*How signaling modalities link oogenesis to embryogenesis

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OR

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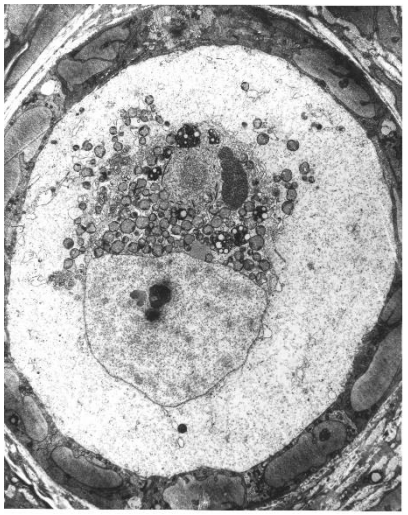
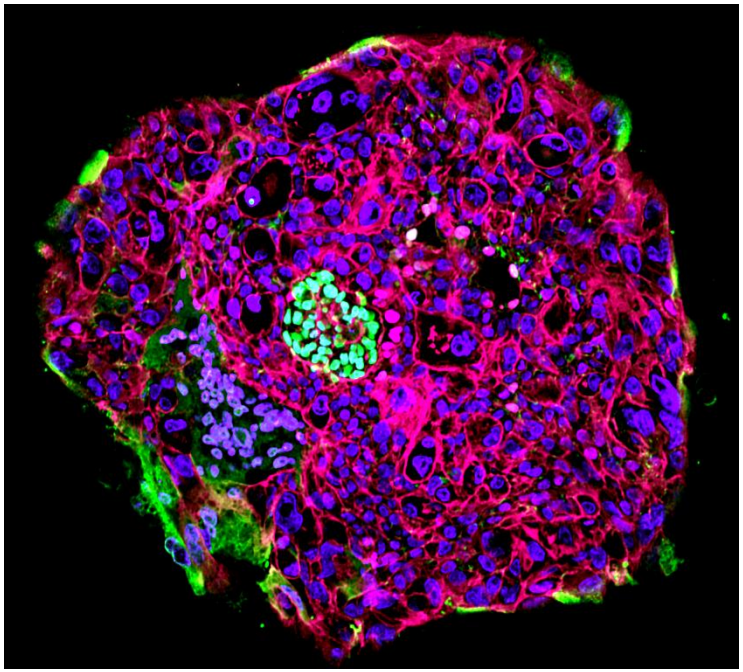
How signaling modalities link oogenesis to embryogenesis

To there:



Hertig, 1967 Human primordial follicle



Deglincerti and colleagues
Nature. 2016 May 4;533:251-4.
doi: 10.1038/nature17948.
Cultured human embryo

OVARIAN CLUB VIII

BUILDING A BRIDGE BETWEEN SCIENCE AND CLINICAL PRACTICE

4-6 NOVEMBER, 2016 · PARIS, FRANCE

Or Here !!!

Disclosure information:

Receive payment from-
Springer/Nature Publishing as JARG EiC
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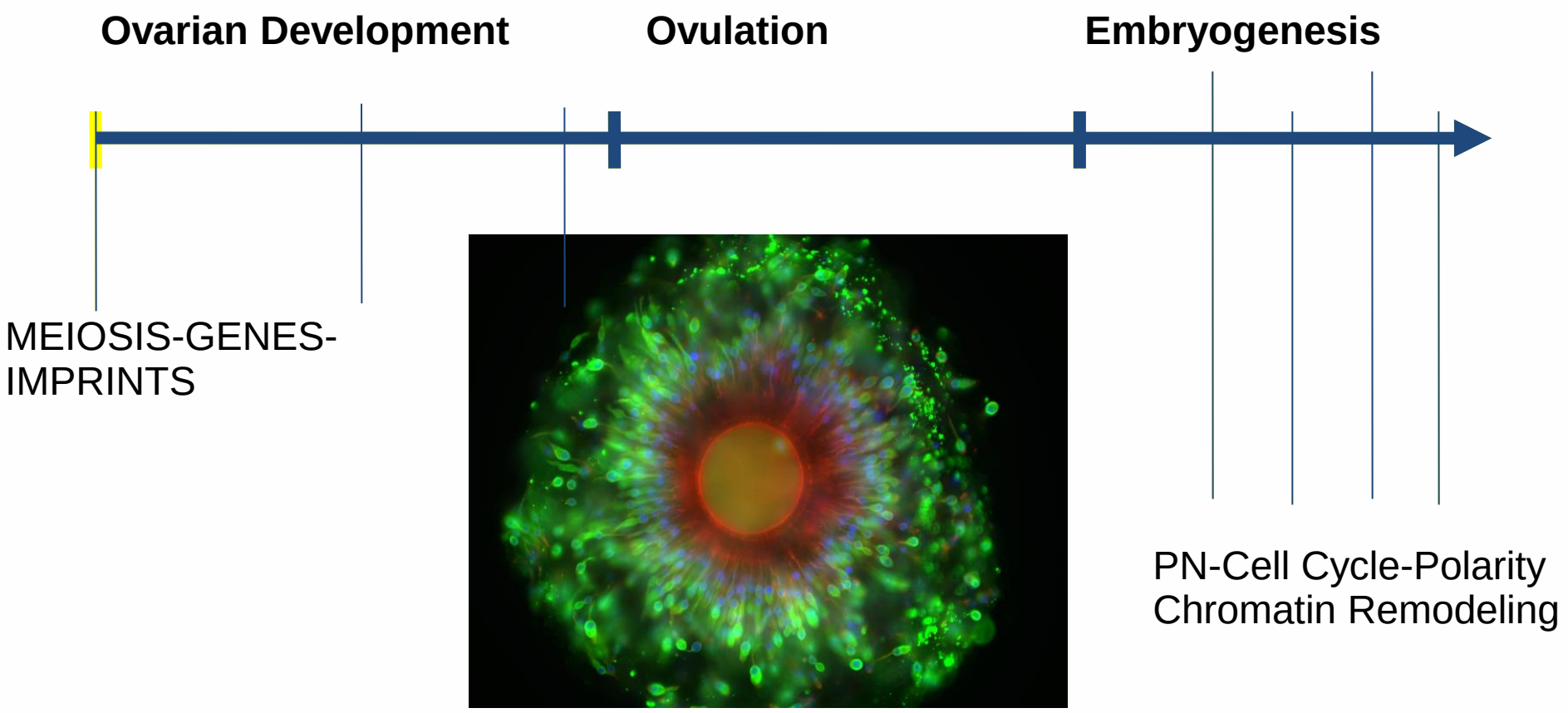
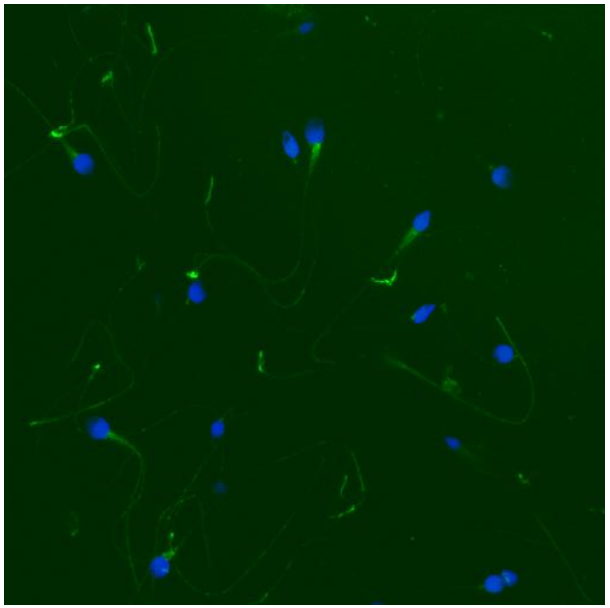
Outline

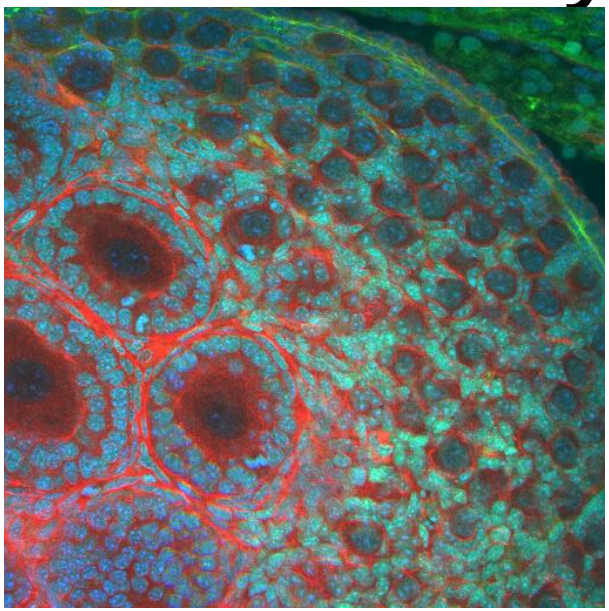
- What types of signaling modalities exist in the follicle
- What is the physiological significance of changing oocyte-cumulus cell communication
- Before, during, and after ovulation
- Impact on the preimplantation embryo
- Can oogenesis be recapitulated in vitro

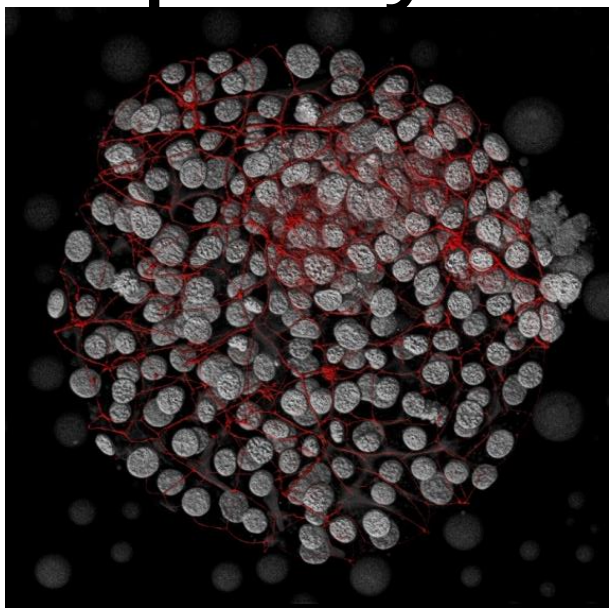
Oocyte Quality Is a Developmental Continuum Extending into Embryogenesis



What are the innate (gametic) determinants of embryo quality?







Two genomes (or is it 3?)
Maternal effect gene products….molecules
Mostly maternal organelles
Sperm donations in kind (centrosomes, miRNAs)
A cortical scaffold to store a
protect products of oogenes

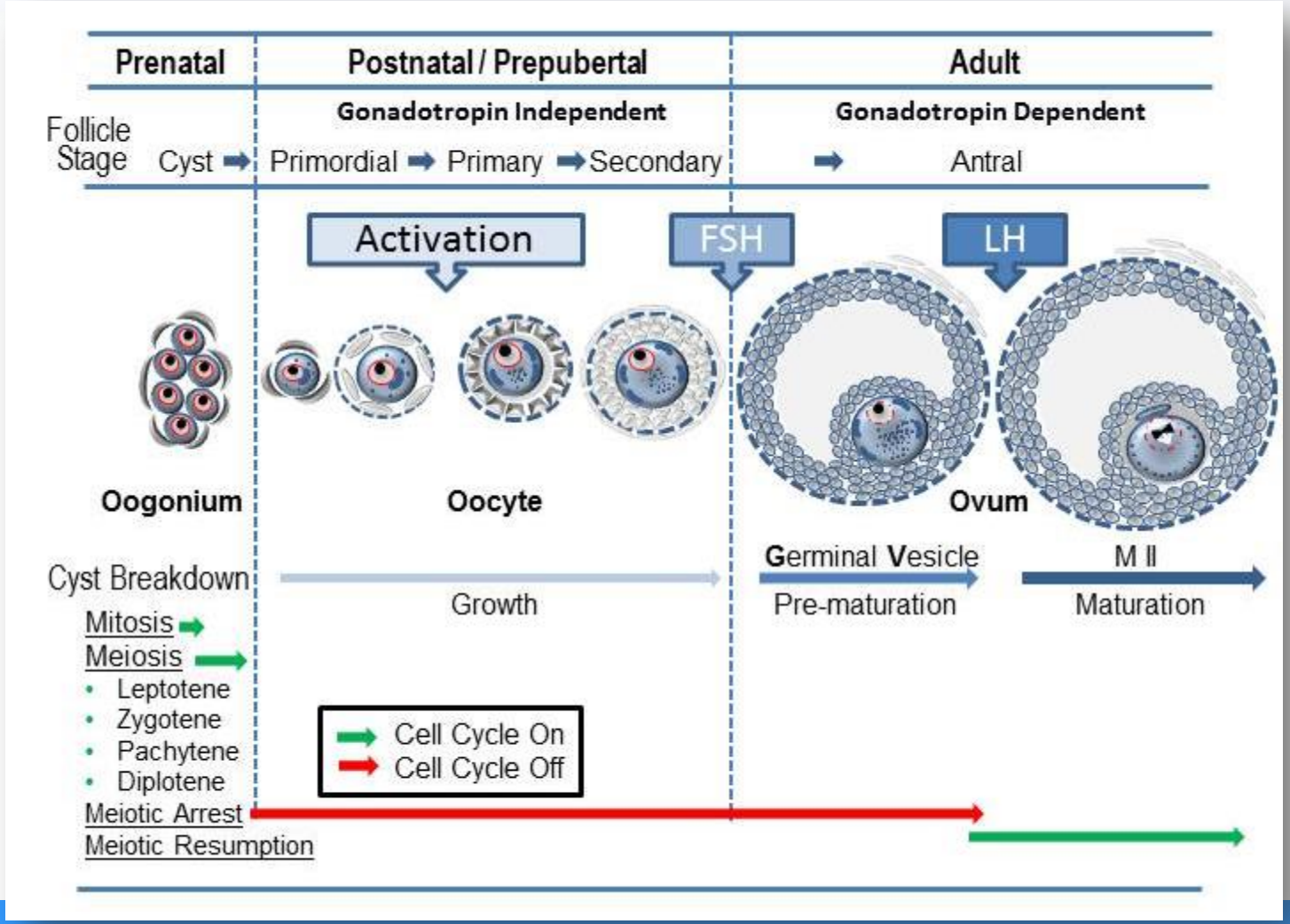
A Subcortical Maternal Complex Essential for Preimplantation Mouse Embryogenesis

Lei Li[1,*] Boris Baibakov,[1] and Jurrien Dean[1]
[1]Laboratory of Cellular and Developmental Biology, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA
[*]Correspondence: lile@mail.nih.gov
DOI 10.1016/j.devcel.2008.07.010

