

# *Histology & Embryology Periodical*

*Department of Histology and Embryology  
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Editorial board:

MUDr. Klára Matoušková, MPH  
klara.matouskova@lf3.cuni.cz  
MUDr. Lucie Hubičková-Heringová, Ph.D.  
MUDr. Eva Maňáková, Ph.D.

Full text available at:

<http://www.lf3.cuni.cz/en/departments/histologie/hep/>

## **What's up...**

April brings along the next-to-the last course of the module "Cellular Basis of Medicine", course 5 "Development of cells and tissues". The course comprises of two parts; in the first part we shall unearth the understanding to the regular developmental mechanisms which are the cells put through. The latter part of the course shall awaken you to all the pathological processes in cells and tissues, to the causes & effects, and the mechanisms of such processes.

The syllabus for the first part of the course 5 includes following;

### **Lectures on Histology & Embryology**

**Case presentation: Thalidomid**

**Basic morphogenetic processes**

**Cell Signaling in Development**

**Blastogenesis**

**Notogenesis & Neurulation:** formation of the notochord and neural tube (week 3 and 4)

**Organogenetic period;** all internal organs in humans initiate development within the 3<sup>rd</sup> to 8<sup>th</sup> weeks

**Histogenesis;** the formation and origin of tissues from undifferentiated cells

**Developmental toxicology & pharmacology in pregnancy;** birth defects from external causes with focus on medicinal drugs

**Aging:** cell level mechanisms of aging & morphology of aging cells

### **Practices on Histology and Embryology**

#### **Extraembryonic organs & placenta**

**Early embryonic development:** practical demonstration of a research on early chick embryos!

**A clinical detective story!** A case presentation of an exposition to a certain medicine taken during pregnancy.

### **Lectures and Practices on Genetics**

#### **Regeneration & Reparation**

#### **Genetic determination**

Reproductive genetics of humans & pre-implantation genetics

## **Reminder...**

The upcoming course "Development of cells and tissues" is particularly challenging as it brings tons of new terms. Do not underestimate your understanding to the peculiar expressions and definitions! Have your books at hand, get a pencil and a piece of paper, draw with colors, make flashcards and memos to comprehend the variety of processes and mechanisms! Be creative and think it through! The sooner you familiarize yourself with the new terminology the better!

## Morphogenesis upon Implantation:

### The “Black Box” of Development

#### Cracks Open<sup>1</sup>

Before reading the following article recall what you know about the first week of development and then, study carefully this picture:

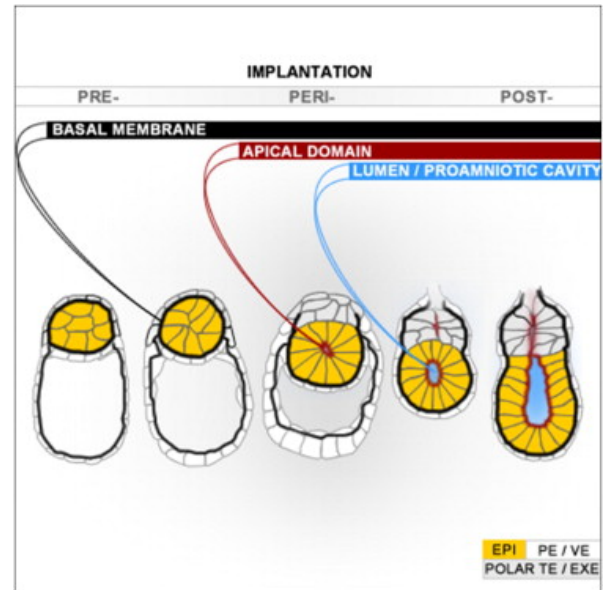
This model of early morphogenesis summarizes some of the key findings by the scientific team of **Dr. Bedzhov** and **Dr Zernicka-Goetz** from the Gurdon Institute (remember **Dr. John B. Gurdon** from the last Periodical?), University of Cambridge, UK.<sup>2</sup>

The first two drawings, a rendering of the pre-implantation development, should be familiar to you. Yes, this is a **blastocyst** and you recognize the cells of epiblast (yellow), hypoblast, trophoblast and the basal membrane (black line).

**Q:** Are you familiar with the term of “hatching”? What process is a prerequisite for “hatching” of a blastocyst? And how the blastocyst responds to its’ hatching?

