Histology & Embryology Periodical

Department of Histology and Embryology

Third Faculty of Medicine, Charles University in Prague

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In this issue:

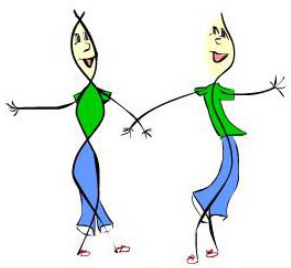
What´s up…

February 23 – the summer semester begins with the fourth course of the Module „Cellular Basis of Medicine" called „**Genetic information and its´ expression**".

Histology and embryology play just a small role in this course; a lecture on **gametology** in the week 3 and practices on **male and female reproductive systems** in the fourth and fifth week respectively. In this issue of the Periodical you will read an article about the importance of the nucleoid acids, the carriers of genetic information, during early development.

Course 5 „**Development of cells and tissues**" is, on the other hand, where histology and embryology will dominate. We will start the course in the week 6 with a lecture on the classic and tragic case that made the public well aware of the field of teratology (the study of birth defects).

Prescriptions of **thalidomide** to pregnant women from its commercial introduction in 1957 until it was banned in 1961 caused several thousands of children born with malformations of their limbs all over the world (except for the USA and Eastern Europe where the drugs common on the other side of the "Iron Curtain" were not available).



If you are interested in the history and present of thalidomide, you are welcome to join us on **March 31**, at **11,30am** in the Syllaba lecture hall!

For „prep" reading on the subject in the general media, see an article in the Newsweek from 2012:

http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655,
or a BBC article from November 2011:
http://www.bbc.com/news/magazine-15536544.

Fig.1 A bronze statue by a sculptor Bonifatius Stirnberg unveiled in August 2012 by Harald Stock, then chief executive of Grünenthal at Stolberg, Germany. The ceremony was the first apology for the thousands of lives affected by the drug Grünenthal Company put to the market as "safe for pregnant and nursing women". The Thalidomide foundation however did not accept the apology [1]

The second lecture of the course on development will present the very foundation of embryology; **basic morphogenetic processes**! There is absolutely no exception from the knowledge of the processes therefore, book the date; **April 1, 11,30am** at the Syllaba lecture hall.

In the April 2014 issue of the Periodical was published an article „Morphogenesis during implantation":
http://www.lf3.cuni.cz/opencms/export/sites/www.lf3.cuni.cz/en/departments/histologie/hep/HEP-2014-02-en-2014-04-09.pdf

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[1] [1]BBC News Health. *Thalidomide insulting apology, campaigners say*.[online]. Last update 1.9.2012. [Quoted 8.2.2015]. Available from: http://www.bbc.com/news/health-19448046

Reminders...

In the summer semester, too you will work closely with your **workbooks.** There is going to be one difference from the winter semester. Beginning with the very next practical, drawings and sketching of tissues, cells and other formation observed in a microscope will **no longer** to be **optional**!

Besides lectures and practicals, there will be two exciting **seminars** on embryology and teratology; in our lab we will demonstrate early development on real chic embryos (!), and there will be a detective story in which you will try to find out about the risks on an unborn baby of a pregnant woman using a certain pharmaceutical.

MicroRNA: Connection between Stem and Cancer Cells

(Lin28 - let-7 - DIS3l2)

Ribonucleotide acids (RNA) seem to live in the shadow of the more famous DNA. The two differ in three major aspects; RNA uses the pyrimidine base **uracil** instead of thymidine, RNA's backbone is made of a **ribose** sugar and phosphates, and RNA exists as a **single strand** vs the paired double-strand of DNA.

MessengerRNA holds information for protein synthesis, tRNA delivers amino acids to the ribosomes, yet rRNA provides a connection between the amino acids to make proteins (a process known as translation). But heck, that would not be quite enough for one of the basic ingredient of life!

There are more than the three basic RNAs. In eukaryotic cells there are a number of non-coding RNAs of great importance and abundance. And the tiny, 22 nucleotide microRNA, is one of them….