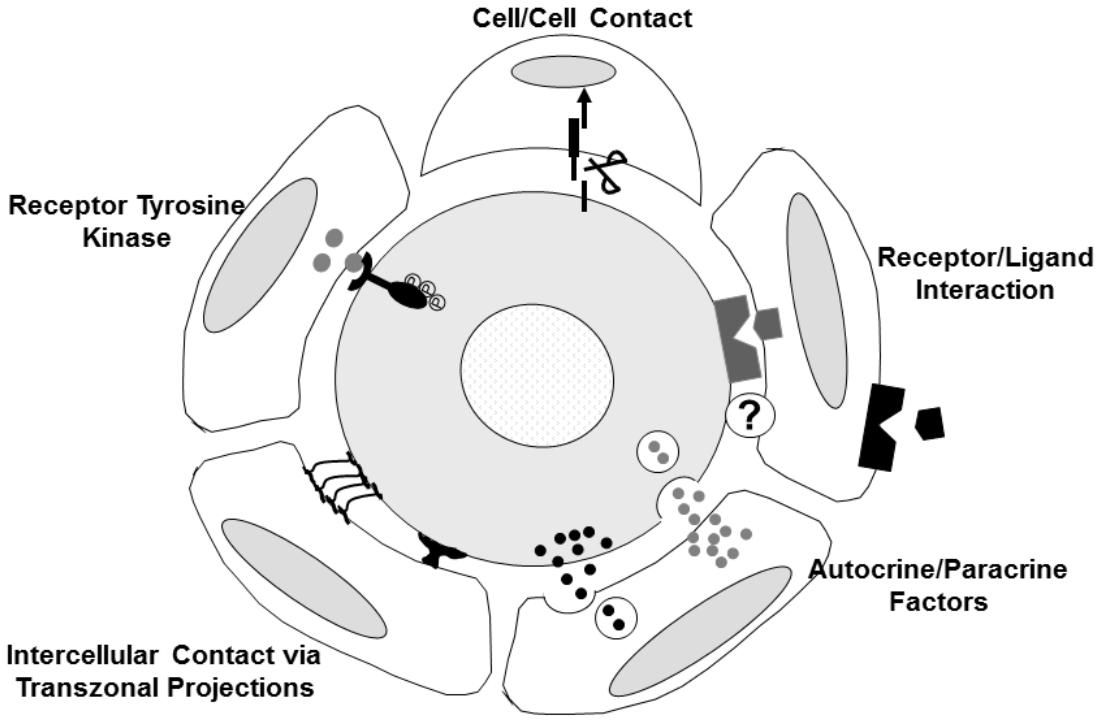
Maturing in the Style of Eggs and Follicles

- Follicles activate from primordials
- Grow to increase somatic cell number (hyperplasia) and support germ cell hypertrophy
- Acquire gonadotropin sensitivity along with steroidogenic capacity
- Acquire ovulation competency for both the mural and cumulus compartments
- Oocytes undergo hypertrophy along with initial stages of follicle growth
- Erase imprints and prepare to reimprint the zygote
- Acquire in sequence the ability to resume and complete meiosis, fertilization potential, and support embryo
- The COMPETENCIES that link oocyte to embryo quality are acquired in the follicle

Status quo


Prenatal
Postnatal / Prepubertal
Adult
Gonadotropin Independent
Gonadotropin Dependent
Follicle Stage
Cyst
Primordial
Primary
Secondary
Antral
Activation
FSH
LH
Oogonium
Oocyte
Ovum
Cyst Breakdown
Growth
Germinal Vesicle
Pre-maturation
M II
Maturation
Mitosis
Meiosis
Leptotene
Zygotene
Pachytene
Diplotene
Meiotic Arrest
Meiotic Resumption
Cell Cycle On
Cell Cycle Off

Multiple Cell Communication Pathways



McGinnis LK, Limback SD, Albertini DF (2013) Signaling modalities during oogenesis in mammals. In P M Wassarman, editor: Current Topics in Developmental Biology, Vol. 102,Academic Press, pp. 227-242. ISBN: 978-0-12-416024-8

In the beginning-as the follicle forms

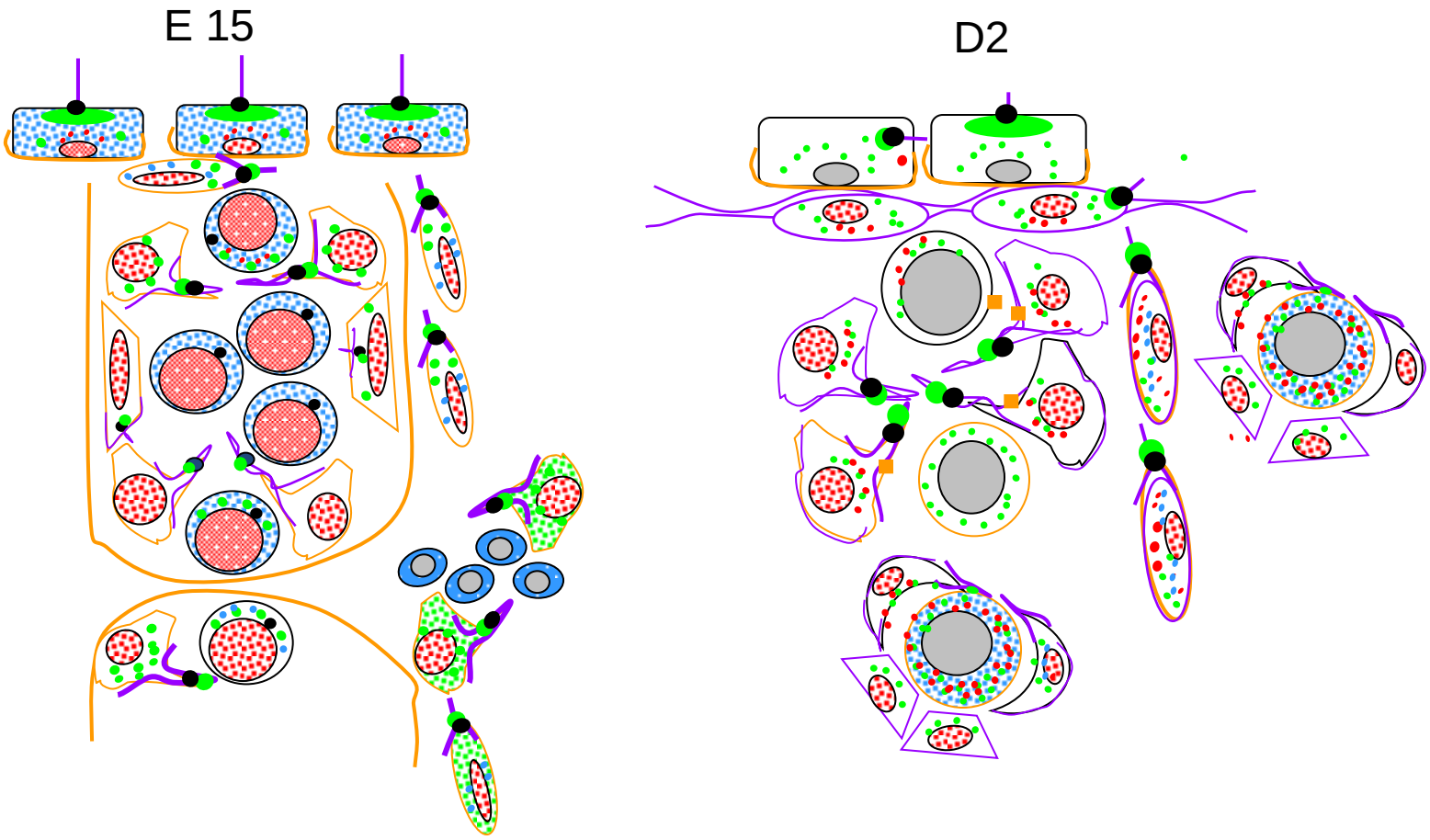
Cyst breakdown or something else generating primordials?
Notch signaling at the front or back end?

RESEARCH ARTICLE Open Access

Notch2 is required in somatic cells for breakdown of ovarian germ-cell nests and formation of primordial follicles

Jingxia Xu[1,2] and Thomas Gridley[3*]

Xu and Gridley *BMC Biology* 2013, **11**:13
http://www.biomedcentral.com/1741-7007/11/13



Bone morphogenetic protein 2 promotes primordial follicle formation in the ovary

Prabuddha Chakraborty[1] & Shyamal K. Roy[1,2]

Activation of Primordial Follicles

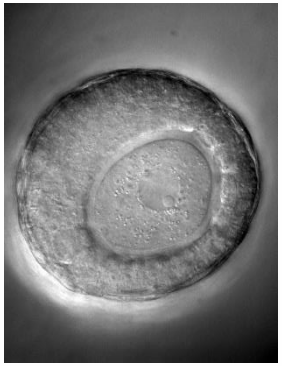
Primordial Follicles "signaled" by environment

BMPs
Activin
KIT ligand
YAP
Cortical tension

Small follicles

In flux

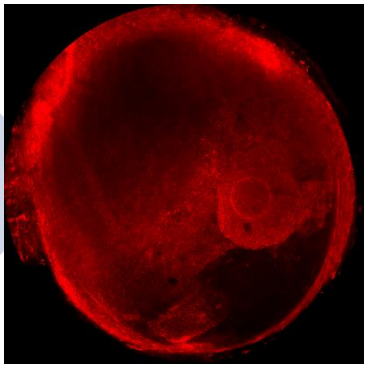
AMH production



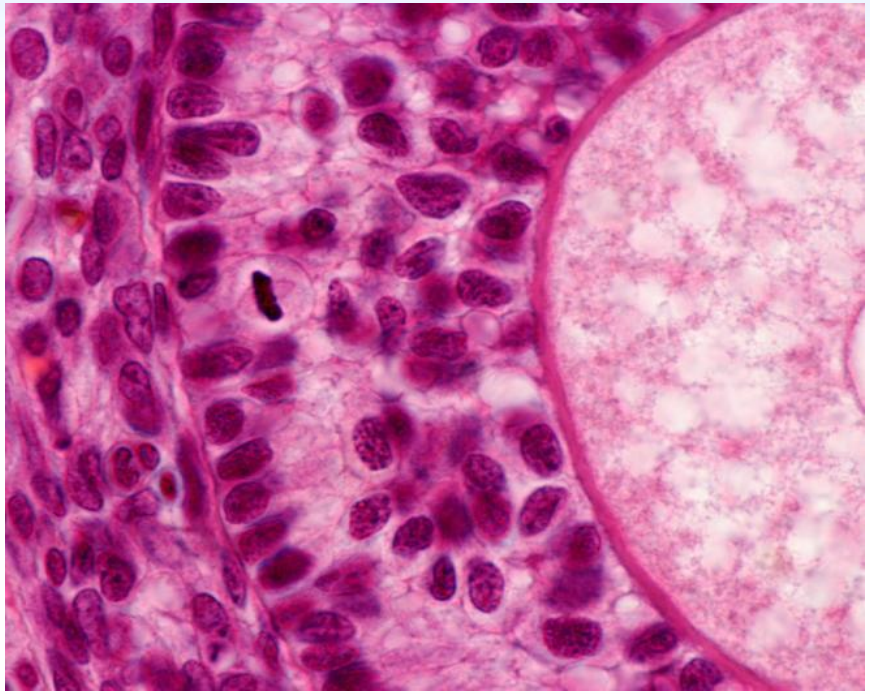
FSH
LH
BMP15
IGFs

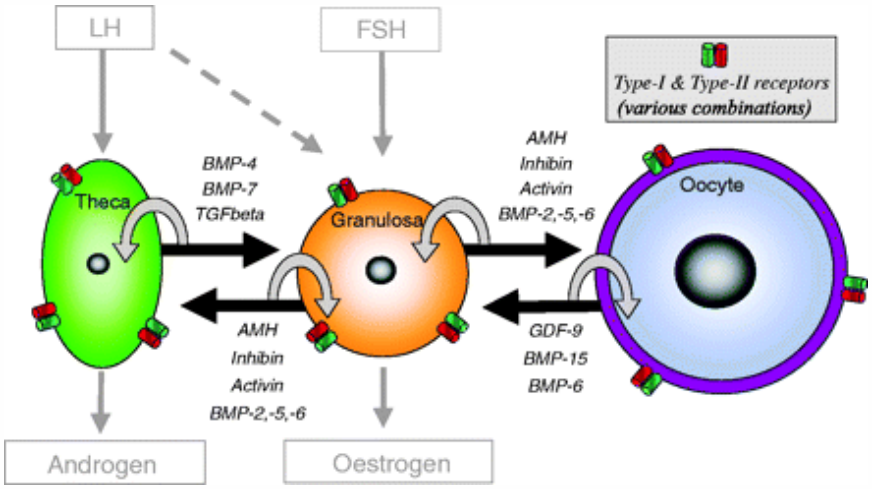
Graafian follicles

EGFs
cGMP

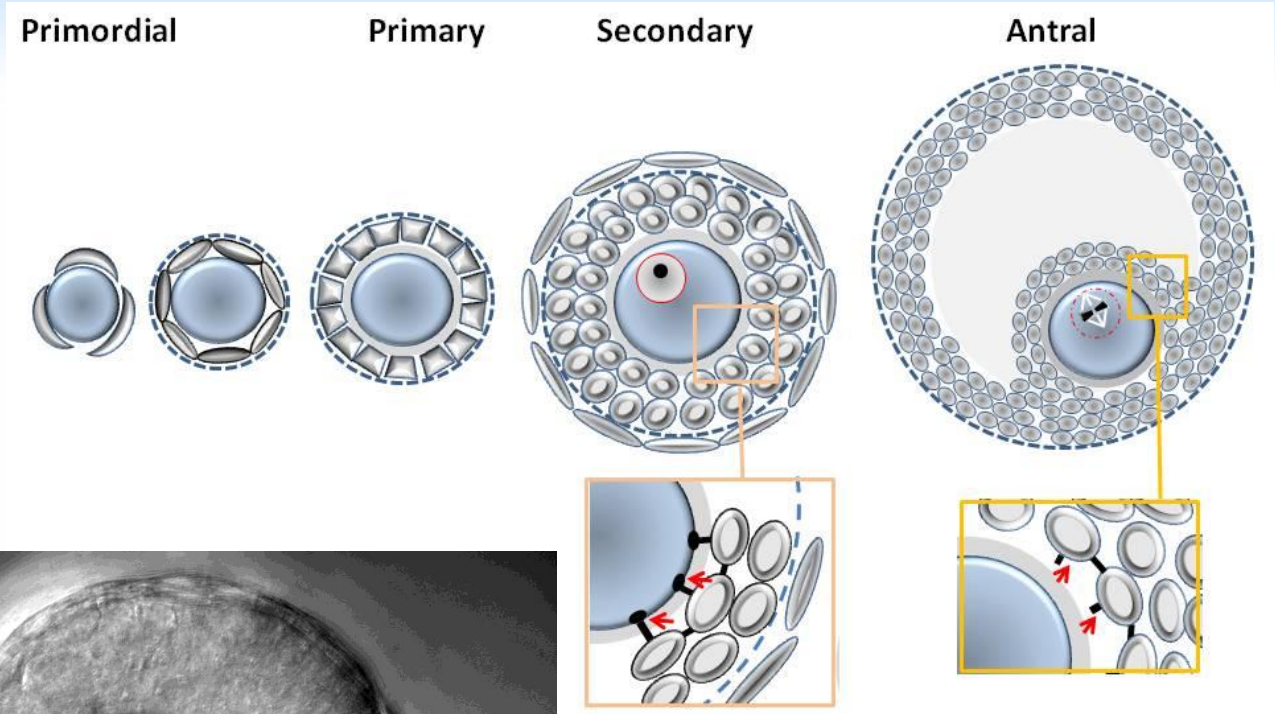


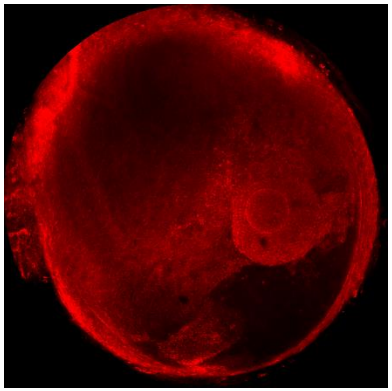
Building a follicle is a complicated process



