Propojení výuky oborů Molekulární a buněčné biologie a Ochrany a tvorby životního prostředí OPVK (CZ.1.07/2.2.00/28.0032)

The genetics of ageing

Petr Pálka

David Rozsypal

Nature Vol 464, 25th March 2010

Cynthia J.Kenyon

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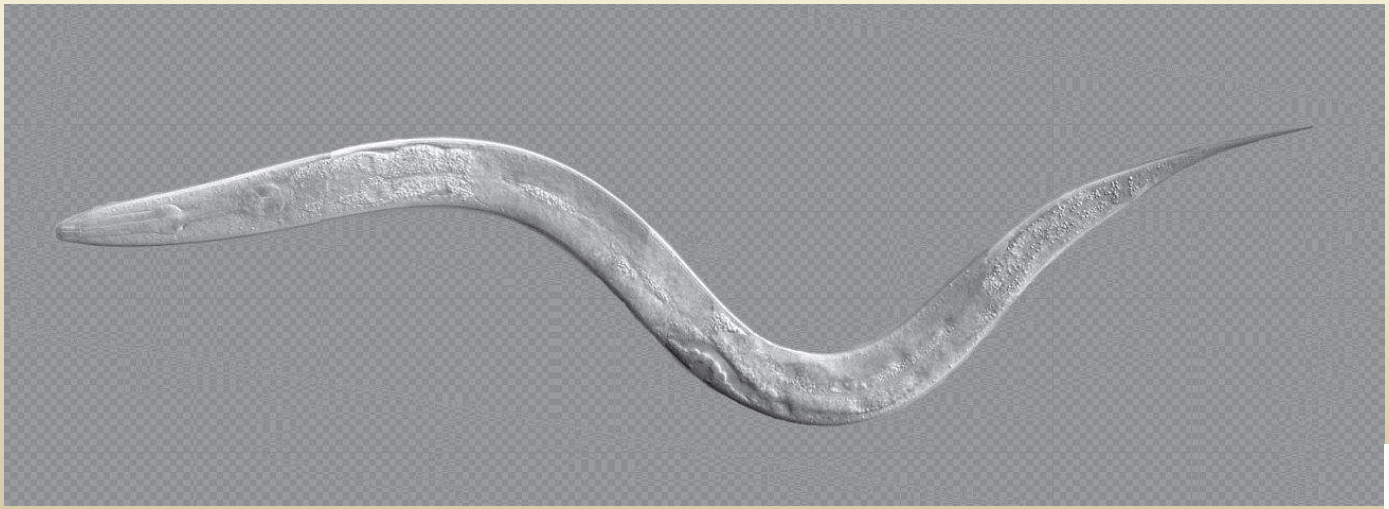
Introduction

- The nematode Caenorhabditis elegans ages and dies in a few weeks, but humans can live for 100 years or more.
- Assuming that the ancestor we share with nematodes aged rapidly, this means that over evolutionary time
- mutations have increased lifespan more than 2,000-fold.



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- For many years, molecular biologists interested in regulatory mechanisms.
- They expected, that the tissue decline associated with ageing is a passive and entropic process.
- Now we know, that the ageing process is the same as other biological processes, so we can regulate it.
- This regulations were discovered in small and short-lived organisms such as yeast, worms and flies.
- Many people assume that extending lifespan by slowing ageing would mean certain death from, from example Alzheimer's disease, but mutations that slow ageing also delay age-related disease.

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Ageing – The Causes

- A discipline that studies the ageing is called gerontology – it observes changes associated with ageing.
- The causes are telomeres – telomerase enzyme activity; apoptosis – activity decline of genes that cause apoptosis -> autoimmune diseases; glycation - pathological connection between proteins and glucose; Mutations – the number of mutations increases with age; Free radicals – overproduction change the activity of enzymes, organelles, membrane; the number of lipofuscin increases.

