Session 10: Looking forward while celebrating the past

Lectures

L10.1

Precise medicine

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The Human Genome Project, arguably the most ambitious biomedical project of the twentieth century set the stage for the genomic based medicine. The idea is simple, each person has slightly different genetic background, hence we should tailor treatment according to the individual blueprint. Moreover, other factors such as environment and life style can affect effectiveness of a specific treatment. However, this is relatively new idea and there's still a lot of problems to be solved ranging from biology to ethics before we will see this approach at every doctor's office. Nevertheless, it seems that we are witnessing new paradigm shift in diseases treatment comparable only to changes in medicine after Pasteur's discoveries in the nineteenth century.

L10.2

Francis Crick: From DNA to neurobiology

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Few questions are more profound than how exactly is information stored in biological structures. Francis Crick is famously known for discovering both a storage mechanism and a code for genetic information. When it comes to neural information – Crick pioneered investigating after moving to the USA – the distinction between the storage and the code is fuzzy at best. Neurons and synapses change as we learn, and their properties govern the programs the brain runs.

Still, Crick managed to offer both population level storage mechanism and predictive way of neural coding. My short speech will try to explain the workings of the predictive brain and apply this knowledge to throw light on creative scientific enterprise. How Francis Crick worked will be best explained by what he discovered.

L10.3

The Genetic Code

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In the early 1950s one of the most important, unsolved biological questions was the nature of the genes, the mechanisms of their action and their relationship to proteins. Several attempts have been made to interpret the available experimental evidence, and to construct models that could explain how the genes influence growth, development and other functions of organisms and how they can direct production of specific proteins. However, there was no widely accepted consensus even with regard to the substance the genes are made of and much less the mechanisms of protein synthesis.

The properties of the double helical structure of DNA described by Watson and Crick in 1953 were immediately recognized as having biological significance. The ability to accommodate any sequence of bases suggested that DNA is "the code which carries the genetical information" that can be faithfully copied by virtue of strands complementarity. The discovery of DNA structure initiated the quest for the genetic code a means of translating the information contained within genes and specified by the sequence of four bases in DNA into sequences of twenty amino acids in proteins. In the subsequent years, there were two ways to address the problem of the genetic code. On one hand, there were attempts to solve the puzzle using theoretical methods of mathematics and cryptography. This approach was initiated by George Gamow and involved a number of scientists, members of the RNA Tie Club, an informal group with the aim to "solve the riddle of the RNA structure and to understand how it built proteins". On the other hand, the data that fueled theoretical considerations were produced by experiments results of which allowed to define the components and mechanisms of the machinery underlying transfer of genetic information from DNA to proteins. The development of methods of RNA synthesis and cell-free translation allowed Marshall Nirenberg to devise a system that allowed assigning amino acids to their corresponding base triplets in the genetic code table.

In December of 1966, the last nucleotide triplet in the genetic code has been deciphered. The end product, the table of the genetic code, was a crowning achievement of thirteen years efforts to unravel the mechanisms underlying functioning of all living organisms on the molecular level.

L10.4

Why Nature introduced sulfur to the wobble nucleosides of transfer RNAs

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The tRNA molecules carry a majority of post-transcriptionally modified nucleosides, as they contain almost 90 out of total ca 150 found in DNA and various forms of RNA. About 40 of them are modified uridines (Us) and 2-thiouridines (S2Us) present in the first (wobble) position of the anticodon. The U/S2U are critical for precise reading of genetic information because they can recognize synonymous mRNA codons 3'-ending with A and G. According to the original Crick's hypothesis, uridine can form a base pair with either A or G. Replacement of oxygen-2 of the uracil ring with a sulfur atom is observed for at least 10 wobble uridines of tRNAs. Early data suggested that S2U is introduced into the wobble position to preserve hybridization to A, whereas the wobble pairing with G should be restricted due to less effective hydrogen bonding between the N1H donor of Gua and the sulfur acceptor of 2-thiouracil. However, the results of subsequent biological studies were contradictory to the above idea, and actually suggested preferable reading of the 3'-G-ending codons by anticodons containing 5-substituted S2U. The most pronounced were results demonstrating that anticodons with wobble mnm5S2U or cmnm5S2U (of cytosolic tRNAs) and tm5S2U (of mitochondrial tRNAs) all promote the reading of, both, NNA and NNG-ending codons.

We have determined thermodynamic stability of duplexes containing model U-G base pairs (Sochacka *et al.*, 2015, *Nucleic Acids Res* **43**: 2499) as well as pKa values and ionization properties of the set of eighteen R5U/S2Us depending on electron withdrawing/donating properties of the C5 substituents (Sochacka *et al.*, submitted). Besides, we calculated their ionized fractions in pH 7.4 and have shown that S2U units bearing the substituents with a positively charged 5-aminomethyl group to a significant extent (50-70%) exist in the N3H deprotonated (ionized) form. The lecture will focus on the features of 5-substituents of U/S2U which determine electron density in the nucleobase ring and define their potential for reading G at the 3'-end of the mRNA codons (Duechler *et al.*, 2016, *Cell Mol Life Sci*).

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