**A:** During “hatching” a blastocyst emerges from zona pellucida. In the span of approximately two days while the blastocyst floats in the uterine secretion, zona pellucida gradually degenerates and disappears. Shedding of the zona pellucida permits the hatched blastocyst to increase rapidly in size.<sup>3</sup>

The third image of the model however, shows something you have hardly seen before; a **rosette-like structure** formed by the cells of epiblast (EPI). Before implantation the epiblast comprises round-shaped cells. As the embryo proceeds through the implantation, these cells of EPI become “wedge shaped, with their thinner parts clustering to give a rosette-like structure”<sup>2</sup>. Such an organization of epiblast was found absolutely crucial in formation of egg-cylinder and thus, in proper embryonic development. The researchers conclude that “the first major morphogenetic step in the transition of the epiblast from pre- to post- implantation stages is its progressive reorganization from a relatively



simple ball to a more complex rosette-like structure that is built of polarized cells”.<sup>2</sup>

As the cells of epiblast rearrange themselves into rosettes, they polarize. While e.g. **aPKC** (atypical protein kinase C marking the apical domain), **F-actin** and **E-cadherin** in implanting embryos localize on the apical site of the wedge-shaped cells, the Golgi apparatus and the nucleus find their position basally. As a consequence of apical concentration of actin the cells of epiblast, now rearranged into rosettes, constrict apically.

Generally speaking, there are two mechanism of formation of a lumen in epithelia; “a **cavitation**, referring a process driven by apoptosis or a hollowing. **Hollowing** results from membrane separation and was confirmed in the research as the process of lumen formation in the embryonic peri-implantation.”<sup>2</sup>

**Q:** What do you think, underlies the polarizing of epiblast? How do the cells know their axis?

**A:** It is trophoblast (sometimes called as extra-embryonic trophoectoderm) that secretes laminins to assemble a basal membrane. The basal membrane then creates a niche for the polarizing cells of epiblast. The proteins of the extracellular matrix provide polarization cues that signal through **integrin receptors** to orient the establishment of basal-apical axis of the cells of epiblast.<sup>2</sup>

As a result of enacting an axis, the cells of epiblast change their shape via apical constriction

countered by apically localized adherent junctions and form a rosette-like structure.<sup>2</sup>

The rosette-like structure of epiblast initiate forming of **egg cylinder**. In the model, formation of an egg cylinder is depicted on the last two images. A small luminal space appears in the center of the rosette. Take a notion that the cells of epiblast and extraembryonic ectoderm are now in direct contact. The basal membrane resembles “a basket in which the basal sites of the epiblast are anchored through integrins.” You see on the last drawing that the lumen of the epiblast cup enlarges and, together with the intermembranous space of the extra-embryonic ectoderm, forms the mature proamniotic cavity. “At this point, the egg cylinder formation is complete.”<sup>2</sup>

Highlights of the research:

- Apoptosis is not essential for the peri-implantation morphogenesis
- Basal membrane proteins create a niche for epiblast
- Polarization and apical constriction reorganize the epiblast into a rosette
- The proamniotic cavity is formed through hollowing mechanism<sup>2</sup>

**“Perplexity is the beginning of knowledge”**

**Khalil Gibran**

**Q:** Can you name the basic morphogenetic processes?

**A:** **Proliferation, migration, association and apoptosis**, to give account of the basic four.

Could the morphogenetic event that transforms the amorphous epiblast into a rosette of polarized cells, so called „**hollowing**“, be the next one?

**What do you remember...**

**.. male genital duct system**

The male genital duct system contains:

- ♥ *tubuli recti*
- ♥ *rete testis*
- ♥ *ductuli efferentes*
- ♥ *ductus epididymidis*
- ♥ *ductus deferens*
- ♥ *ductus ejaculatorius*

**Q:** What type of epithelia lines vas deferens?

**A/Q:** Pseudostratified columnar epithelium/  
Where else in the male reproductive system there is such type of epithelium?

**A:** Epididymis

Mnemonic

**Wolffian (mesonephric) duct derivatives:**

“Gardner’s SEED”

Female:

Gartner’s duct cyst

Male:

Seminal vesicles

Epididymis

Ejaculatory duct

Ductus deference

There are **three layers of smooth muscle** in the vas deferens. There is an inner longitudinal, a middle circular, and an outer longitudinal.

**Q:** What is the surface modification seen on the cells of epididymis?

**A/Q:** Stereocilia. Stereocilia are, simply said, very long, immotile microvilli. Any other location of stereocilia in the human body?

**A:** Of course, the proximal part of the ductus deferens. And.... yes! The hair cells of the inner ear.

The vas deference is the longest part of the excurrent duct system. Ascending along the posterior border of the testis it then enters the abdomen as a component of the spermatic cord (*funiculus spermaticus*).

### Mnemonic

#### **Spermatic Cord**

“Piles Don’t Contribute To A Good Sex Life”

Pampiniform plexus  
Ductus deference  
Cremastery muscle  
Testicular artery  
Artery of the ductus deference  
Genital branch of the *nervus genitofemoralis*  
Sympathetic nerve fibres  
Lymphatic vessels

Mind a slight modification of this mnemonic; a cremastery muscle holds in its *fascia* also a cremastery artery and a vein, and **n. ilioinguinalis** alongside with *n. genitofemoralis* listed above. Also, *funiculus spermaticus* includes ***fascia spermatica interna***.