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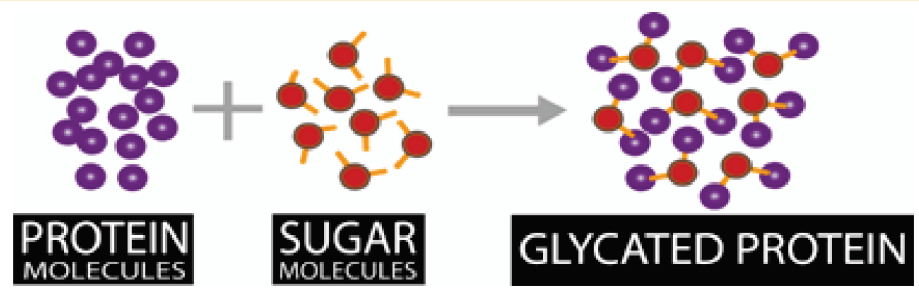
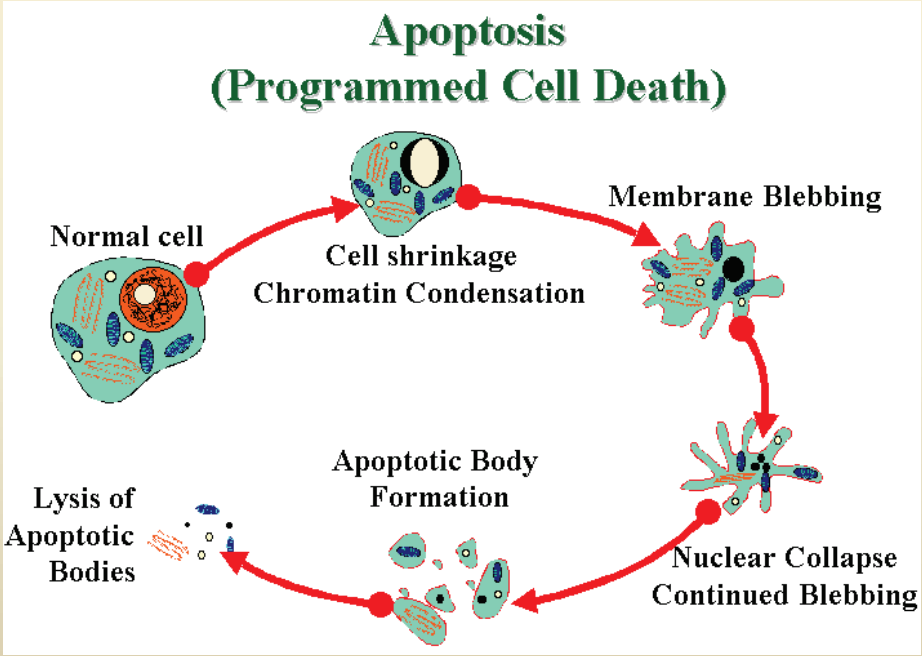
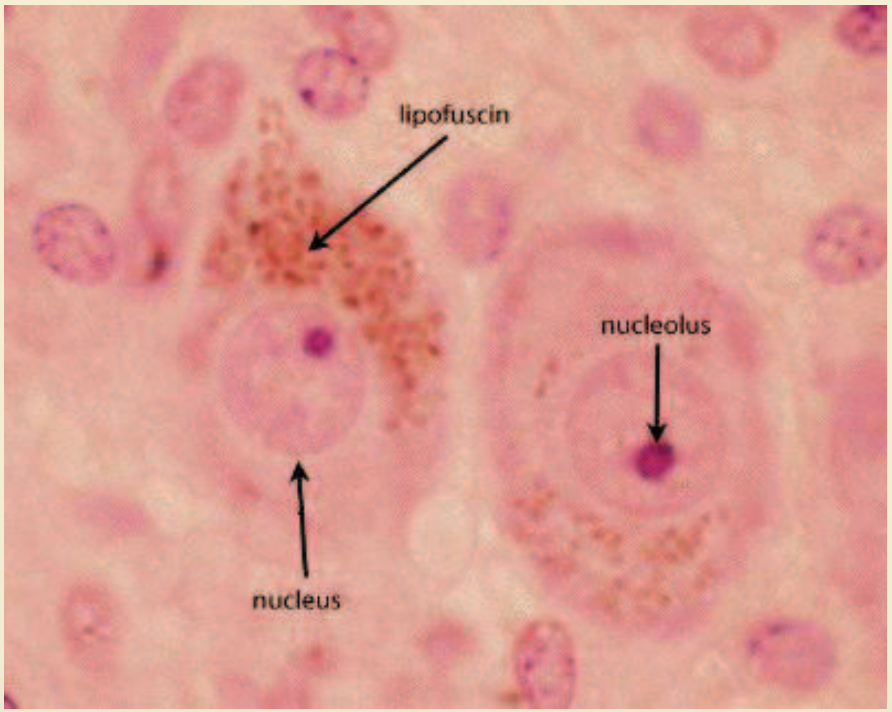






The effect of mutations

- Many mutations that extend lifespan affect stress-response genes or nutrient sensors.
- It depends on the amount of food that organism eat up
- When food is plentiful and stress levels are low, these genes support growth and reproduction
- When the conditions are advers, the activities of these genes change -> as a consequence the animal undergoes a global physiological shift towards cell protection and maintenance.
- This shift protects the animal from environmental stresses and it also extends lifespan.