MicroRNA and its´ involvement in regulating gene expression has been thoroughly studied ever since the first miRNA was discovered at the Massachusetts Institute of Technology in 1993.[2] Victor Ambros, a postdoc of Prof. Robert Horvitz, identified, among others, a gene for a protein they called **Lin28**. They discovered abundance of Lin28 protein in embryonic cells, less later in development and none in well differentiated cells.

*Ribonucleotide acids (RNA) can be considered from several perspectives. For one, we can sort them out as coding RNA, which is, of course, the **mRNA,** and non-coding RNAs (ncRNA).*

*The best known ncRNA are **tRNA** and ribosomal **rRNA**. However, besides the two, there is a long line of less known ncRNA. In eukaryotic cells there is, e.g. a group of **regulatory RNA**. Regulatory RNAs include microRNA (**miRNA**) and small interfering RNA (**siRNA**) regulating gene expression, or the long noncodingRNA (**lncRNA**) that is involved in regulation of gene transcription, and in epigenetic regulation.*

Want to hear the entire story? Well, you need to meet the rest of the crew; **let-7**, the second discovered miRNA, protein **DIS3l2** (aka the exoribonuclease that later decomposes pre-let7) and several **enzymes**. Ready?

At the beginning there was the protein Lin28, and seven years later came into light microRNA called let-7[3]. It turned out that Lin28 and let-7 have quite the opposite effect in a cell; while **let-7 turns off genes that promote cell division, Lin28 activates cell division** but their relationship was unclear. It was in 2008 that Richard Gregory and George Daley collaborated to show at the molecular level that Lin28 represses let-7 maturation. "To present the pluripotency of the cell you have to down regulate let-7, and the way the cell does that is by making Lin28"[4]. And a year later, Dr. Gregory and his team found enzymes called a **TUTase** (3´terminal uridylyl transferase). Lin28 orders TUTase to add a **polyUridyl** tale on pre-let7 and that simple act inhibits maturation of let-7 in stem cells and in some cancer cells.[5] Wonder how?

DIS3l2 comes to the stage in 2013! DiS3l2 represents the missing player to complete the story. It is an enzyme that truly loves uridyl! DIS3l2 likes uridyl so much that as soon as it makes contact along the string of 'U', it reads the string to confirm it is what he wants, and then letter by letter begins to break it down until the entire let-7 is gone. [6,7,8].

Do you like icing on a cake? Here you are; investigator Leemor Joshua-Tor at Cold Spring Harbor Laboratories in New York, USA identified the

[2] Lee, R., C., Feinbaum, R.,L., Ambros, V. *The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14*. The Cell, 1993**. 75 (5**)., p843–854.

[3] Reinhart, B.,J., Slack, F.,J., Basson, M., Pasquinelli, A.,E., Bettinger, J.,C., Rougvie, A.,E., Horvitz, H.,R., Ruvkun, G. *The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans*. Nature, 2000. 403(672) pp901-6.

[4] Vishawatan, S.R., Daley, G.Q., Gregory, R.I. *Selective blockade of microRNA processing by Lin28*. Science, 2008. **320** (5872) pp. 97-100

[5] Hagan, J.P., Piskounova, E., Gregory, R., I. Lin28 recruits the TUTase Zcchc11 to inhibit let-7 maturation in mouse embryonic stem cells.
Natural Structural & Molecular Biology. 2009.16(10) pp 1021-5.

[6] Gallouzi, I.,E., Wilusz, J. *A DIStinctively novel exoribonuclease that really likes U*.
The EMBO Journal, 2013. **32** (13). pp.1799-801

[7] Chang, H.,M., Triboulet, R., Thornton, J.,E., Gregory, R.,I. *. A role for the Perlman syndrome exonuclease Dis3l2 in the Lin28-let-7 pathway*. Nature. 2013. **497**(7448):244-8.