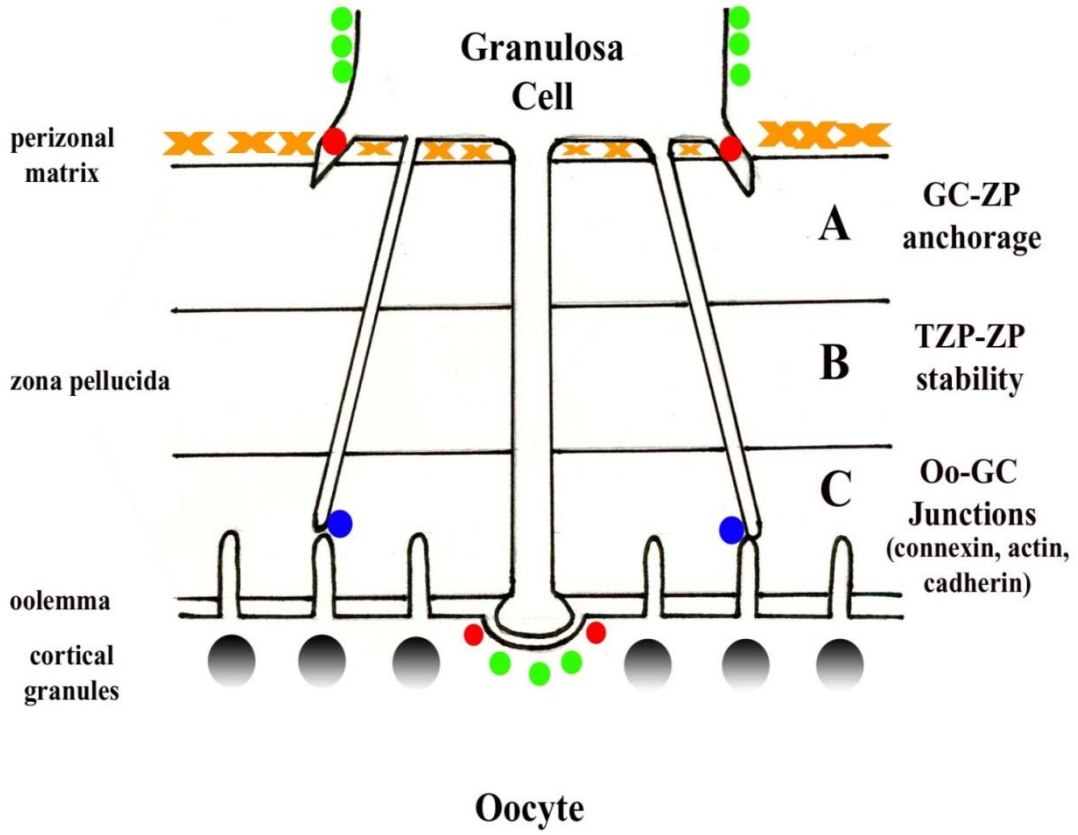


Growth and Maturation of the Graafian Follicle

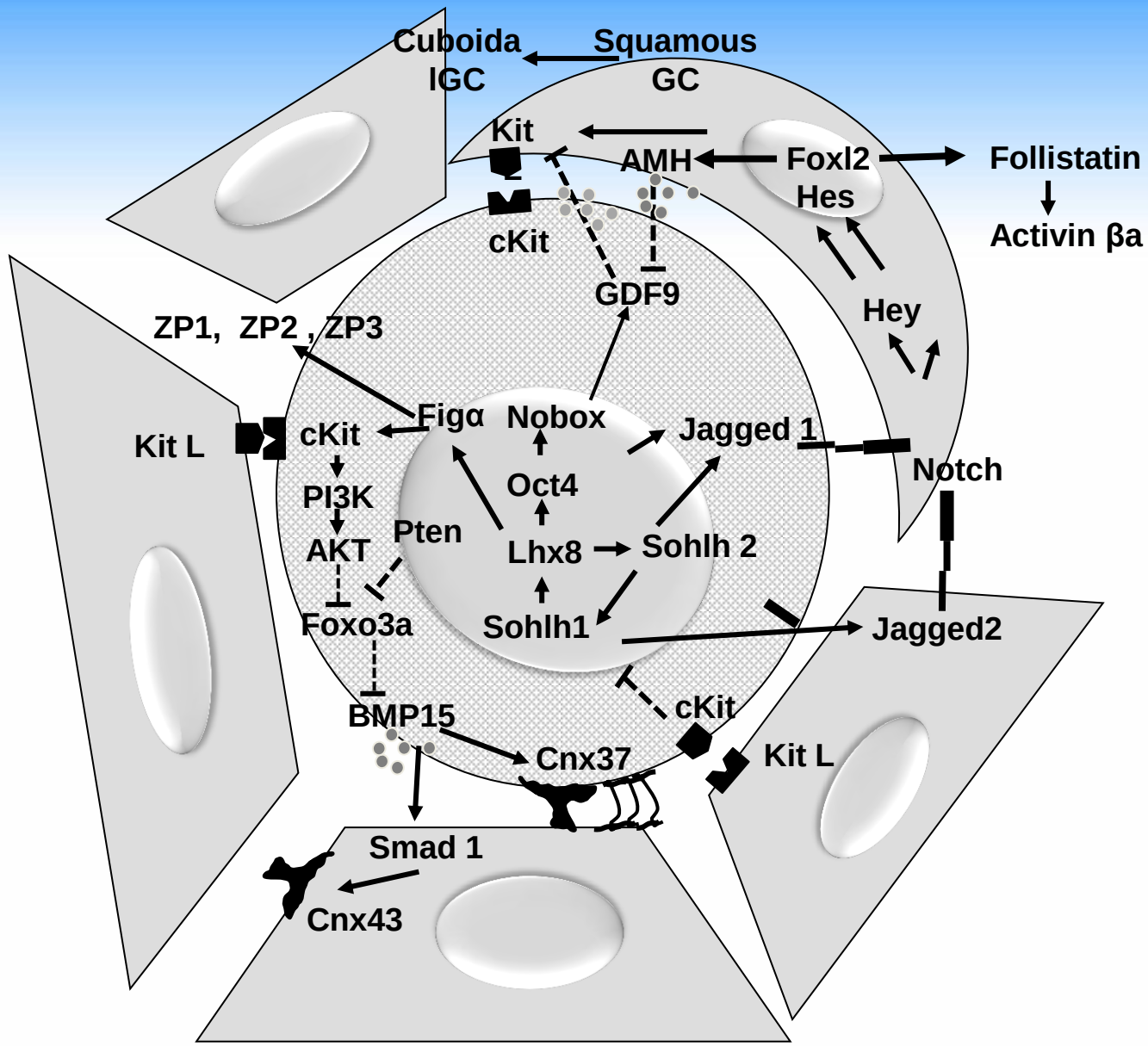




The Oocyte-Granulosa Interface: Circa 2007



Growth and expansion-in real time

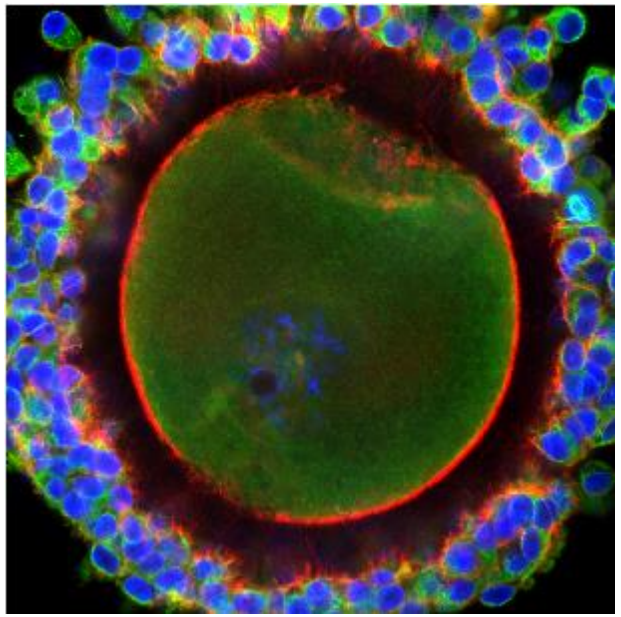


McGinnis LK, Limback SD, Albertini DF (2013) Signaling modalities during oogenesis in mammals. In P M Wassarman, editor: Current Topics in Developmental Biology, Vol. 102,Academic Press, pp. 227-242. ISBN: 978-0-12-416024-8

Metabolic Symbiosis

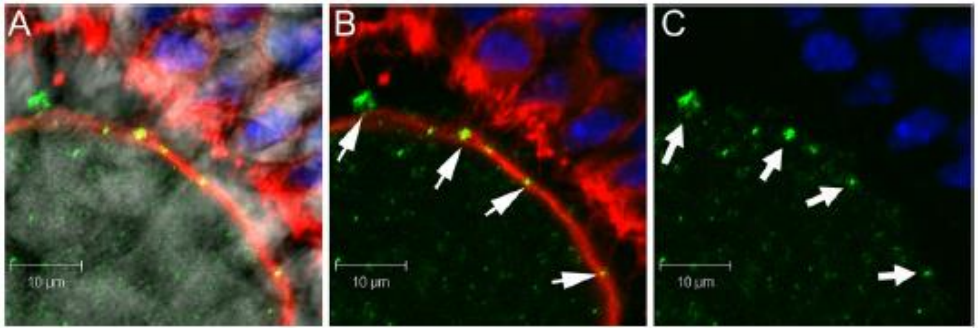
- Sharing Metabolism via gap junctions for most metabolic substrates, amino acids, choline, uridine, cholesterol (but not folate (Baltz, Schultz, Eppig)
- Sharing “informative” molecules via unknown mechanisms including miRNAs (Robert, Sirard)

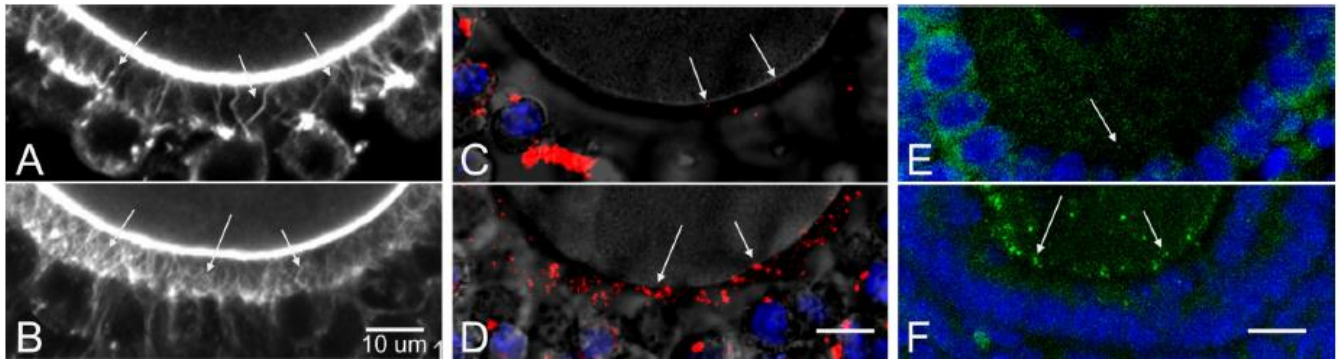
Sharing organelles (?) by direct exchange of cytoplasm, receptor-mediated endocytosis, exosomes



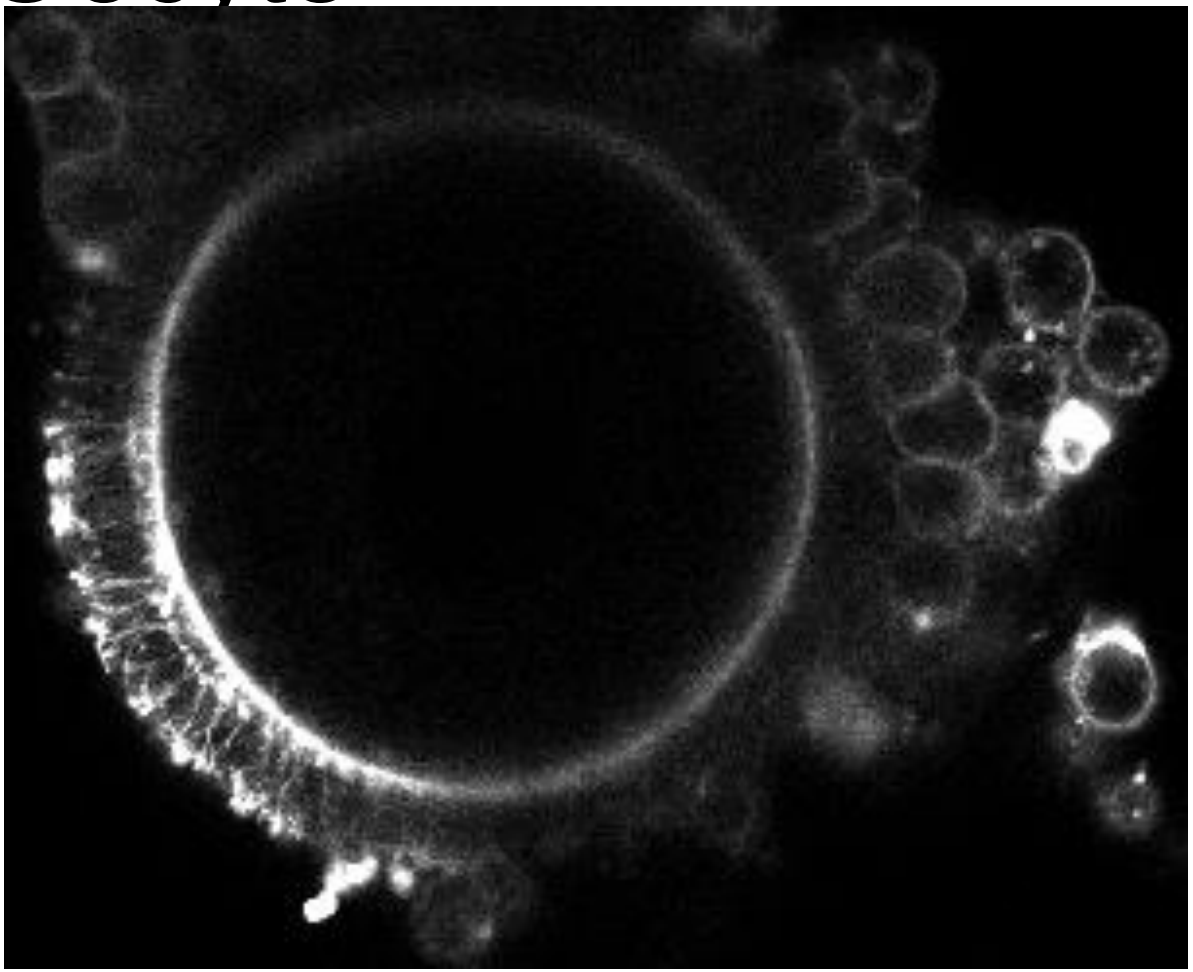
Role of focal adhesion kinase in oocyte-follicle communication

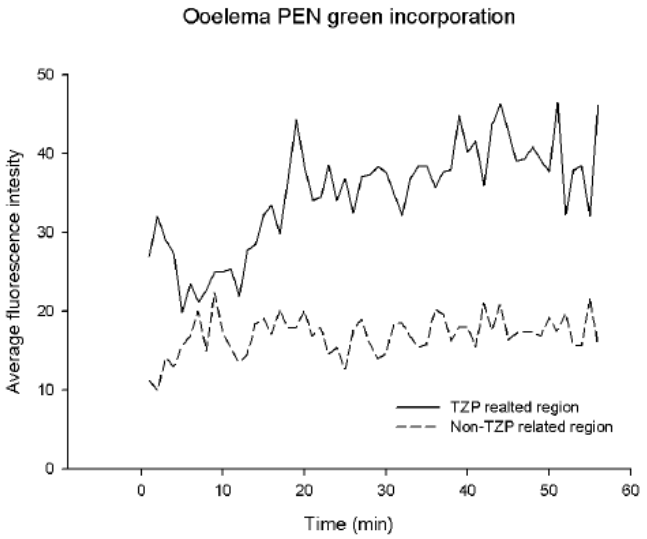
McGinnis and Kinsey, Mol Reprod Dev. 2015 February ; 82(2): 90–102. doi:10.1002/mrd.22446.