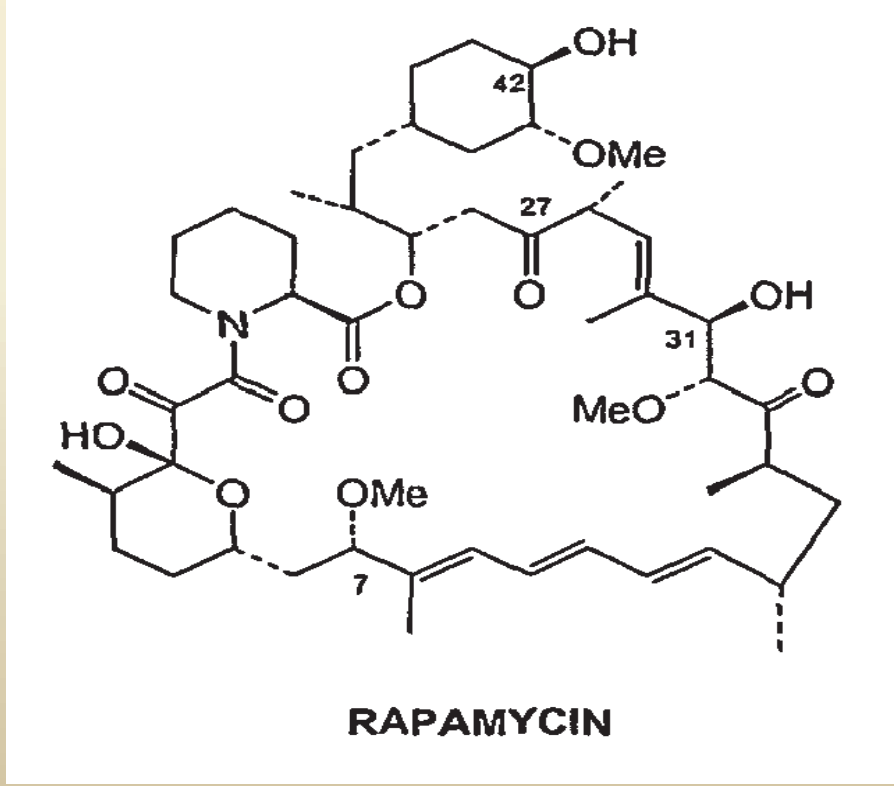
Dietary restriction

- The best known of signals is dietary restriction, which extends lifespan in many species, from yeast to primates.
- This effect was discovered in studies with rats during the Great Depression, amid concern that chronic hunger might shorten lifespan.

- If we reduce food energy by 30 to 50 percent under the normal value, their life will extend up to half.
- Reduced energy leads to metabolic changes and modification of gene expression.

Rapamycin

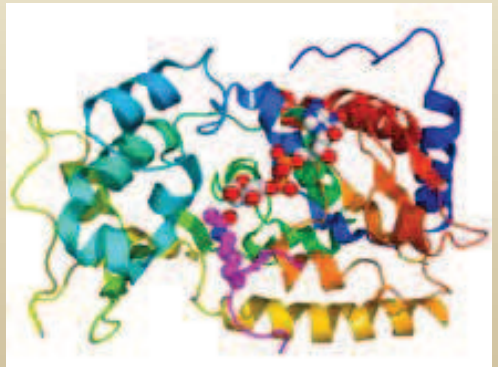
- Dietary restriction is actively regulated by nutrient-sensing pathways involving the kinase target of rapamycin
- Rapamycin is an inhibitor of the Ser/Thr protein kinase named "mammalian target of rapamycin" (mTOR) that regulates cell growth and metabolism in response to environmental cues.



RAPAMYCIN

Sirtuins (SIR, Sir2 proteins)

- It represents a group of enzymes that remove acetyl and the other acid residues from modified amino acid lysine -> thereby regulate a wide spectrum of cellular processes.
- Under these conditions (dietary restriction) there is a massive deacetylation of proteins in cells.
- Sirtuins help to run a defensive reaction against stressful situation, that includes deficit of food.
- Some studies show that sirtuins are involved in longevity control (mice with nonfunctional some sirtuins have shorter life).
- Now we searching activators of sirtuins which could have a positive effect on the length and quality life (for example Resveratrol).