[8] Ustianenko, D. et al. *Mammalian DIS3l2 exoribonuclease T´targets the uridylated precursor of let-7 miRNAs*. RNA Journal, 2013. **19.** pp. 1632-1638.

structure of Dis3l2 using **x-ray crystallography**. It looks like a funnel and a molecule of let-7 fits just perfectly! [9]

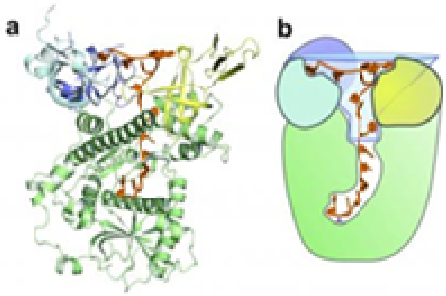

Fig2. a/x-ray crystallography of Dis3l2 (green) and pre-let7 (orange). b/a scheme picture of the same, see the polyU tale inside the funnel-like shape of Dis3l2.[9]

It is a simple story after all; a cell synthetizes a protein Lin28 which employs two enzymes TUT4 and TUT7 to add a short string of uridine bases to precursor of miRNA let-7. Those "U" are read by nuclease Dis3l2 and in its' funnel-like cavity chews it all up. There is no one in the cell to tame cell division which is quite useful early in development however, at the end of embryonic period or even in adulthood, uncontrolled cell division has serious consequences.

The findings therefore help to explain the connection between cancer and embryonic development, says Daley. "**There is a yin and yang between the Lin28 RNA binding protein and its main target, the let-7 microRNA"**, he explains. "**This yin-yang is carefully orchestrated during organismal and tissue development and [is] dysregulated in cancer formation**"[10]

Perlman syndrome

Perlman syndrome is a rare, autosomal recessive disorder present at birth, characterized with one common feature: everything is ***too big****.*

Symptoms include: ***macrocephaly, macrosomia, visceromegaly*** *but also* ***dysmorphic facial features****,* ***polyhydramnios*** *(excess of amniotic fluid in the amniotic sac). The prognosis is very poor, most neonates die early, those who survive have an increased risk of serious kidney cancer.*

Perlman syndrome is localized on the ***chromosome 2****, and it's been known that there is a link between the syndrome and* ***Dis3l2.*** *However what exactly, on a molecular level, was happening, it had been an enigma, just until recently.*

A human gene for Dis3l2 is mutated e.g. in Perlman syndrome and Dr. Gregory presumes that it is "unlikely that this enzyme exists solely to degrade the precursor to let-7" as there are many other molecules with polyU tails [10]. The story told therefore will likely be continued....

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Have you read an interesting article?

Did you have a pressing question during a practical or a lectures but no time or opportunity to ask?

Did you find your sketched picture of a tissue or similar really well done, worth sharing?

Do you even feel to write a short article on an appropriate topic to be published?

Your inquiries, ideas, written or sketched contributions are always welcome!
Please, send an email on ***klara.matouskova@lf3.cuni.cz*** ***or drop it off at the secretariat of the Department of Histology and Embryology!***

[9] Faehnle, C., R., Walleshauser, J., Joshua-Tor, L. *Mechanism of Dis3l2 substrate recognition in the Lin-28-let-7 pathway*. Nature, 2014. 514 (7521). pp 252-6.

[10] Taylor. A.P. *The Protein at the end of the Tunnel*. HHMI bulletin. Winter ´15. **28** (1).

Endocrine disruptors II: Atrazine

Atrazine is a synthetic product used as an herbicide. It was invented in the 1950' in a lab of the Swiss company Geigy and since its introduction to the market it was a popular and widely used pesticide in agriculture, forestry, and controlling weeds along rights-off-way. In low concentrations atrazine works as a selective herbicide inhibiting photosynthesis, while in high concentration becomes a total herbicide.

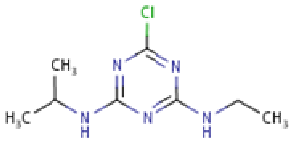

Fig3. Triazine chemical structure of atrazine.