### **Eponyms**

#### **„Graafian follicle“**

##### **Regnier de Graaf**

In 1641, in the same year René Descartés published his *Meditations on First Philosophy*, amidst cruelties of the Thirty Years’ War, in a small Dutch town of Shoonhoven, little boy named Regnier was born. In the course of his short life, he became one of the most influential scientists of his times while some of his discoveries contributed greatly to the modern

understanding of the female mammalian reproductive system.

De Graaf became a student at the University of Utrecht and later at Leiden University, only to earn his medical degree from the University of Angers, France. And when the British took over Nieuw Amsterdam and renamed it New York, de Graaf couldn’t care less. That year, in 1664, he finished and released his first known publication, a paper on pancreatic secretions, saliva, and bile.

„Although de Graaf did some dissection and research on the male reproductive organs, his treatise on the subject was largely a summation of existing knowledge. His discovery of the ovarian structure that would later be labeled Graafian follicle however meant a significant step forward in the field of reproductive biology.

Interestingly, all de Graaf’s work took place more than 150 years before Karl Ernst von Baer first identified the ovum in 1827. Though the egg had not technically been discovered at the time de Graaf was doing his research, reproductive anatomists and biologists of the time were conceptually aware of it. De Graaf deduced its existence from his knowledge of ectopic pregnancies. “<sup>4</sup>

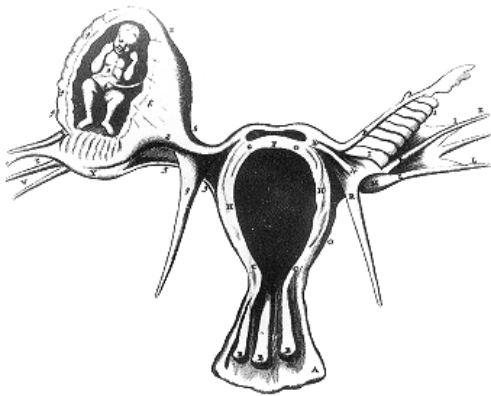
In is amazing what de Graaf was able to see and deduct without the help of real microscopic equipment. Speaking of microscopes, they say that „a few months before his death de Graaf recommended, as a correspondent of the Royal Society in London, that attention be paid to **Antonie van Leeuwenhoek** and his work on the improvement of the microscope”.<sup>5</sup> What a providence!

Let’s list several more accomplishments of de Graaf; he was “one of the first anatomists to adopt the term “ovary”. His illustrations, very specific, detailed, and anatomically correct remain particularly useful. Also, by comparing the pre- and post-mating ovaries he described the morphological changes that accompany the ovary’s functioning, and he was the first to discover the glandular origin of *corpus luteum*, an important milestone in the history of

endocrinology”<sup>4</sup>! If he concerned himself with the triumphs of the Dutch fleet he might have been pleased to see that only a few days before his expire the Dutch recaptured New York from the English (and he would never see that the English regained the city, and much more, only a year later). Regnier de Graaf died August 17, 1673.

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<sup>5</sup> Wikipedia Contributors, 2014. Regnier de Graaf. Wikipedia, The Free Encyclopedia. Date of last revision 29 January 2014 at 5:11 [cit. 18 March 2014]. Available from:  
[http://en.wikipedia.org/w/index.php?title=Regnier\\_de\\_Graaf&oldid=592913082](http://en.wikipedia.org/w/index.php?title=Regnier_de_Graaf&oldid=592913082)



Picture: Ectopic pregnancy by Regnier de Graaf<sup>5</sup>

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<sup>1</sup> The Gurdon Institute. (2014) Rewriting the text books: Scientists crack open 'black box' of development [Press release] Available from:  
[http://www.eurekalert.org/pub\\_releases/2014-02/uoc-rtt021314.php](http://www.eurekalert.org/pub_releases/2014-02/uoc-rtt021314.php)

<sup>2</sup> Bedzhov Ivan, Zernicka-Goetz Magdalena. Self-Organizing Properties of Mouse Pluripotent Cells Initiate Morphogenesis upon Implantation. *Cell* **156** (5),1032-1044. Available from:  
[http://www.cell.com/abstract/S0092-8674\(14\)00075-0](http://www.cell.com/abstract/S0092-8674(14)00075-0)

<sup>3</sup> Ross, Michael H. a Pawlina, Wojciech. *Histology: a text and atlas: with correlated cell and molecular biology*. 6.ed. Baltimor, MD USA: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2011. ISBN: 978-0-7817-7200-6.

<sup>4</sup> Dupont Ellen, M.. Regnier de Graaf. In: *The Embryo Project Encyclopedia* [online]. Arizona State University, School of Live Sciences. 25.9.2013 [cit. 8.4.2014]. ISSN: 1940-503. Available from:  
<http://embryo.asu.edu/handle/10776/1746>