Resveratrol

- There is a question whether it would be other way to ‘‘run“ effect of dietary restriction than the reduced amount of food.
- It was found that some substances such really works. Many of them come from natural sources.
- There is an effort to isolate such substances and possibly introduce and synthetic production.
- An example of these substances is resveratrol.

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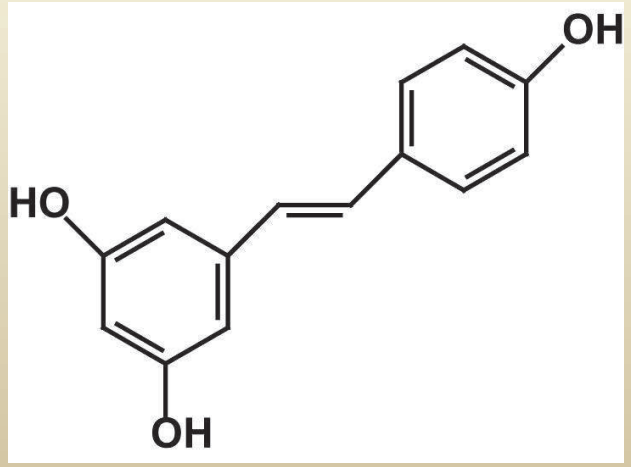
Resveratrol

- Resveratrol is able to replicating the effect of calorie restriction in the body.
- There was an experiment with laboratory mice and mouse, which was administered resveratrol, has a higher muscle activity and endurance.



Utilization

- Nowadays, resveratrol is used as a dietary supplement.

- These supplements are required goods in USA, but in Europe we can expect increased interest in these preparations.

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Future

- In my opinion these preparations we will see more often, because of desire for health and immortality goes along with humanity since time immemorial and it can not be assumed that in our time, it should be otherwise.

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Thank you for your attention

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Mystery childhood paralysis stumps researchers