There are several ways of **exposure** to atrazine; the most common way for farmers and other users is inhalation of the herbicide fumes and it can be consumed with food treated with the herbicide however, the most common way of exposure to the general public is **contaminated drinking water**. Atrazine is considered "slightly toxic", and it does not accumulate in organisms. However the growing body of evidence indicates that atrazine is a suspect carcinogen and endocrine disruptor.

> *Endocrine disruptor is a compound, either natural or synthetic, which alters the hormonal system or homeostatic system of an organism.*

The European Union banned use of atrazine after a 12 year trial in 2004. It turned out that the herbicide caused long-term contamination of groundwater. However many European countries banned atrazine long before, e.g. Italy and Germany as early as in 1991. On the other hand, atrazine has been imported and used in the USA, Canada, Mexico, Venezuela, Australia, Thailand, Japan and South Africa[11]. Atrazine in the USA is the second most used pesticide. There is about 76milion pounds of atrazine released into the environment in the USA only.[12] USA uses **22%** of the world estimate pesticide use, the latest data of the EPA (U.S. Environmental Protection Agency) shows **1.1 billion pounds** of pesticides used in 2007[13]. In 1947, when the US population was about a half (144 million[14]) of what it is today, the production of synthetic pesticides was about ten times smaller (124.259.000 pounds)[15].

In 1970 two companies from Basel, Switzerland, J. R. Geigy ltd and CIBA, merged, and in 1996 merged again with Sandoz to form **Novartis**.

In 2000 two pharma-ceutical companies Novartis and Astra-Zeneca merged their agricultural division to form a new company **Syngenta**.

Syngenta is the sole producer and importer of atrazine.

Source: Syngenta [online]. Available from: http://www.syngenta.com/global/corporate/en/about-syngenta/Pages/company-history.aspx

[11] Syngenta. *Herbicides – Gesaprim ®AATREX ®*. [online]. [Citated 3.2.2015] Available from: http://www.syngenta.com/global/corporate/en/products-and-innovation/product-brands/crop-protection/herbicides/Pages/gesaprim-aatrex.aspx

[12] EPA. *Pesticide News Story: EPA Releases Report Containing Latest Estimates of Pesticide Use in the United States.* [online].Last updated 17.2.2011. [Citated 9.2.2015]. Available from: http://epa.gov/oppfead1/cb/csb_page/updates/2011/sales-usage06-07.html

[13] EPA. Pesticides market estimate: Usage 2006-2007.[online].[Cited 9.2.2015]. Available from: http://www.epa.gov/opp00001/pestsales/07pestsales/usage2007.htm

[14] US census bureau

[15] Carson, R., L. *Silent Spring* 1962. First Marine Book, ed. 2002.

After several decades of use, testing in both 2003 and 2004, showed atrazine measurable in over **90**% of samples taken from drinking water systems over the USA[16].

> *The most hormonally sensitive tissues are organs of reproduction therefore endocrine disruptors' most common effected tissue are testes, breasts or prostate.*

One of the scientists who has studied the molecule of atrazine for many years is biologist **Tyrone Hayes** from University of California, Berkley. Prof. Hayes performed and published studies suggesting a teratogenic effect of atrazine on the male individuals of the frog *Xenopus laevis*. He found out that exposure of the male frog to very low concentrations of atrazine (30times lower than the U.S. limit for atrazine in drinking water which is 0.003mg/L[17]) were "chemically castrated and as adults entirely feminized". Atrazine increases aromatase expression therefore influences reproductive organs during development and causes low sperm count in men exposed in adulthood[18].

"I'm not saying it's safe for humans. I'm not saying it's unsafe for humans. All I'm saying is that it makes hermaphrodites of frogs." Tyron Hayes

In 1999 The U.S. Geological Survey's National Water-Quality assessment study provided a national-scale analysis of the occurrence and concentration of pesticides in streams and groundwater. I found that 61% of stream waters in agricultural and urban areas are contaminated with pesticides, and that 90% of the shallow ground water samples were contaminated with one or more pesticides. [19].