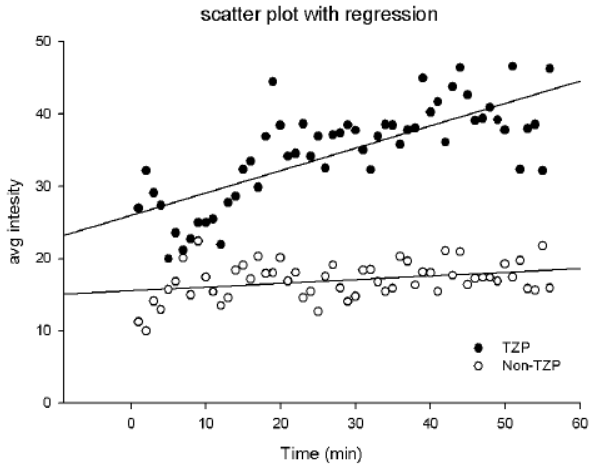




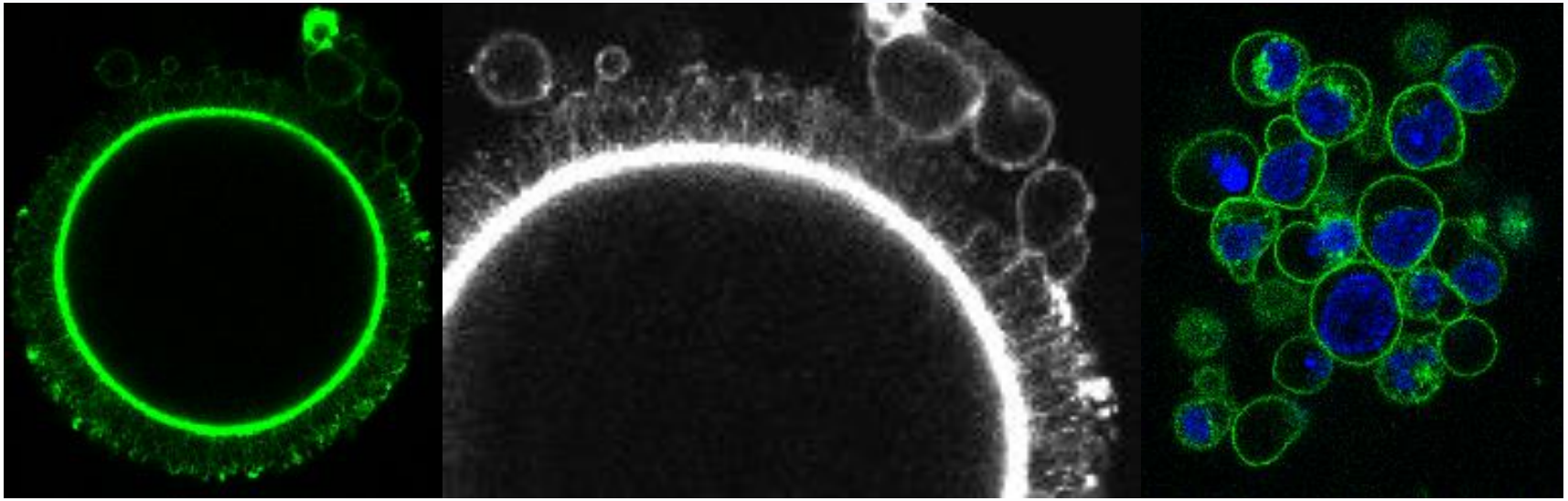
Penn-Green Labeled Bovine Oocyte







Tracking Cholesterol Movement



Penn-Green, 10 min, 37C Bovine Cumulus-Oocyte-Complex

Eppig et al., 2010, De Novo Cholesterol Synthesis occurs in cumulus cells and Incorporation into oocyte requires contact with oolemma

Membrane bound cholesterol diffuses through TZPs (transzonal projections)

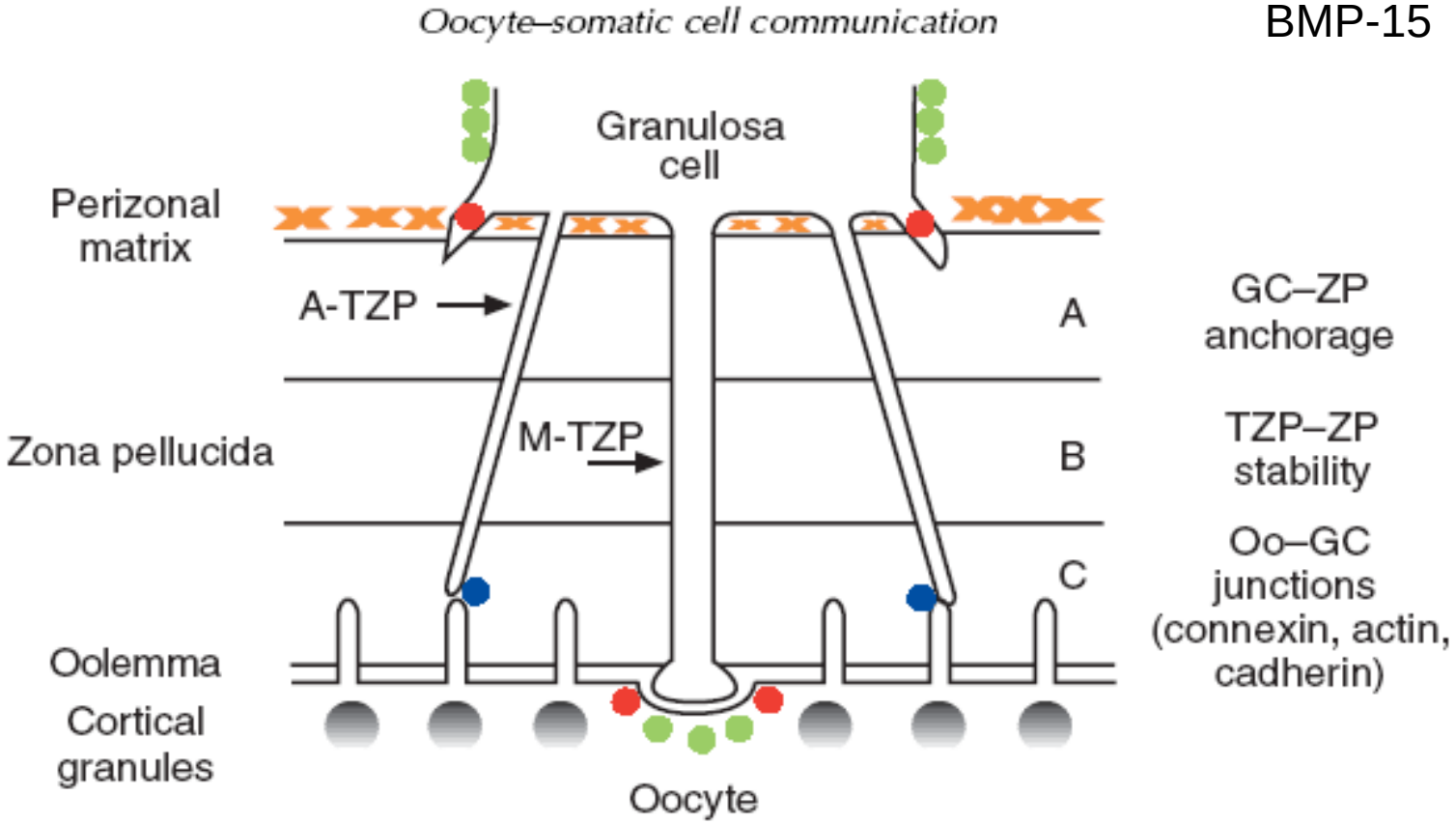
Adjusting Communication Needs-Remodelling The Interface

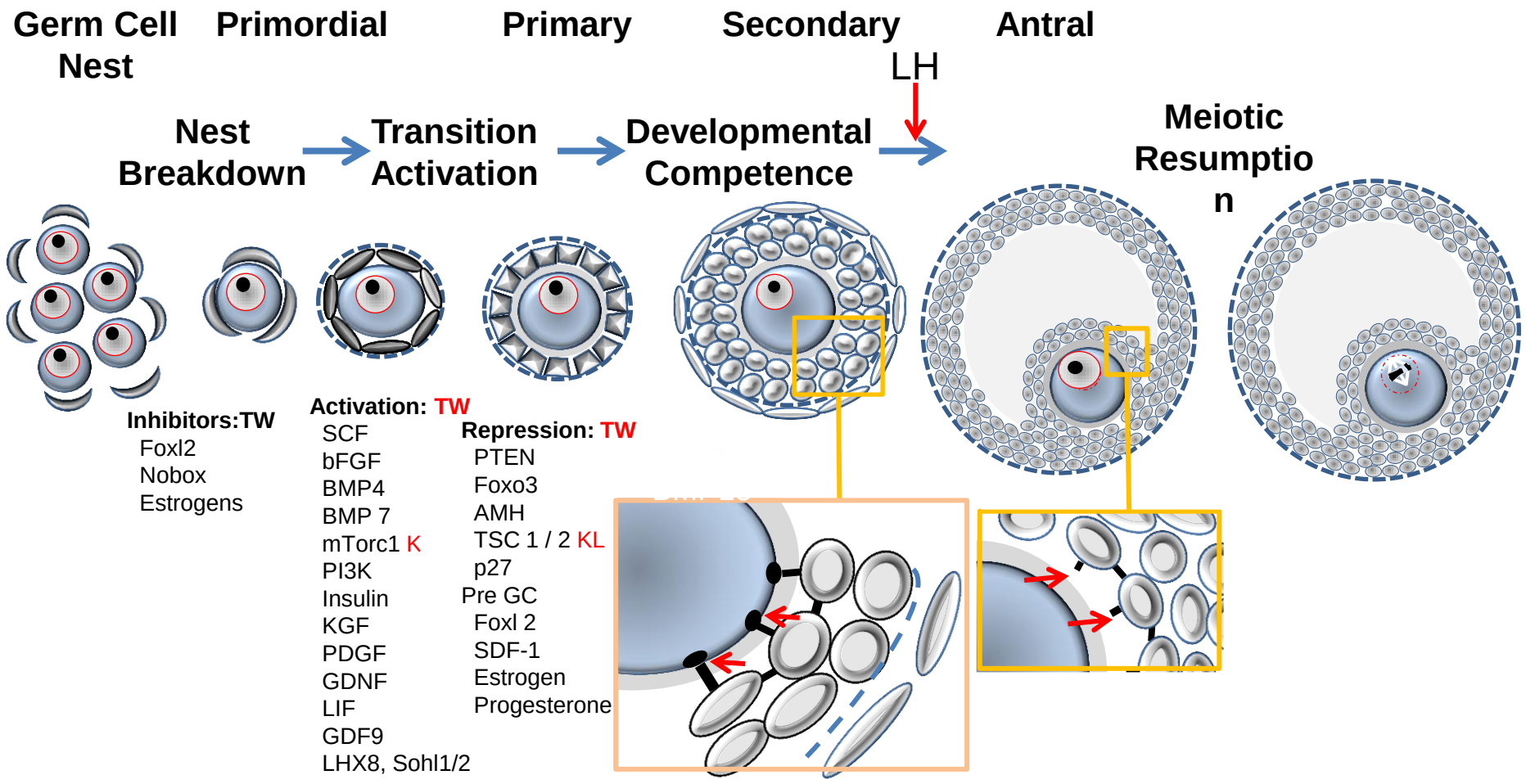
Gap junction

ATP
GSH
Sterols
Pyruvate
cAMP

Paracrine

Kit Ligand
GDF9
BMP-15





TW: Woodruff, 2009; K Liu, 2013; Matzuk LI, 2013;

The signals for follicle activation

RESEARCH ARTICLE

Control of Oocyte Reawakening by Kit

Hatice Duygu Saatcioglu[☯], **Ileana Cuevas**[☯], **Diego H. Castrillon***

Department of Pathology and Cecil H. and Ida Green Center for Reproductive Biology Sciences, UT Southwestern Medical Center, Dallas, Texas, United States of America

☯ These authors contributed equally to this work.
* diego.castrillon@utsouthwestern.edu

Citation: Saatcioglu HD, Cuevas I, Castrillon DH (2016) Control of Oocyte Reawakening by Kit. PLoS Genet 12(8): e1006215. doi:10.1371/journal.pgen.1006215