Jana Poláková

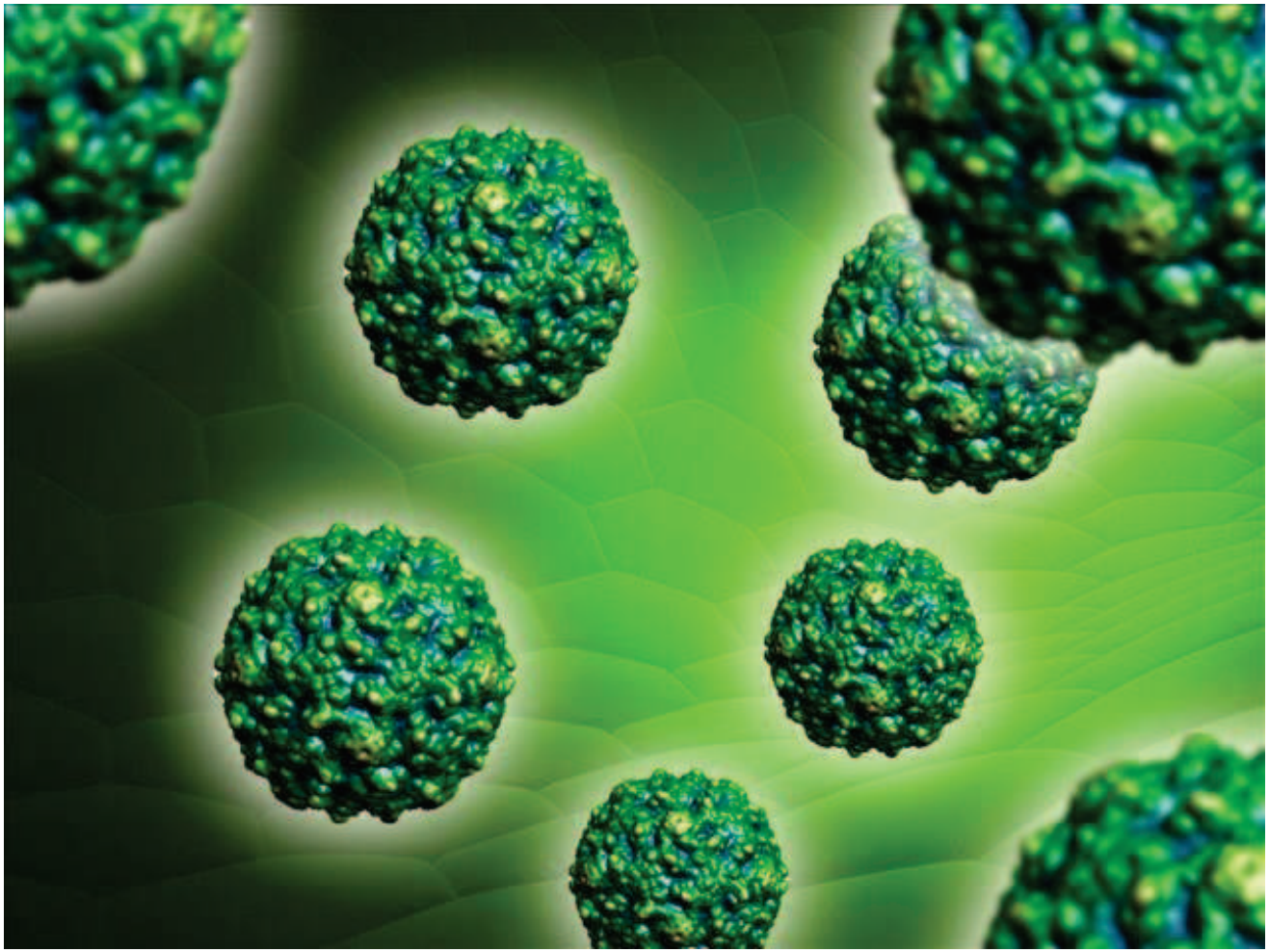
Ewen Callaway
Nature
28 January 2015

New form of paralysis

- Since August 2014 → more than 100 children in the U.S. → mysterious paralysis
- Symptoms: fever, losing strenght in limbs
- Enterovirus D68 (EV-D68) – leading candidate for the cause of the paralysis

What is Enterovirus D68?

- First identified in California in 1962
- One of more than 100 non-polio enteroviruses
- Can cause mild to severe respiratory illness
- Most at risk – infants, children, teenagers → → no immunity from previous exposures



http://kytx.images.worldnow.com/images/4739629_G.jpeg

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- EV-D68 – uncommon among enteroviruses circulating worldwide
- 2014 – EV-D68 was a predominant type of enterovirus circulating in the USA
- Genome sequencing → EV-D68 is most closely related to viruses that caused pneumonia illness in Thailand

The evidence between EV-D68 and paralysis

- It has mostly to do with the timing: the cases of paralysis appeared during a wider outbreak of EV-D68

- Researchers detected EV-D68 in nasal swabs from 8 out 41 people with paralysis who were tested, and another 9 people tested positive for related viruses

- A team led by Samuel Dominguez describes cluster of 12 cases of paralysis that began between August and October 2014
- Nasal swabs from 8 of 11 children affected contained enteroviruses, with 5 of them containing EV-D68
- Lesions of uncertain nature in the children's spinal cords and brainstems, detected using MRI scans, were characteristic of other enteroviruses, such as polio

Other investigating

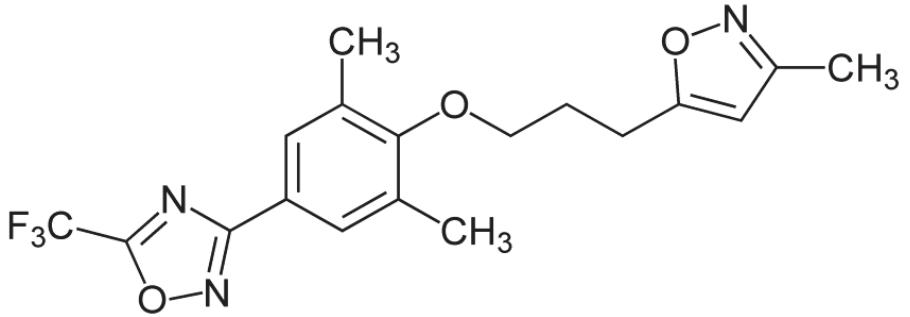
- EV-D68 – trigerring an immune response that cause the nerve damage?
- University of Texas – collect blood from children with paralysis to see whether anything in it can damage laboratory-grown motor neurons
- University of Baltimore – compare the genomes of children with paralysis against the genomes of their siblings, who may have also been exposed to the virus

EV-D68 – cause or coincidence ???

http://www.mychamplainvalley.com/media/lib/210/5/f/e/5fe170c1-b185-4edb-92b8-5a893266ae16/Story.jpg

Treatment

- no antiviral treatments for enteroviruses
- Michael Rossmann‘s team – molecular structure of EV-D68 → experimental drug effective against other rhinoviruses binds to a portion of the virus involved in infecting cells
- Pleconaril – prevents from replicating



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More cases?

- Enteroviruses – always in circulation
- More tests to detect the virus
- *Will it be this virus again this year, or will it be something different?*

Thank you for your attention

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