The highest concentrations were found in May and June. Does the annual peak correlates with greater risks to pregnancies conceived in those months? **Paul Winchester**, a professor of pediatrics at the Indiana University school of Medicine in 2009 carried a study to test a hypothesis that if pesticides

> *In case of targeting the subpopulation, endocrine disruptor shows an effect as a teratogen. Similarly like for adult tissues, the most common birth defects are those of organs of reproductive systems.*

can affect prenatal development there will be more birth defect in babies conceived during the annual peak of pesticides in drinking water. Indeed, the study found a significant association between the season of elevated agrochemicals and birth defects such as spina bifida, cleft lip or palate, heart malformation and other circulatory and respiratory anomalies, musculoskeletal anomalies, Down syndrome. [20]

There are however studies that seem to disprove the results of the studies mentioned above and present different conclusions. For example, an impact journal Birth Defect Research published in its' issue from June 2014 as many as four papers regarding atrazine in development. Three out of the four papers were however directly funded by the manufacturer of atrazine. The papers conclude "no effect on any

[16] Wu, M., Quirindongo, M., Sass, J., Wetzler, A. *Still poisoning the Well*. The Nature resource Defence Council (NDRC), 2010. Available from: http://www.nrdc.org/health/atrazine/files/atrazine10.pdf

[17] Agency for toxic substances and disease registry (ATSDR).2003. Toxicological Profile for Atrazine. Atlanta, GA: US Department of health and human services, Public health services.

[18] WuQuian, F., et al. Atrazine-Induced aromataze expression is SF-1 dependent:Implication for Endocrinne disruption in wildlife and reproductive cancers in humans. Environmental Health Perspectives, 2007. **115** (5). pp. 720-727.

[19] USGS. Last Update: march 2006. Available from: http://pubs.usgs.gov/fs/2006/3028/

[20] Winchester, P.D., Huskins, J., Ying, J. *Agrichemicals in surface water and birth defect in the United States*. Acta Paediatrica 2009. **98.** Pp 664-669.

endocrine or reproductive outcomes"[21], "neither atrazine nor its metabolites…affected rat or rabbit embryo-fetal development", or "in our review… poor quality of data and the lack of robust findings across studies…"[22]

Cui bono?

Scientific methodology asks, how reliable is the research? Is it valid? Is it credible?

In an ideal world, people would make rational decisions, scientific studies would confirm or find unfounded a hypothesis, and public offices would make decision in the best interest of the public, the purpose for which they were founded in the first place. In the real world however, don't we sometimes cut the branch we sit on?

The case of atrazine is where we can practice our critical thinking toward the information provided. We might think all science verifiable and unbiased. Well, take it as a hypothesis; test it, confirm, falsify, verify… and test again.

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[21] Forador, Ch.,D., Coder, P.S., Tisdel, M., Yi, K., D., Simpkins, J., W., Handa, R., J., Breckenridge, Ch., B. *The Effect of Atrazine Administered by Gavage or in Diet on the LH Surge and Reproductive Performance in Intact Female Sprague-Dawley and Long Evans Rats*. Birth Defects Research (part B), 2014. 101., pp.262-275.

[22] Goodman, M, Mandel, J., S., Desesso, J., M., Scialli, A., R. *Atrazine and Pregnancy outcomes: A systematic reviw or Epidemiologic Evidence*. Birth Defect Res (part B).2014. 101, pp 215-236.

Repetitio mater studiorum….

…. neuroglia cells

Link the important milestones in the research of glia with their initiators:

1/ 1907, this Italian psychiatrist published a paper in which he added to the hypotheses on glia, two on his own; a/ **glia protect neurons** and b/glia produce **substances of chemotaxis** important for growth of an axon, and formation and developing of synapses, particularly when neurons are far from each other.

