PRAKTIKA V LETNÍM SEMESTRU- výukový týden 9: Transmembránový transport. Protein folding, ubiquitin proteasomový systém.

Seminář proběhne online v prostředí msteams pro jednotlivé kruhy **v době konání praktik, tj 7 30- 10 30**
Odpovědný vyučující –Petr Bušek

Studijní literatura, kterou nastudují VŠICHNI studenti před konáním semináře:

*** Transport** *Matouš B.et al, Základy lékařské chemie a biochemie, Galen, 2010 str 355-357, doporučená: Harper 30th ed, chapter 40- Membranes: Structure and Function*
*** Sbalování proteinů, chaperony, proteasom** *Matouš B. et al, Základy lékařské chemie a biochemie, Galen, 2010 str 314-316, 328-329, doporučená: Harper 30th ed, chapter 49- pp 618-620*
* https://hopkinscf.org/knowledge/cftr/ informace o CFTR a jeho roli v patogenezi cystické fibrosy
* „review summary" článku Goedert, M., *NEURODEGENERATION. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Abeta, tau, and alpha-synuclein.* Science, 2015. **349**(6248): p. 1255555. Viz níže

DŮLEŽITÉ!

Každý student vypracuje krátký „domácí úkol" vycházející z náplně praktika/semináře (viz níže). Vypracujte ručně, foto/sken odpovědí (otázky netřeba opisovat… ☺) zašlete do 1 týdne od konání semináře na petr.busek2@lf1.cuni.cz . DO PŘEDMĚTU UVEĎTE PŘÍJMENÍ, JMÉNO A KRUH. Vypracování úkolu je podmínkou pro zisk zápočtu za letní semestr.

Jméno Kruh

1) Zakreslete strukturu minimálně dvou základních sloučenin, které jsou součástí plasmatické membrány lidských buněk.
2) V jedné až dvou větách shrňte, co rozhoduje o tom, zda konkrétní sloučenina bude procházet biologickou membránou.
3) V jedné až dvou větách vysvětlete, co jsou chaperony.
4) V jedné až třech větách popište proteasom a vysvětlete jeho funkci.

Těším se na setkání ve virtuálním prostoru, Petr Bušek.

REVIEW SUMMARY

NEURODEGENERATION

Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein

Michel Goedert*

BACKGROUND: Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common human neurodegenerative diseases. AD is primarily a dementing disease, and PD is a movement disorder. Together, they affect around 50 million people worldwide, with the vast majority of disease cases being sporadic. Their incidence increases with age. Like most neurodegenerative diseases, AD and PD are caused by the aggregation of a small number of proteins, with filament assemblies constituting the end-point of protein aggregation. AD is characterized by the presence of abundant extracellular plaques made of amyloid assemblies of Aβ peptides and intraneuronal inclusions made of assembled tau protein. Some dominantly inherited cases of AD are caused by mutations in the gene encoding the amyloid precursor protein (APP), the cleavage of which gives rise to Aβ. In these cases, dysfunction of APP precedes dysfunction of tau. In contrast, mutations in *MAPT*, the tau gene, give rise to dominantly inherited frontotemporal dementia and parkinsonism, with abundant tau inclusions in the absence of Aβ plaques. Extrapolation to the much more common sporadic cases of AD has given rise to the amyloid cascade hypothesis, which postulates that Aβ aggregation causes the formation of tau inclusions, synaptic dysfunction, nerve cell death, and brain shrinkage. However, tau inclusions correlate better with cognitive impairment, and Aβ may exert its effects through tau. Strategies targeting the formation of Aβ and tau assemblies are valuable for the development of mechanism-based therapies. Unlike AD, in which two distinct amyloid assemblies are present, PD is characterized by intracellular deposits, Lewy bodies and neurites, both composed of the protein α-synuclein. Dominantly inherited forms of PD are caused by mutations in *SNCA*, the α-synuclein gene. More than 95% of those diagnosed with PD have Lewy inclusions.

