ovary needs a stroma

The complexity of ovarian somatic cells and their extracellular matrix

Can this knowledge base prompt practical and tractable strategies for building an artificial ovary
The Evo-Devo Perspective

With the acquisition of an organoid stroma rich ovary (mammals), comes the reduction in dependence on stem cell renewal in germ and somatic lineages.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Germ Layers</th>
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<tbody>
<tr>
<td>Hydra</td>
<td>2</td>
</tr>
<tr>
<td>Endoderm/Ectoderm</td>
<td></td>
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<tr>
<td>Arthropods</td>
<td>2.5</td>
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<tr>
<td>Endo-Ecto-Mesoderm</td>
<td></td>
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<tr>
<td>Mammals (Macaque)</td>
<td>3.0</td>
</tr>
<tr>
<td>Endo-Ecto-Mesoderm</td>
<td></td>
</tr>
</tbody>
</table>
Phylogenetic principles

From 2-3 germ layers
From germ line stem cells to somatic line stem cells
Primitive ovaries
Vertebrate complexities

Innervation/vascularity/sorting of somatic stem cells to support cyclicity versus seasonal activation de novo
Naked Mole Rats—An ovarian aging model-2015

While dominant female reproduces, subordinates enter permanent state of quiescence.
Day 5

Day 28

Day 90

A “life” in the reproductive lifespan of a NMR ovary

2 year old subordinate

12 year old subordinate
A stroma-less avascular ovary: the role of GDF9-1998

GDF9 -/- KO mice lack a stroma and fail develop a vasculature by 8 weeks of age
A contractile cortex-a chance observation-2005

Cortical strips contract in an ATP-dependent myosin-mediated mechanism
Cell type amplification and diversification upon onset of cyclicity - The ovary in action
Stromal lineages: Conventional Thinking

Somatic Progenitor

Mesenchymal
- myofibroblast
- vascularity

Epithelial

Neuronal
Tuj1 bovine
Stroma then and now

More than a passive support matrix of CT/ECM
Biophysical properties of elasticity, tension, stiffness impart information to contents
Contractility/relaxation requires orientation and anchoring
Stromal composition and mechanical properties change with age/disease conditions
Erase and Rewind: Epigenetic Conversion of Cell Fate
Georgia Pennarossa & Alessandro Zenobi & Cecilia E. Gandolfi & Elena F. M. Manzoni & Fulvio Gandolfi & Tiziana A. L. Brevini
Basic choices

Quiescence <-> Proliferation

Senescence
Terminal Differentiation

Non-dividing

Proliferation
Dividing
• Somatic cell complexity
Zonation within cortex (Macaque, adult)
Autonomics
Types of innervation
Nestin Bovine-cortical strips
Integration by actin filaments

Trilaminar cortex elicits myofibroblast transformation upon follicle activation by establishing Actin-ECM signaling
Fibrosis and the aging ovary

Reproductive age-associated fibrosis in the stroma of the mammalian ovary
Shawn M Briley1,*, Susmita Jasti1,*, Jennifer M McCracken2, Jessica E Hornick3, Barbara Fegley1,4, Michele T Pritchard2 and Francesca E Duncan1,†

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I Love New York
Organs on Chips

**Scientists hope that these devices will one day replace animal models of disease and help advance personalized medicine.**

By Diana Kwon | August 28, 2017
Conclusions

Building an ovary is complicated, possibly more so than building an oocyte
The stroma embodies much more than a supportive matrix
Somatic cell plasticity from a progenitor pool provides specializations needed to sustain follicular remodeling in an otherwise fibrotic future
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