2/ 1919-1921; a Spanish neuroscientist who discovered **microglia** using carbon silver (Ag_2CO_3) method, the same way he later found out about **oligodendroglia**!

3/ German neuroanatomist. During his short life (he died at the age of 29 due to typhoid fever) he perfected describing of **neuron**, axon and dendrites (he called them protoplasmatic projections) and as early as **1860** he stated that there must be a whole network of dendrites, all connected in one huge system.

4/ German physician, anthropologist, pathologist, editor and a politician. He was the first to coin a name for neuroglia (he did not discovered them, it happened 32 years earlier). He called them the "**nervenkitt**", a glue in the nervous tissue, translated to Greek you get neuroglia.

5/ Is not it wonderful to have great relatives?! Paul Ehrlich, the Nobel Prize laureate, introduced this German pathologist, his first cousin, to the secrets of **staining** in histology. And it paid off, indeed. Ever since scientists could stain tissues for myelin, elastin, fibrin or bacteria.

6/ Italian physician and cytologist who's investigations into the structures of the **nervous tissue** earned him the Nobel Prize for Physiology or Medicine in 1906.

7/ Along with our "man no. 6" this Spanish histologist was also awarded the Nobel Prize for Physiology or Medicine in 1906 for establishing the **neuron as the basic unit** of the nervous tissue.

*

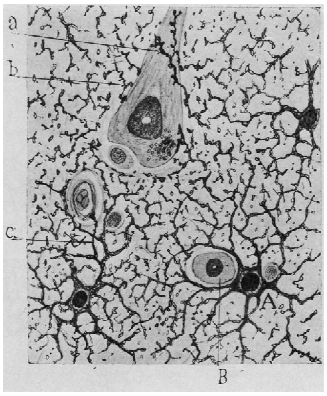


Fig4. Ramón y Cajal, a sketch of protoplasmic astrocyte. A – astrocyte, B – neuron, a & b – pericelular pedicles , c – fine pericellular pedicle.

A/ Karl Weigert

B/ Rudolf Virchow

C/Camillo Golgi

D/ Otto Friedrich Karl Deiters

E/ Pío del Río Hortega

F/ Ernesto Lugaro

G/ Santiago Ramón y Cajal

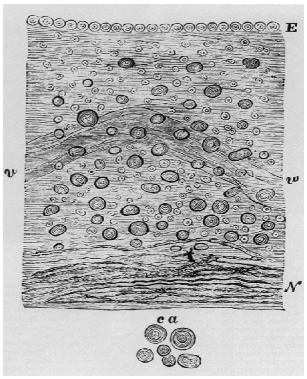


Fig5. Rudolf Virchow, a picture of "nervenkitt". *E – ependyma, v-w – vein, N – neurite , ca – corpora amylacea*

Results:

