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Sano Computational Medicine Seminars

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Regulatory network of cellular gene expression

Abstract

The central dogma of molecular genetics describes a flow of information encoded into a sequence of DNA nucleotides. DNA is inherited from parents and passed to a progeny of the next generation. DNA has to be transcribed into a messenger RNA and next translated into polypeptides to express this information as biological traits. Only a fraction of genes is active in a cell. Gene expression is regulated by interaction between proteins named transcription factors and short DNA sequences outside the coding region of a gene. Our understanding of this process was challenged by discovery of microRNAs. Endogenous microRNA molecules (miRs) were discovered in 1993 by Rosalind Lee and Victor Ambros during studies on lin-4 gene mutations of the roundworm Caenorhabditis elegans. In the consequence, these mutations arrest a development of the model organism at the larval stage L1. RNA product of lin-4 transcription does not encode any protein. The transcript is short, only 61 nucleotides and is complementary to the untranslated region of the proper LIN-4 gene.

Currently, short processed transcripts of 22-24 nucleotides are named miRs. Andrew Fire and Craig Mello experimented with an artificial miR, which sequence was complementary to the heavy myosin chain of the muscle. They discovered how to obtain a biological effect of such a miR. For that purpose, a double stranded RNA was necessary. The model of C. elegans once again turned out useful to study regulation of genetic expression. Endogenous miRs are products of a class of genes, which transcripts are substrates to specific rybonucleases: Drosha and Dicer. The enzymes trim precursor double stranded pre-miRs to short miRs of less than 25 nucleotides in length. One of these strands is mounted into a pocket of another rybonuclease - RNA-induced silencing complex (RISC), whereas the other one is degraded. A single stranded miR is a guide targeting

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the enzyme to a coding mRNA. When a perfect complementarity between the guide and a target exists, mRNA is degraded. If there are mismatches, translation process is blocked. There are over 3500 human genes encoding pre-miRs, some of them transcribed in many tissues, others only in particular populations of cells.

It is estimated that one third of human protein-coding transcripts can be degraded or blocked by miRs. A single miR molecule can bind to as much as 100 different protein coding transcripts. Only a few miRs have their conventional names, most are identified by numbers. For example, miR-430 regulates organogenesis and development of foetal brain. Mir-124 in concert with miRs 290–295 and miR-302 regulates differentiation of stem cells into neurons. Unbiased profile of miRs was investigated in cancer cells or in blood plasma of patients with cancer to understand tumour progression or to detect early steps of carcinogenesis. The regulatory network of miRs will be illustrated during the seminar using data collected in our own studies.

Prof. Marek Sanak - geneticist and molecular biologist, professor of medical sciences, the author of more than 230 research papers. In 1997, together with Andrzej Szczeklik, he received the Lancet Investigators Award for research on bronchial asthma. He is Head of the Department of Molecular Biology and Clinical Genetics of the Jagiellonian University Medical College, Head of the Department of Biochemical and Molecular Diagnostics at the University Hospital in Kraków, the Jagiellonian University Rector's Plenipotentiary for Science and Development in the Medical College, and member of the Polish Academy of Learning. https://nauka-polska.pl/#/profile/scientist?id=16314&lang=en&_k=e9qokd
https://en.wikipedia.org/wiki/Marek_Sanak

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