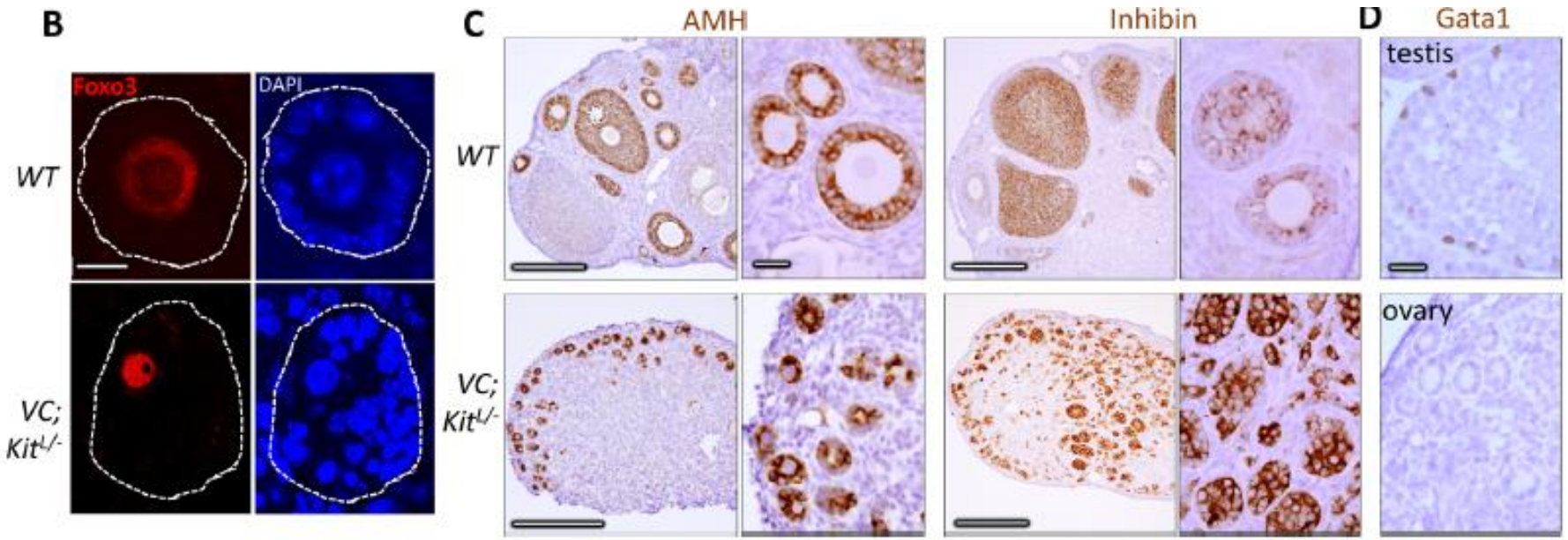
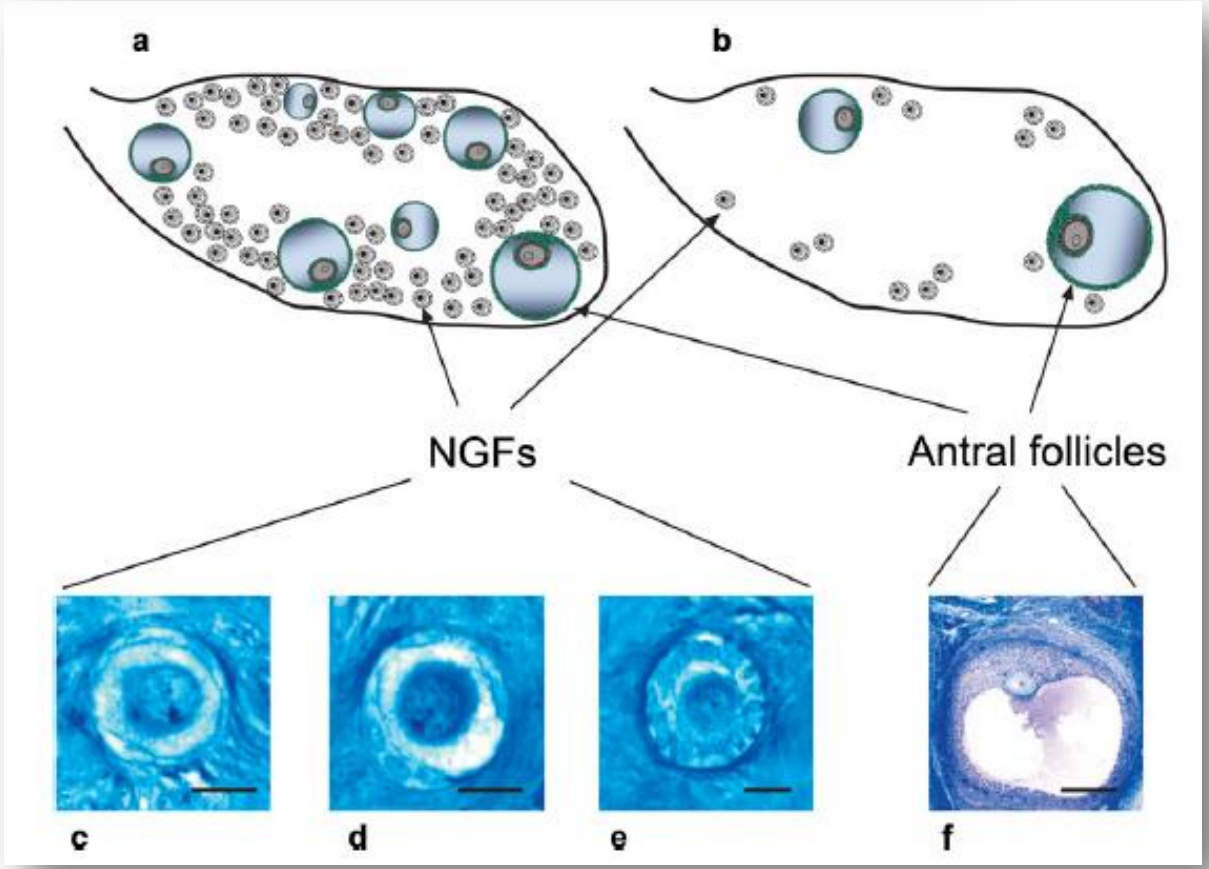


Fig 7. Marker studies of Kit-deficient oocytes are consistent with specific defect in oocyte reawakening via Foxo3. (A) Immunohistochemistry for

Human Reproduction Vol.23, No.3 pp. 699–708, 2008 doi:10.1093/humrep/dem408
Advance Access publication on January 12, 2008

A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause

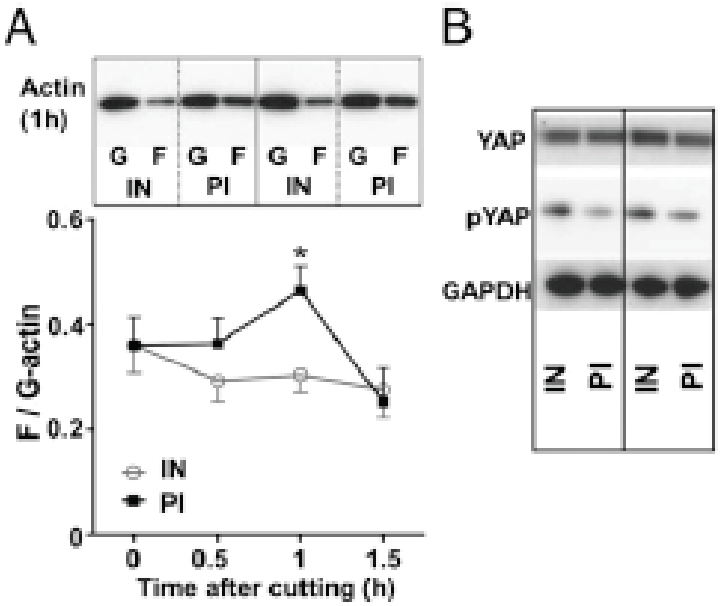
Karl R. Hansen[1,5], Nicholas S. Knowlton[2], Angela C. Thyer[3], Jay S. Charleston[4], Michael R. Soules[3] and Nancy A. Klein[3]

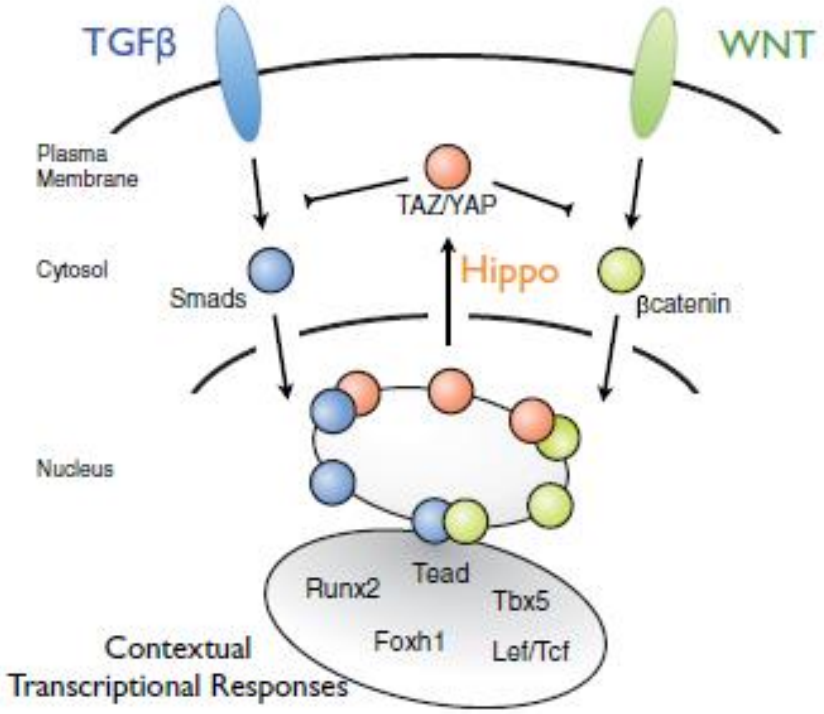


Controlling follicle activation

Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment

Kazuhiro Kawamura[a,b,1,2], Yuan Cheng[c,1], Nao Suzuki[a], Masashi Deguchi[c], Yorino Sato[a,c], Seido Takae[a,c], Chi-hong Ho[c], Nanami Kawamura[b,d], Midori Tamura[a], Shu Hashimoto[e], Yodo Sugishita[a], Yoshiharu Morimoto[e], Yoshihiko Hosoi[f], Nobuhito Yoshioka[a], Bunpei Ishizuka[d,2], and Aaron J. Hsueh[c,2]





Kawamura K, et al. Proc Natl Acad Sci USA 2013;110:17474–9.

Force Generation through the Actin Cytoskeleton

Androgens regulate ovarian follicular development by increasing follicle stimulating hormone receptor and *microRNA-125b* expression

Aritro Sen[a,b,1], Hen Prizant[a], Allison Light[a], Anindita Biswas[a], Emily Hayes[a], Ho-Joon Lee[b], David Barad[b], Norbert Gleicher[b], and Stephen R. Hammes[a,1]

Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment

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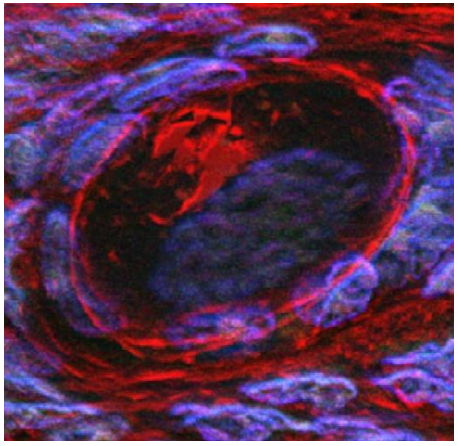
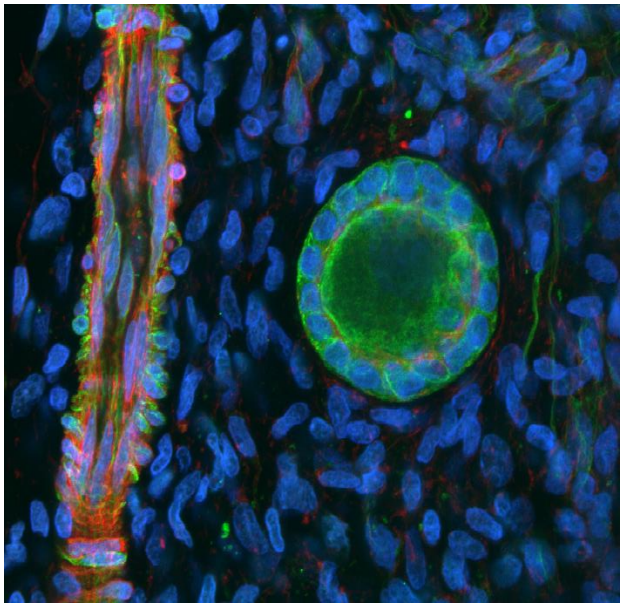


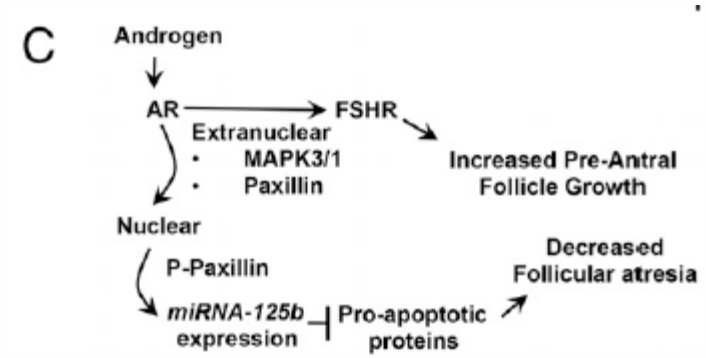


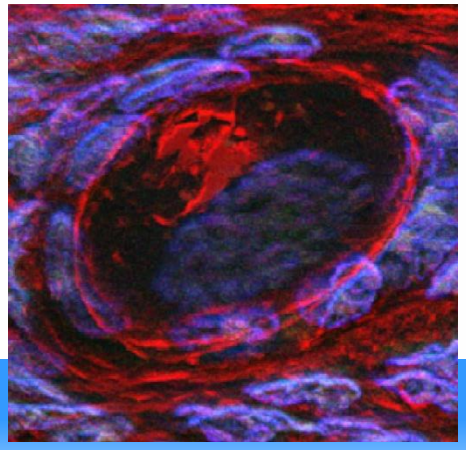
Actin binding protein mobilization during follicle activation

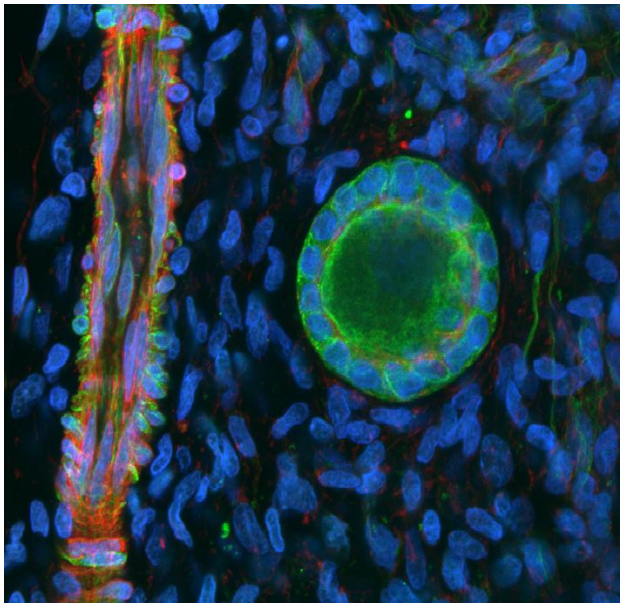
For example……

Androgens regulate ovarian follicular development by increasing follicle stimulating hormone receptor and *microRNA-125b* expression

Aritro Sen[a,b,1], Hen Prizant[a], Allison Light[a], Anindita Biswas[a], Emily Hayes[a], Ho-Joon Lee[b], David Barad[b], Norbert Gleicher[b], and Stephen R. Hammes[a,1]