1-F

2-E

3-D

4-B

5-A

6-C

7-G

Repetitia
in the previous issues

March, 2014

... Epithelial tissues

April, 2014

... Male genital duct system

May, 2014

... Cells of the connective tissue

October, 2014

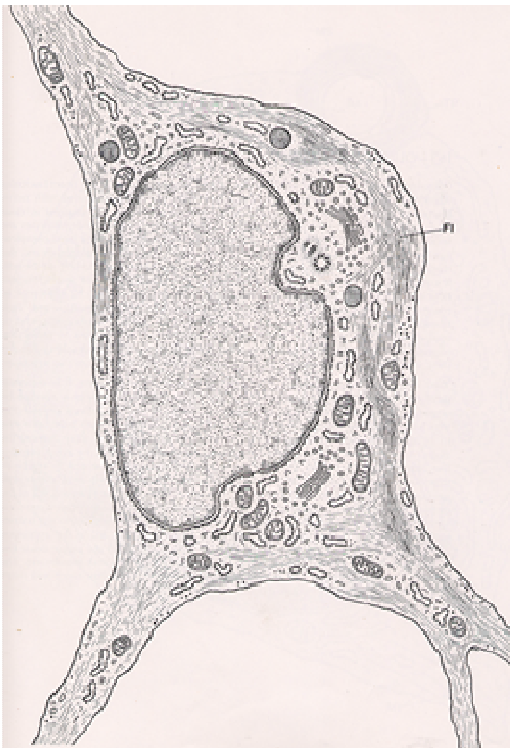
... Cilia

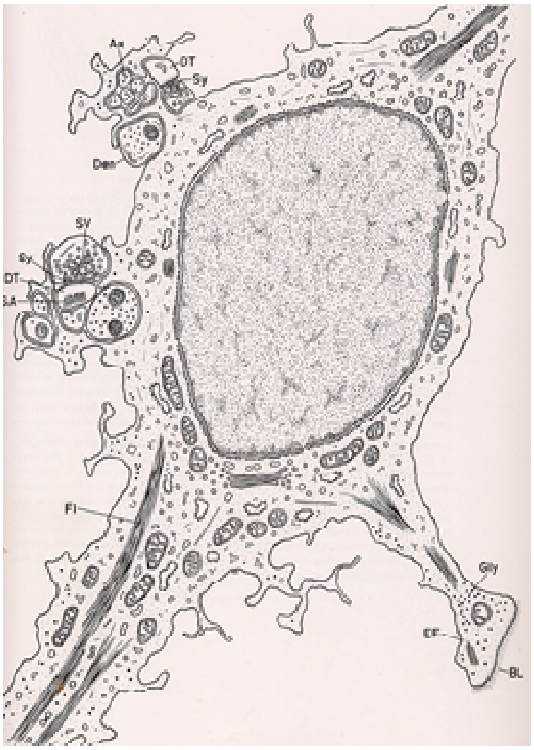
November, 2014

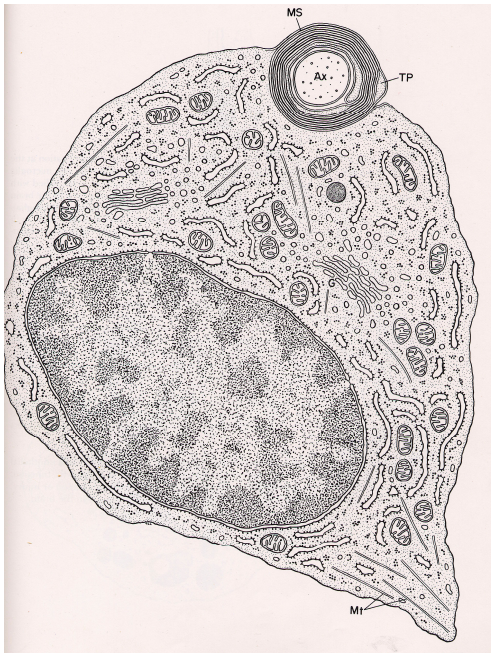
... Apoptosis

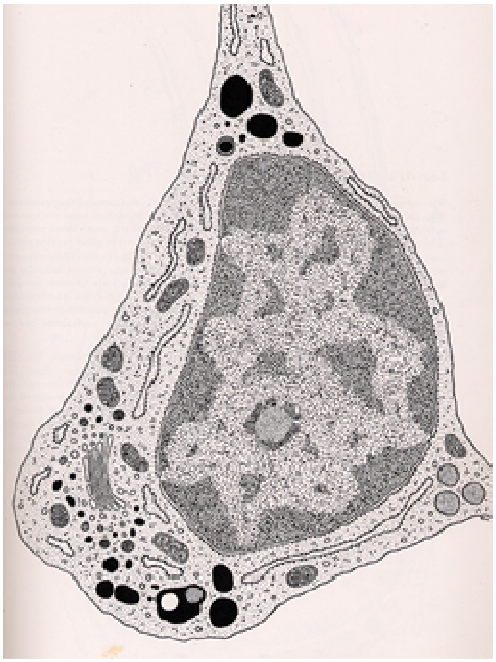
December, 2014

... Myoepithelial cells









Which one is which?

