Oocyte polarity: a sign of oocyte quality?

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Presentation outline

1. Oocyte quality: impact, acquisition and approaches
2. Oocyte polarity: a feature of oocyte maturation
3. Oocyte polarity: a reflection of oocyte quality?
4. Future challenges
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Oocyte Quality: a major determinant of Embryo Quality and Reproductive Success

% Transfers that resulted in Live Births for ART Cycles using Fresh Embryos, from Own and Donor Eggs, by Woman’s Age

Oocyte Quality is an oocyte attribute of major relevance in the efficiency of the reproductive process, which strongly decreases with age!

During Oogenesis the oocyte acquires critical functionalities for initial Development

- Oocyte growth phase:
  - Oocyte diameter increases
  - High transcriptional and translational activity
  - Accumulation of RNA / proteins
  - Building of new structures (zona pellucida, cortical granules)

- Oocyte maturation phase:
  - Nuclear / cytoplasmic events with resumption of meiosis and arrest at MII shortly before ovulation
  - Organelle redistribution
  - Cell polarity and asymmetric division

Maturation

Growth
Successful oogenesis and folliculogenesis require complex paracrine connectivity

Oocyte Quality can be viewed as the acquisition of a series of competences during oogenesis

1. Meiotic
   a. competence to reach the metaphase II arrest
   b. competence to allow correct meiotic chromosome segregation

2. Activation
   competence to fuse with sperm, finish meiosis, block polyspermy, and form pronuclei

3. Developmental
   competence to trigger and support embryonic development

Oocyte Quality is a very complex attribute!

- decreases strongly with age!
- depends on the female clinical situation!
- varies within the same egg cohort!
- can be affected by culture conditions!

However, we infer Oocyte Quality a posteriori

Can we learn to predict Oocyte Quality?
1. Learn from the oocyte / follicle that produced a viable embryo

Ongoing implantation
Individual culture - follow-up : find markers

Live healthy birth

2. Study and manipulate oogenesis in experimental models

- early stages -


- late stages -

Ovulation, Oocyte pick-up
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Immature oocytes exhibit polarity
Eccentric GV specifies animal pole

“All animal eggs have a polar structure” (Raven, 1961)

Asymmetric organization in oocytes intensifies with maturation
During oocyte maturation, asymmetry in the two divisions of meiosis ensures one big gamete and two small polar bodies.

### Two views on how the first meiotic spindle becomes cortically located

- **The first meiotic spindle starts from a central position and moves towards a cortical location**

### In any case at MI the first meiotic spindle is cortically located, with involvement of the actin microfilament system

#### Diagram of possible mechanisms of actin-dependent spindle translocation.
1. Contraction of anti-parallel actin filaments connecting the cortex to the spindle by bipolar myosin II mini thick filaments.
2. Cargo-like transport of the spindle along actin filaments with barbed ends oriented toward the cortex, with myosin II localized at the spindle pole.
3. Actin polymerization-driven motility from the rear.

The second meiotic spindle seems cortically located from the beginning activation.

**Oocyte polarity** ensures asymmetrical division of cytoplasmic content between the gamete and the polar bodies in oocyte maturation and activation.

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• Oocyte IVM was observed about 50 years before clinical IVF has started.
IVM oocytes exhibit less fertilization and developmental competence than In Vivo matured ones (IVO).

Strategies to find morphological evidence to explain functional differences between IVM and IVO oocytes.

Area/Volume and Pole Width of MII meiotic spindle increase in IVM oocytes.

IVM > IVO, IVO-N.
Pole width of MII meiotic spindle is higher in non-gonadotropin supplemented IVM (Basal), intermediate in gonadotropin supplemented IVM (Hyped) and lower in IVO oocytes. Spindle Pole Width seems to inversely relate to cytoplasmic centrosome number. Number of cytoplasmic MTOCs decreases in non-gonadotropin supplemented IVM. 


Spindle anchoring at the cortex is partially lost during non-gonadotropin supplemented IVM

Retention of MTOCs and oocyte volume is partially lost during non-gonadotropin supplemented IVM

Morphological signs of oocyte polarity and asymmetric division partially lost in mouse non-gonadotropin supplemented IVM

Working Model
Morphological signs of oocyte polarity and asymmetric division partially lost in mouse non-gonadotropin supplemented IVM

Are these morphological differences correlated with the described decrease in quality in IVM oocytes?

Fertilization rate: presence of 2-PN 6h post-IVF

Evidence of fertilization competence loss!

Blastomere numbers at the blastocyst stage

Evidence of developmental competence loss!
Oocyte polarity

1. Is an important feature of oocyte maturation
2. May reflect oocyte quality, since partial loss of morphological signs of polarity correlate with a decrease in fertilization and developmental competences

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To assess if manipulating polarity in mouse oocyte maturation will reflect upon the fertilization and developmental competence levels
Symmetric first meiotic division can be forced by compressing cortical ooplasm near the MI meiotic spindle.

Two mini MII oocytes originate instead of one MII oocyte and one PB.

Each of the two mini MII oocytes can be fertilized and cleave, until one quimera morula compacts and one blastocyst is formed.

This means that even a very small oocyte, in the limit of being a very large first polar body, is able to be fertilized and initiate embryo development.
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Asymmetry of the first meiotic division does not seem essential for embryo development.

Asymmetry of the second meiotic division, however, was maintained.

Remaining questions:

- was there a decrease in fertilization and developmental rates?
- had zygotes been separated to develop independently, what would these rates be?
- what would happen in case we prevent asymmetry of second meiotic division?

To assess if manipulating polarity in mouse oocyte maturation will reflect upon the fertilization and developmental competence levels

To probe other models besides the mouse

In humans detectable signs of oocyte polarity loss do not seem to correlate with decrease in fertilization and developmental competence

Existing non-invasive approaches may not be enough to accurately discriminate different categories of oocytes

Pre- and post-ovulatory ageing associate with a loss of oocyte polarity
**Open questions:**

- what are the consequences of preventing asymmetry in the second meiotic division?
- should we focus our attention on the second polar body, besides the spindle?
- will more powerful non-invasive morphological approaches allow us to better associate oocyte polarity and quality?
- can we identify specific human situations or treatments where assessing oocyte polarity will reveal more important than in others?

**New working model**

- Oocyte quality is a relevant property acquired during oogenesis that has remained elusive to predictive studies.
- Oocyte polarity is an important feature of oocyte maturation.
- Oocyte polarity may reflect oocyte quality, since partial loss of morphological signs of polarity correlate with a decrease in fertilization and developmental competences.
- Future studies are needed to assess the value of oocyte polarity as a sign of oocyte quality.

**Take-home messages**

1. Oocyte quality is a relevant property acquired during oogenesis that has remained elusive to predictive studies.
2. Oocyte polarity is an important feature of oocyte maturation.
3. Oocyte polarity may reflect oocyte quality, since partial loss of morphological signs of polarity correlate with a decrease in fertilization and developmental competences.
4. Future studies are needed to assess the value of oocyte polarity as a sign of oocyte quality.

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Probably yes, but it is still not clear how ...

Thank You!