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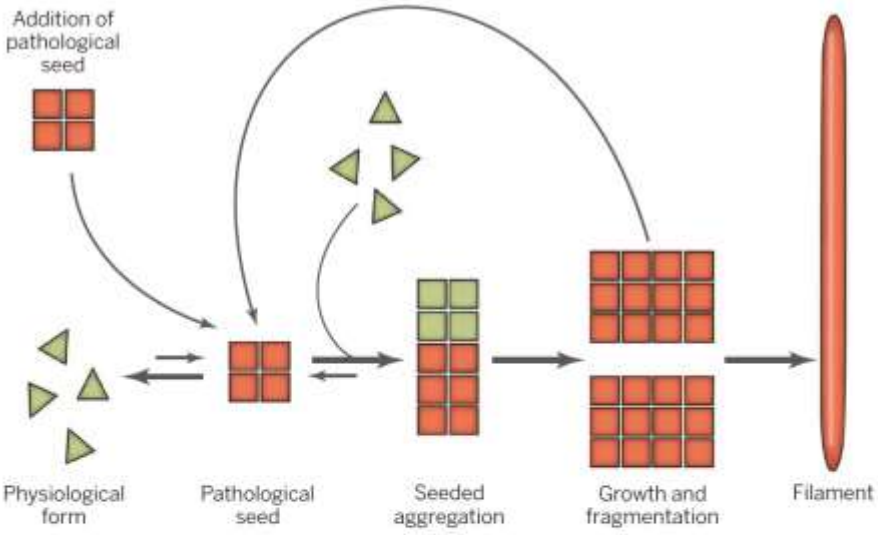
ADVANCES: For many years, the mechanisms underlying AD and PD were widely believed to be cell-autonomous. This implies that the same molecular events, such as the formation of tau and α-synuclein assemblies, occur independently in a large number of cells in an otherwise healthy brain. Recent findings have suggested instead that non–cell-autonomous processes play an important part in AD and PD. Inclusions are thought to form in a small number of cells and—given enough time and, perhaps, a genetic predisposition—spread in a deterministic manner to distant brain regions. The formation of the first Aβ, tau, and α-synuclein inclusions is probably stochastic, with most seeds being degraded. Distinct molecular conformers of aggregated proteins (or strains) may underlie clinically different diseases. This is reminiscent of human prion diseases, such as Creutzfeldt-Jakob disease (CJD). However, there is reluctance to use the term prion for the inclusions of AD and PD. The main reasons are that in contrast to Kuru and CJD, transmission of AD and PD has not been demonstrated between individuals, and most experimental studies have used transgenic animals that overexpress disease proteins.

OUTLOOK: The prion concept appears to apply to all human neurodegenerative diseases with abnormal protein assemblies, including AD and PD. This has brought unity to the field and changed the way we think about these diseases. It has been known for some time that a seed can template aggregation of the homologous protein. However, the ability of protein aggregates to spread through the nervous system had previously been underappreciated. At a practical level, the new findings are helping to elucidate the mechanisms underlying disease, which may have therapeutic implications in all cases. It will be important to identify the molecular species of assembled host proteins responsible for propagation and neurotoxicity. ■



A pathological pathway leading from soluble proteins to insoluble filaments. This pathway is at the heart of human neurodegenerative diseases, including Alzheimer's and Parkinson's diseases. The formation of pathological seeds is a rare and energetically unfavourable event, which requires exposure of backbone amide groups and a high protein concentration. Once a seed has formed, single molecules can change shape and join the growing aggregates. Seed addition induces rapid assembly of the soluble protein. Fragmentation generates new seeds, accelerating the formation of aggregates. Filaments represent the endpoints of aggregation. They are typically unbranched, with a diameter of ~10 nm, and can be several micrometers long. This drawing is not to scale. [Adapted from S. K. Fritschi *et al.*, in *Proteopathic Seeds and Neurodegenerative Diseases*, M. Jucker, Y. Christen Eds. (Springer, Berlin, 2013), pp. 61–69].

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