A/ microglia
B/ astrocyte protoplasmic
C/oligodendroglia
D/astrocyte fibrous

Results:

A/ lower on the right
B/ upper right
C/ lower left
D/ upper left

Eponyms

"Schwann cells"

Theodor Schwann,
the founder of modern histology

Born: December 7, 1810
Neuss, Germany
Died: January 11, 1882
Cologne, Germany

His scientific career accelerated when he met **Johann Peter Műller**. Prof. Műller, only ten year older than Schwann, became an inspiring "guru" in the field of physiology for many of the open minds of these times in Germany. Schwann met Műller's in Berlin in 1830' and started assisting him on his great book of physiology. Műller always emphasized the use of **microscopy** and experimental **approach** to medical science, a rare belief in his times in German medical circles.

At that time, medical science in Germany was held in low esteem when compared to its European contemporaries, and medical education was still based on book learning and maintained a disregard for science being inclined more towards "romantic speculation' or "naked empiricism' [23]. In England, post mortems were frequently performed and seen as a vehicle for expanding anatomical knowledge, in France, following the Revolution, large hospitals were built which had become huge inspiring centers of medical education based on clinical examination and autopsy [24].

Schwann's initial experimental interests brought him to studying **nervous and muscle tissue**. In the peripheral nervous system he discovered the cells which envelope the nerve fibers, now called in his honor, the **Schwann cells** (he could not call them glia yet, as such a term was coined several years later by Rudolf Virchow). He studied muscle contractility, and his findings inspired Du Bois Raymond and many others.

In the digestive system, Muller directed Schwann's attention to the digestive system and Schwann showed the importance of a ferment he named 'pepsin'. Pepsin became the first enzyme to be discovered.

It was believed in Schwann's times, that fleas are born from dust and "maggots would arise from the dead flesh". The

*"The history of the knowledge of the **phenomena of life** and of the organized world can be divided into two main periods. For a long time anatomy, and particularly the anatomy of the human body, was the end of scientific knowledge. Further progress only became possible with the **discovery of the microscope**. A long time had yet to pass until through Schwann before **the cell** was established **as the final biological unit**. It would mean bringing coals to Newcastle were I to describe here the immeasurable progress which biology in all its branches owes to the introduction of this concept of the cell. For this concept is the axis around which the whole of the modem science of life revolves."*

Paul Ehrlich

[23] Ackerknecht, E.H. Rudolf Virchow. *Doctor, Statesmen, Anthropologist*. University of Wisconsin, Madison. 1953

[24] Porter, R. *The Greatest Benefit to Mankind. A medical history of humanity from antiquity to the Present*. Harper Collins, London. 1997.

obsolete idea that living things could arise from inanimate matter is called **spontaneous generation** and was thought by Aristotle. Believe or not, over two thousand years later, the doctrine was still a valid explanation of the origin of living organisms.

Once in 1837 Schwann was dining with Matthias Schleiden and the conversation turned on the nuclei of cells in plants. Schwann remembered having seen similar structures in his own microscopic observations and instantly recognized the importance of connecting the two phenomena. [25] The doctrine of spontaneous generations seemed suspicious to many but it was Theodor Schwann who constituted **the cell theory** and described in his famous paper *Microscopic Investigations on the Accordance in the Structure and Growth of Plants and Animals* (Berlin, 1839, transl. Sydenham Society). Schwann not only verified the existence of cells, he also traced the development of adult tissues such as nails or enamel from early embryonic stages. His generalization regarding the nature of cells became the foundation of modern histology.

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Read more stories on eponyms in the previous issues!

Johann Nathanael Lieberkűhn *(March, 2014)*

Regnier de Graaf *(April, 2014)*

Clopton Havers & Alfred Wilhelm Volkmann *(May, 2014)*

Camillo Golgi *(October, 2014)*

Prof. MUDr. Richard Jelínek, CSc. *(November, 2014)*

Ebola *(December, 2014)*

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