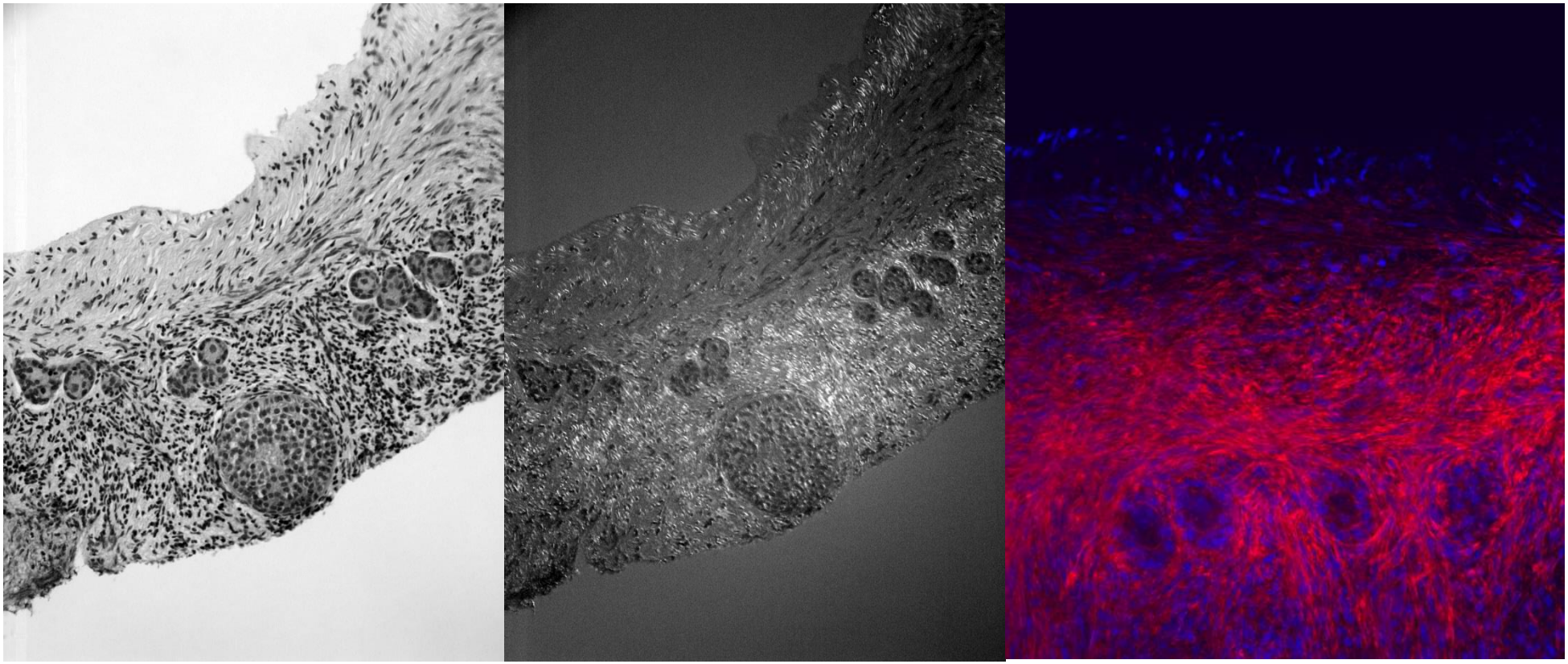






Actin binding protein mobilization during follicle activation

During follicle growth-the stroma



New ways to study, and think about, the ovarian reserve

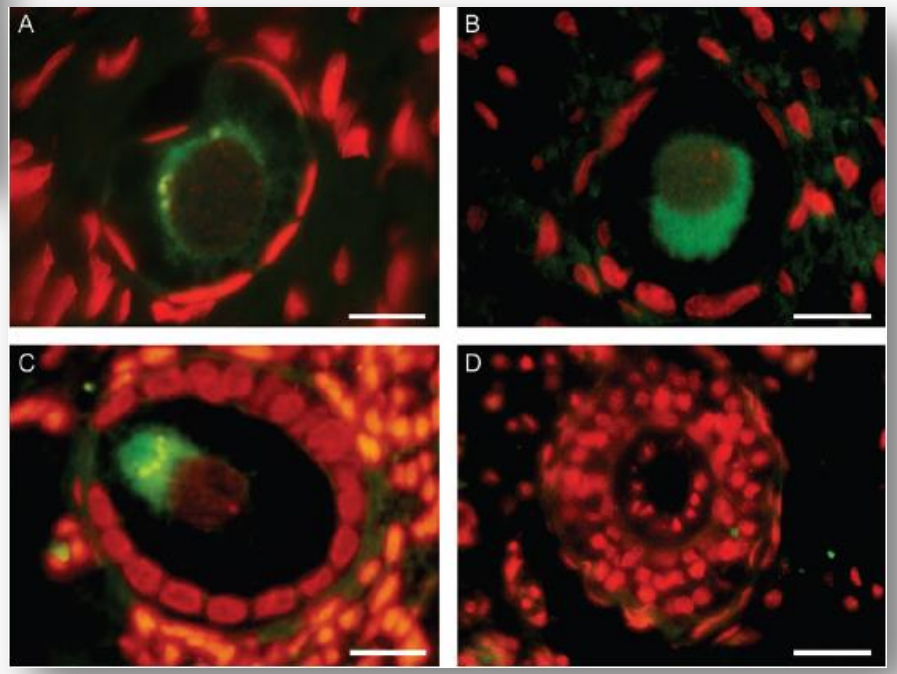
Human Reproduction, Vol.28, No.3 pp. 698–706, 2013
Advanced Access publication on January 12, 2013 doi:10.1093/humrep/des453

human reproduction

ORIGINAL ARTICLE *Reproductive biology*

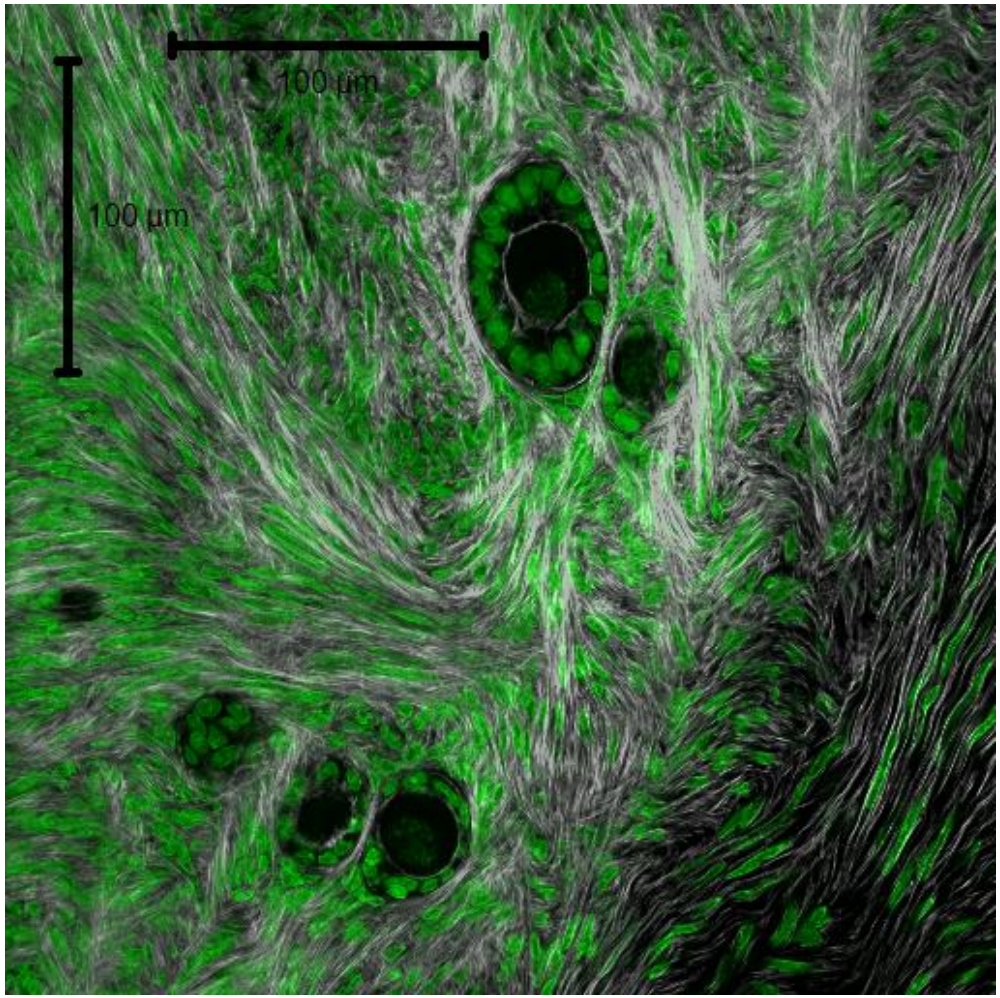
The infant and pubertal human ovary: Balbiani's body-associated *VASA* expression, immunohistochemical detection of apoptosis-related BCL2 and BAX proteins, and DNA fragmentation

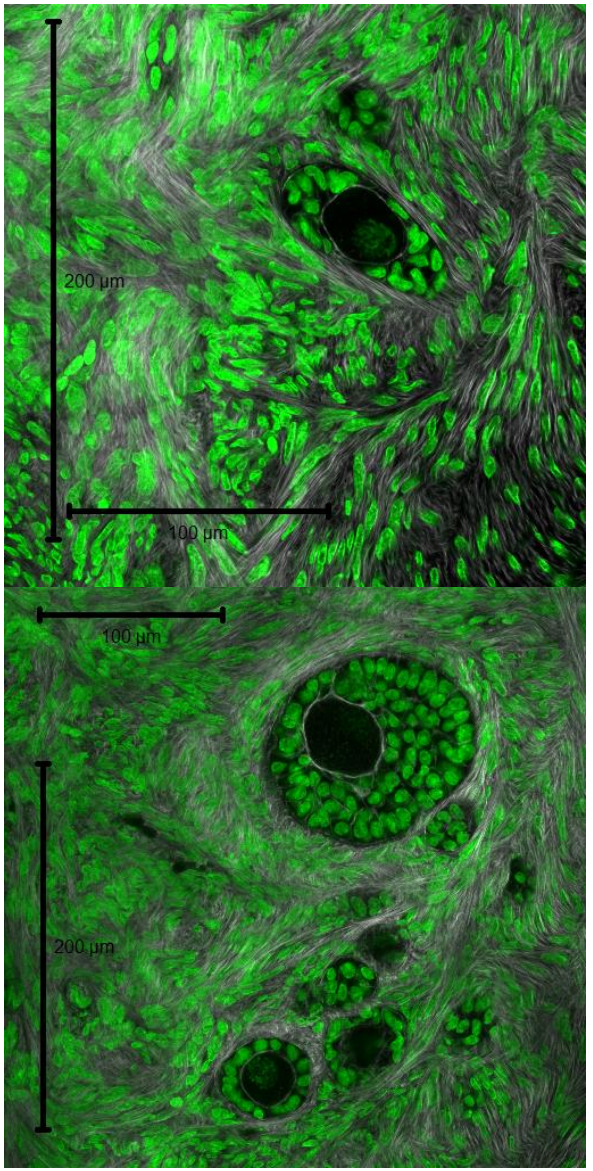
María Itatí Albamonte[1], Mirta S. Albamonte[1], Inés Stella[1], Luis Zuccardi[2], and Alfredo D. Vitullo[1,*]



Infant **Pubertal**

Contractile Stroma





Human Reproduction, Vol.29, No.1 pp. 97–106, 2014
Advanced Access publication on October 17, 2013 doi:10.1093/humrep/det388

human reproduction

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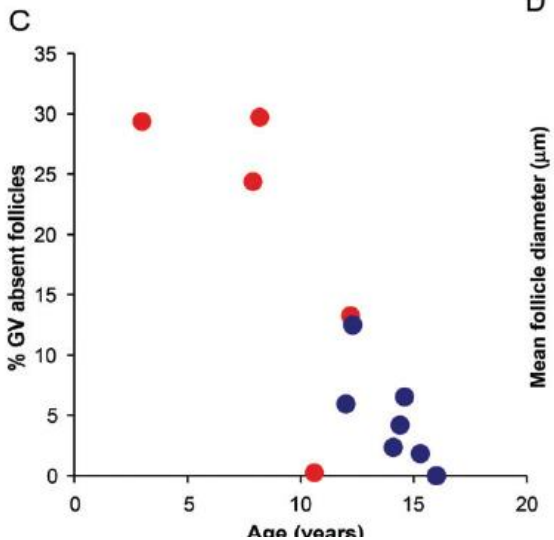
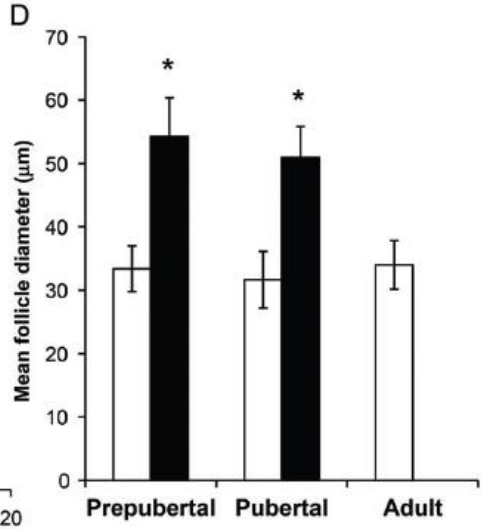
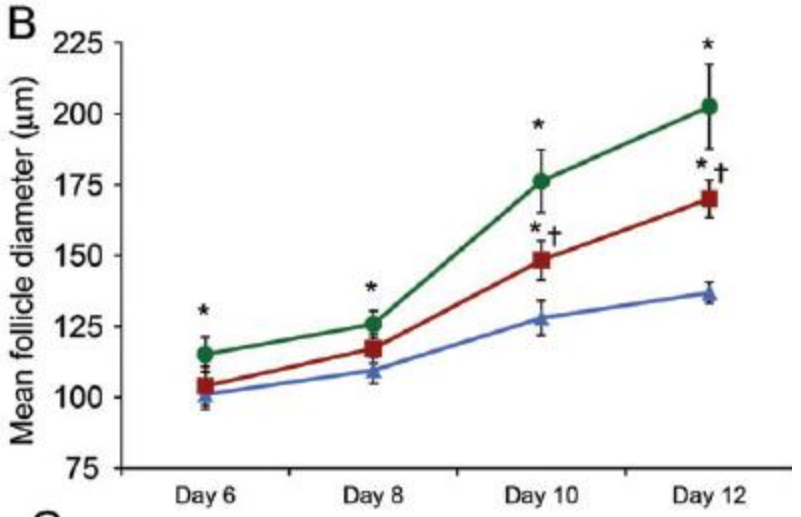
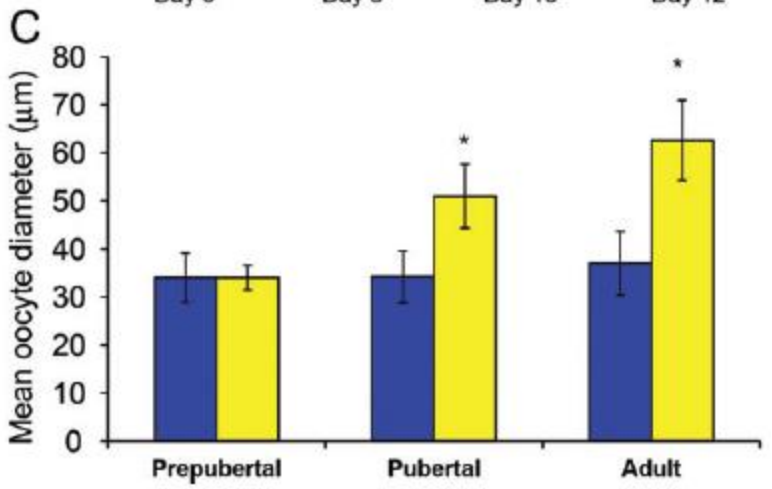






The immature human ovary shows loss of abnormal follicles and increasing follicle developmental competence through childhood and adolescence

R.A. Anderson[1,*], M. McLaughlin[2], W.H.B. Wallace[3], D.F. Albertini[4], and E.E. Telfer[2]



Clinical Implications

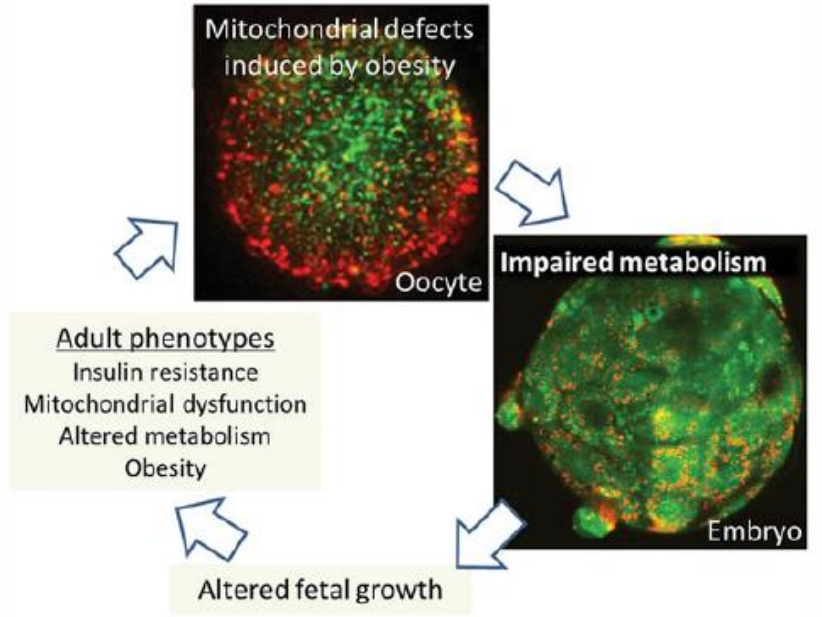
Molecular Human Reproduction, Vol.21, No.1 pp. 23–30, 2015
Advanced Access publication on June 12, 2014 doi:10.1093/molehr/gau042

molecular human reproduction

NEW RESEARCH HORIZON *Review*

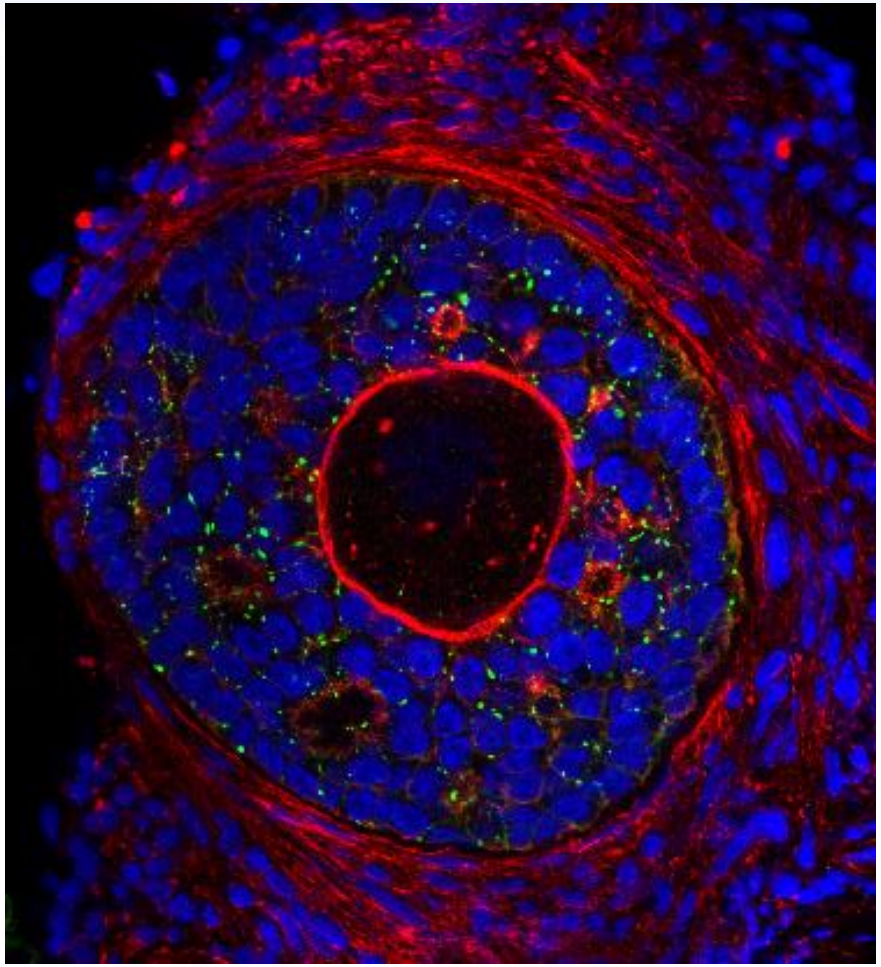
Developmental programming of obesity and insulin resistance: does mitochondrial dysfunction in oocytes play a role?

Nigel Turner[1,*] and Rebecca L. Robker[2]



From Mol Hum Reprod. 2015 Jan;21(1):23-30. Developmental programming of obesity and insulin resistance: does mitochondrial dysfunction in oocytes play a role? Turner N, Robker RL. by permission of Oxford University Press

Dynamic reciprocity-contractile constraints generate force at



Boundary of follicle-the theca as muscle

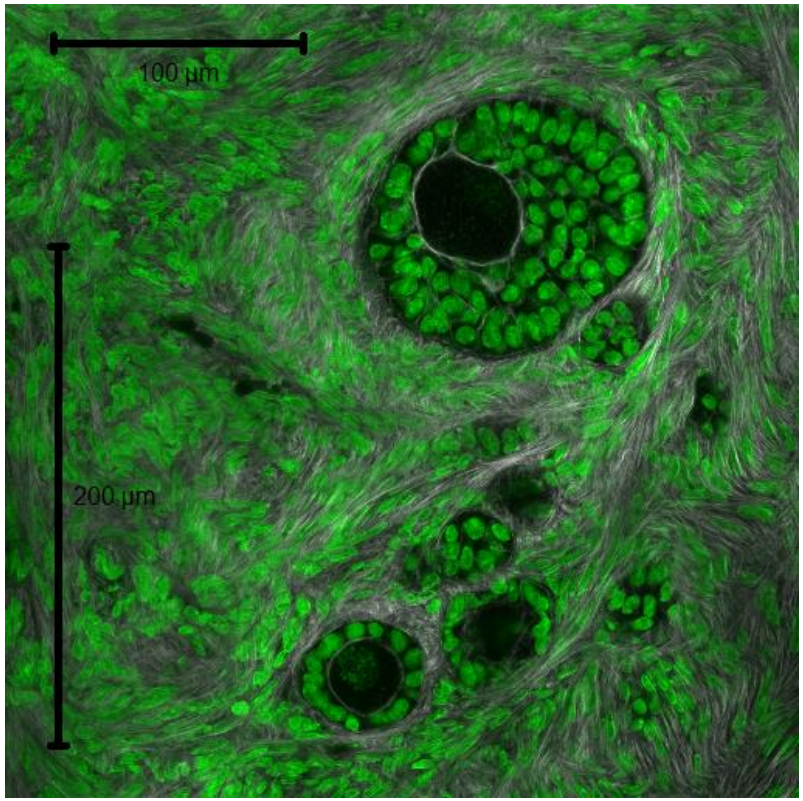
Boundary between oocyte and granulosa

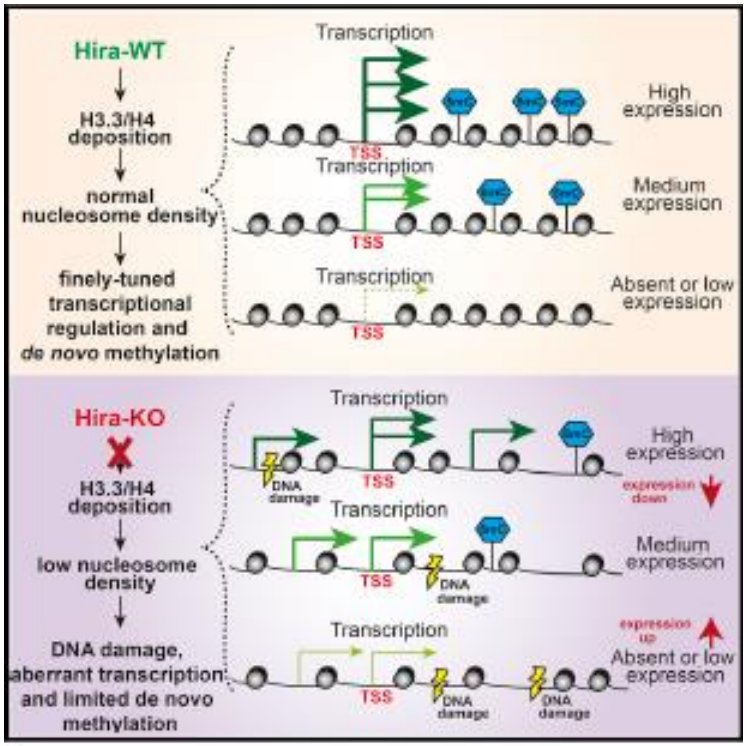
Boundary between granulosa cells

Chromatin Remodelling is Continuous

Molecular Cell

Continuous Histone Replacement by Hira Is Essential for Normal Transcriptional Regulation and De Novo DNA Methylation during Mouse Oogenesis

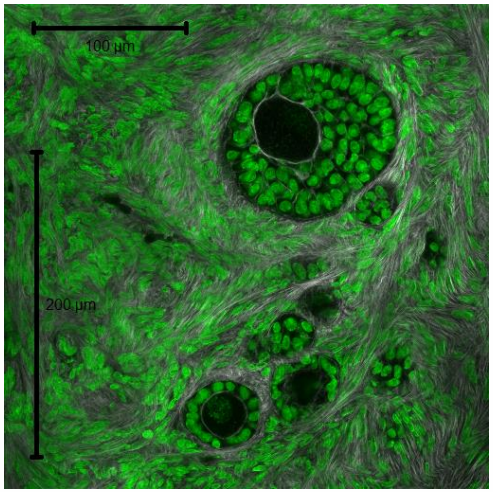


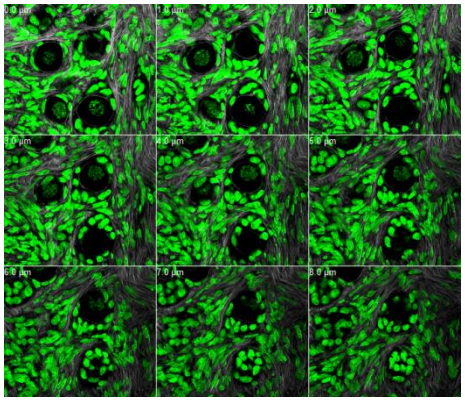


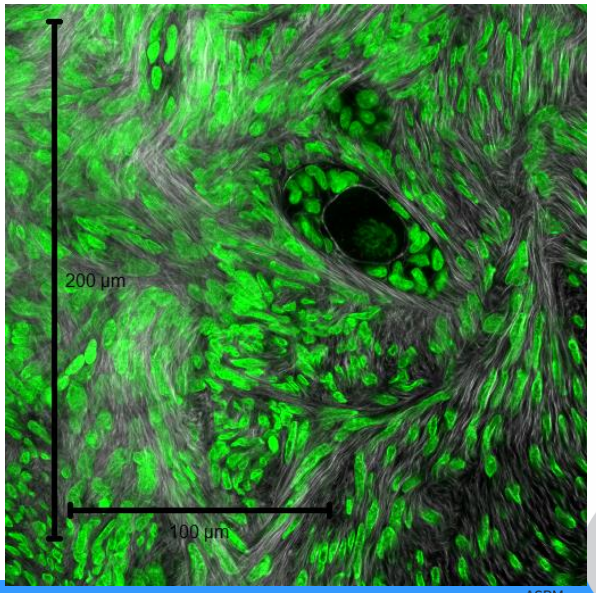
Highlights

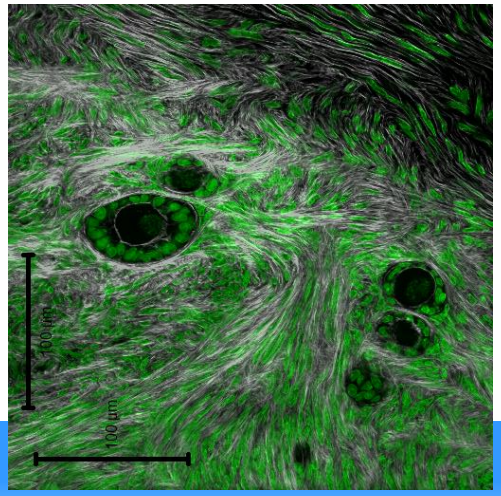
- Histone H3/H4 replacement is continuous and mediated by Hira during mouse oogenesis

Contractile Stroma

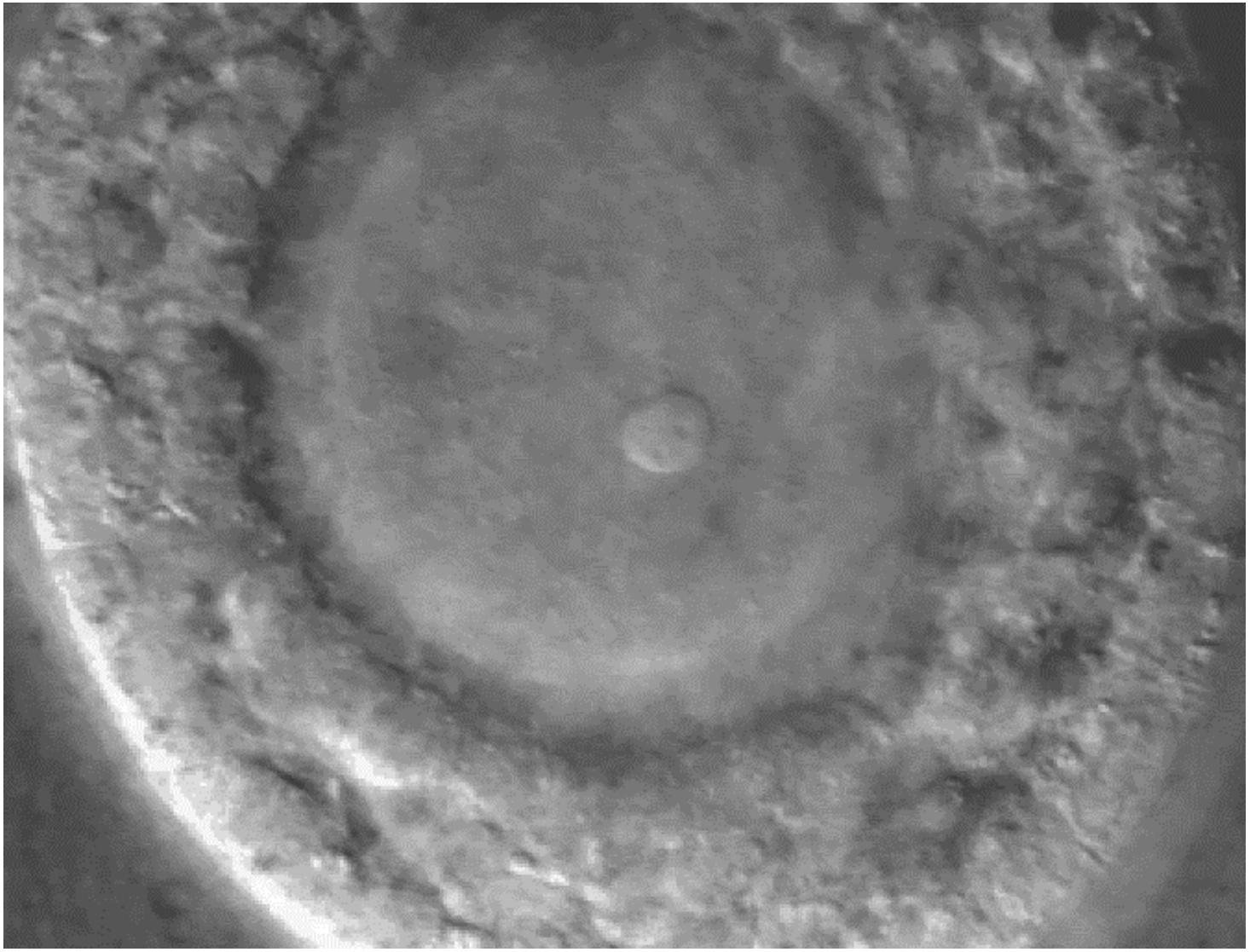








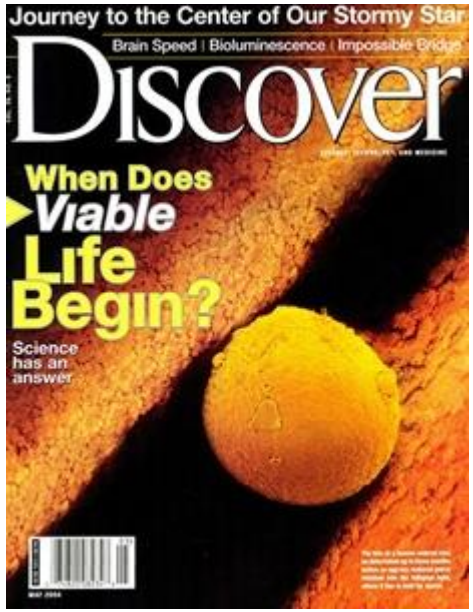
Motility within the follicle

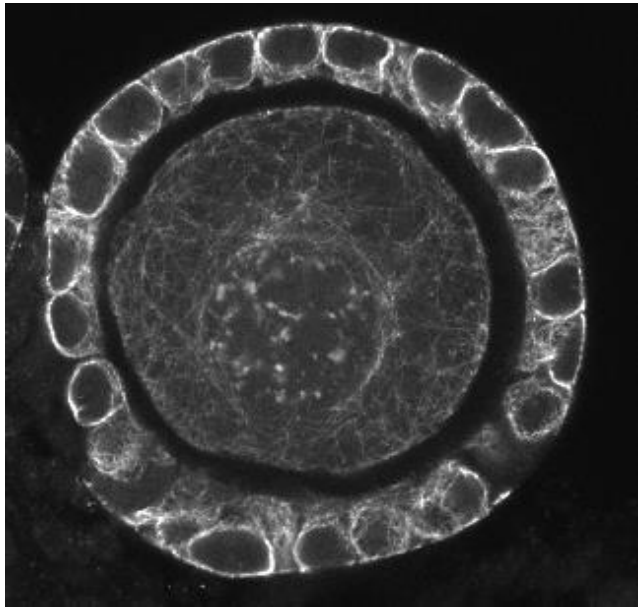


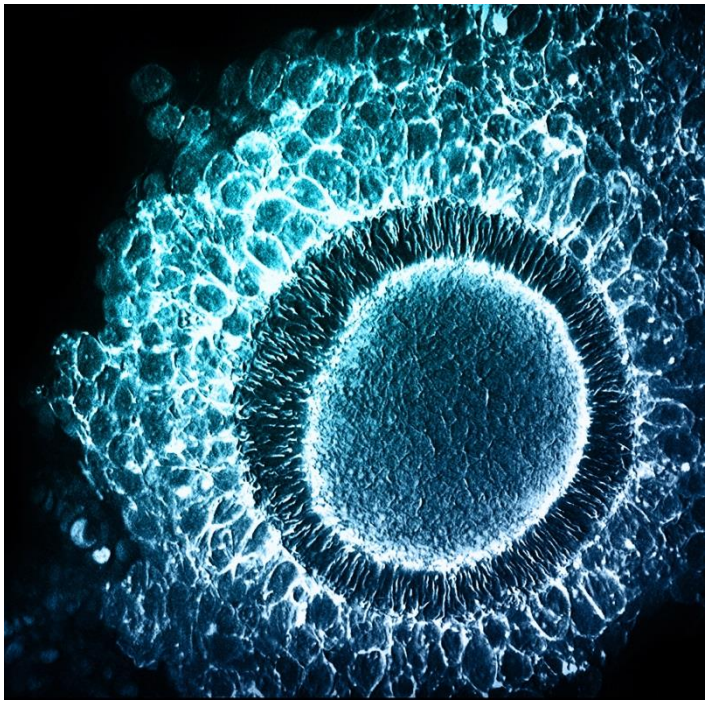
Impact on embryo quality

A Subcortical Maternal Complex Essential for Preimplantation Mouse Embryogenesis

Lei Li,[1,*] Boris Baibakov,[1] and Jurrien Dean[1]
[1]Laboratory of Cellular and Developmental Biology, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA
*Correspondence: lil@mail.nih.gov
DOI 10.1016/j.devcel.2008.07.010







Determinants:embryo-modifying agents

- ***Innate……..***
- Maternal dowry
- Mitochondria
- Cell Junctions
- Ion stores
- Sperm contributions (centrioles, lncRNAs)
- Genomes (nuclear/mitochondrial)
- Imprinting Control System

- ***Acquired……..***
- Maternal Metabolism
- Lifestyle/Diet
- Iatrogenic (COH,Culture,Cryo, Biopsies D3 or D5/6)

A Subcortical Maternal Complex Essential for Preimplantation Mouse Embryogenesis

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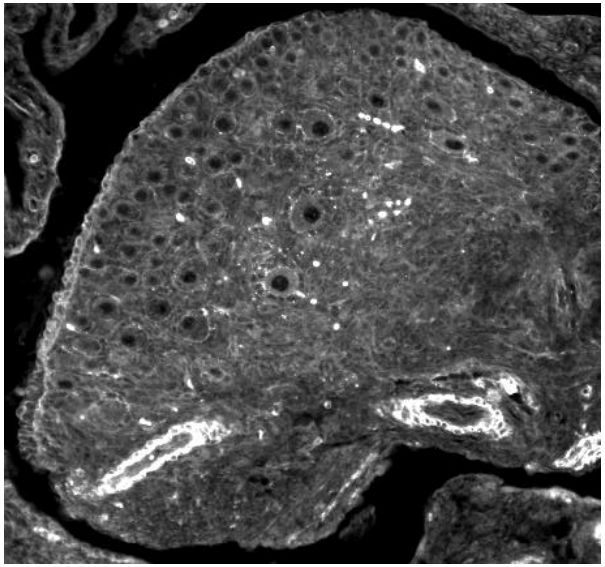
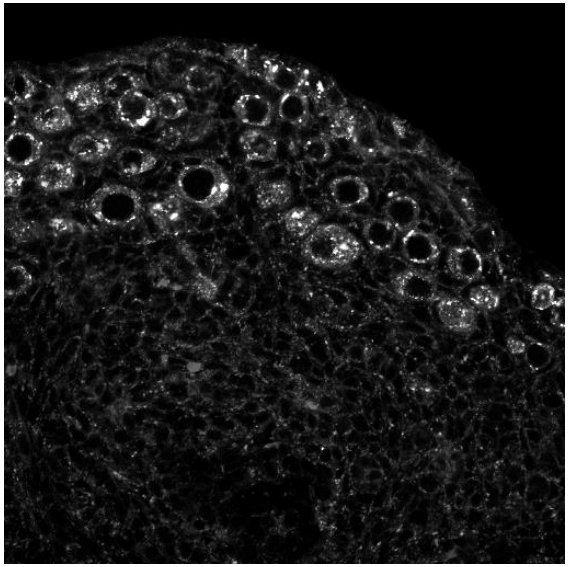
[1]Laboratory of Cellular and Developmental Biology, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA
*Correspondence: lilei@mail.nih.gov
DOI 10.1016/j.devcel.2008.07.010

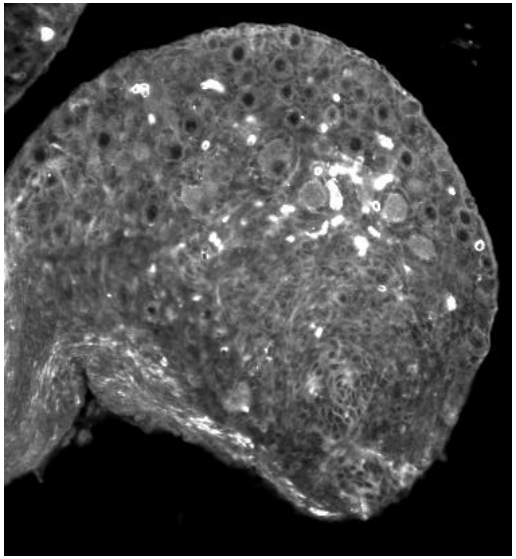
Oogenesis in vitro

Complete *in vitro* generation of fertile oocytes from mouse primordial germ cells

Kanako Morohaku[a], Ren Tanimoto[a], Keisuke Sasaki[a], Ryouka Kawahara-Miki[b], Tomohiro Kono[a], Katsuhiko Hayashi[c,d], Yuji Hirao[e,1], Yayoi Obata[a,1]

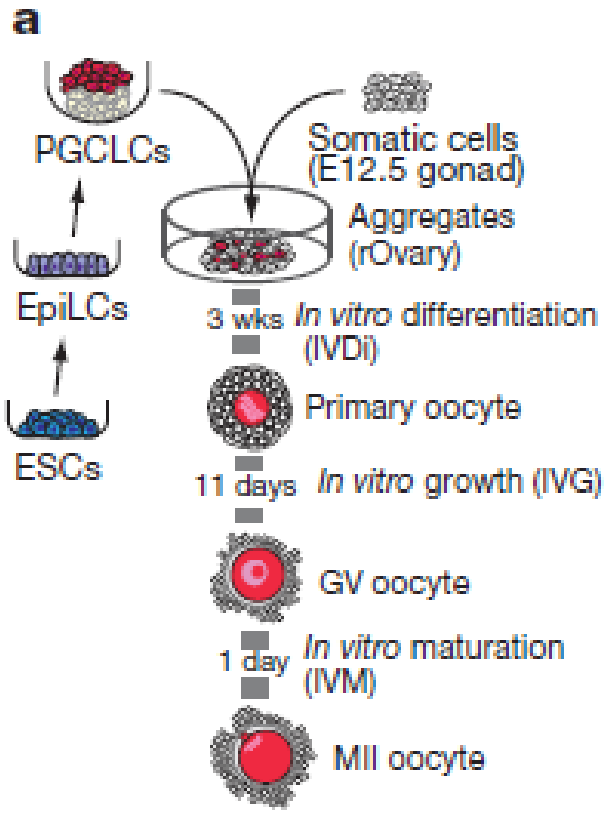






Reconstitution *in vitro* of the entire cycle of the mouse female germ line

Orie Hikabe[1]*, Nobuhiko Hamazaki[1], Go Nagamatsu[1], Yayoi Obata[2], Yuji Hirao[3], Norio Hamada[1,4], So Shimamoto[1], Takuya Imamura[1], Kinichi Nakashima[1], Mitinori Saitou[5,6,7,8] & Katsuhiko Hayashi[1,9]*



At least in the mouse system, there is some degree of autonomy in signaling if the germ somatic pairing is of an equivalent stage of follicle development

Keys were ER antagonism and modest physical Changes to system (PVP)

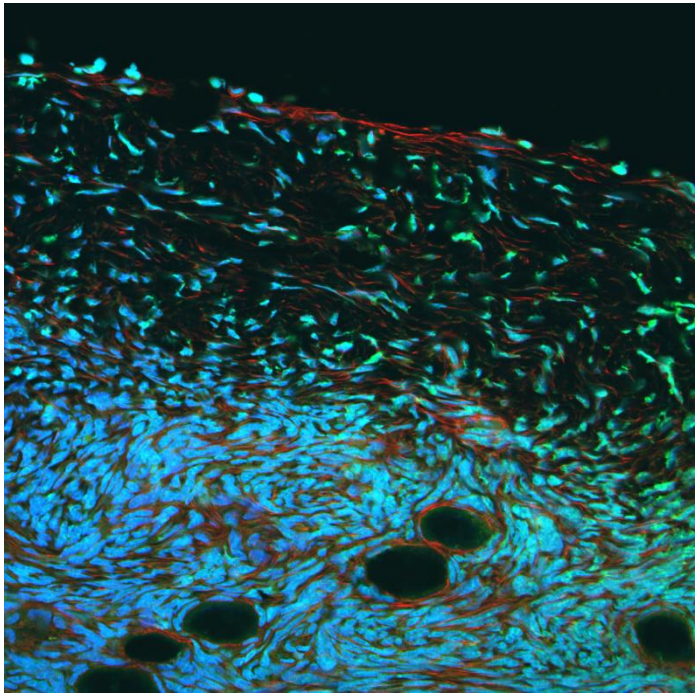
And delayed introduction of FSH/LH

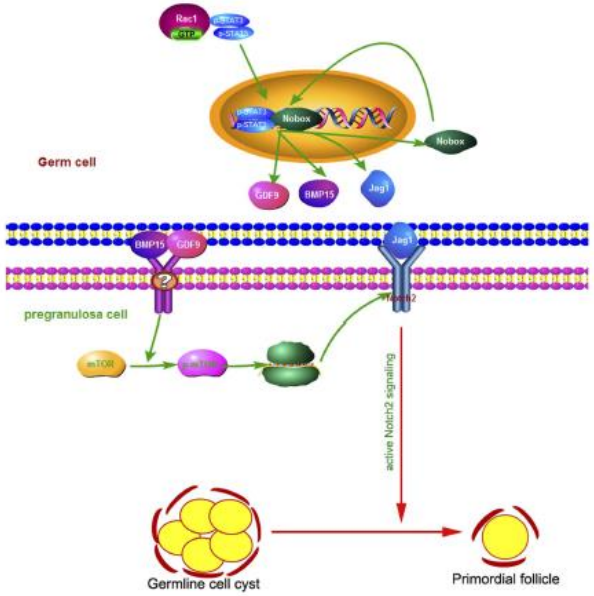
Suggests paracrine players act on cue?

Multiple paracrine pathways

Rac1 modulates the formation of primordial follicles by facilitating STAT3-directed Jagged1, GDF9 and BMP15 transcription in mice

Lihua Zhao*, Xinhua Du*, Kun Huang, Tuo Zhang, Zhen Teng, Wanbao Niu, Chao Wang & Guoliang Xia





Breaching the physical constraints imposed signal transduction from the basement membrane, through the actin cytoskeleton, to the oocyte nucleus

Merci!

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University of Milano

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