Dr Zbigniew Warkocki

Institute of Bioorganic Chemistry PAS, Poznan

Defining roles of LINE-1 mRNA 5’ and 3’ ends in the retrotransposon biology

The human genome comprises over 3 billion base pairs – genetic code letters. If all its fragments were joined together they would form a thread 2 meters long. In other words each tiny human cell encapsulates 2 meters of a very thin DNA thread constituting the human genome. The human genome is important. One could imagine it being highly elaborated and perfectly organized. It should only contain information useful to the development and life cycle of a human being. Surprisingly, the human genome is a mosaic of diverse sequences, among which a half are “genetic parasites” and their fragments.

The biggest group of “genetic parasites” are so called retrotransposons. They characterize by an ability to amplify their copy number by first transcribing a genomic DNA copy into RNA and then placing it in a new genomic location. The latter step requires reverse transcription i.e. conversion of RNA into DNA. Most retrotransposons are genetic fossils reminding of their successful proliferation in the past. There are however some retrotransposons active in modern humans. The retrotransposonal activation takes place in the key stages of human development including gametogenesis and early embryo development. It is then that each human being acquires its individual features.

Retrotransposon activity brings about mostly negative effects. These include sporadic mutations within genes potentially leading to less or more severe genetic disorders. Recently, it has been shown that retrotransposons are responsible for formation of *extra*-nuclear DNA (i.e. localized in the cytoplasm and not in the cell nucleus) which sparks and perpetuates cellular autoimmune response. This in turn underlies some cases of neurodegeneration, cancer and cellular senescence leading to ageing of an entire organism.

In one of my last research publications together with co-authors I demonstrated one of many ways in which retrotransposons are stopped from creating new genomic insertions by cellular enzymes acting on the retrotransposonal RNA (https://doi.org/10.1016/j.cell.2018.07.022). With this project I intend to test whether the described regulatory pathway might lead to a cellular autoimmune response. Besides this I intend to investigate other currently poorly defined molecular mechanisms of retrotransposon regulation in eukaryotic cells. Understanding of the molecular mechanisms of retrotransposon regulation is important. Work of many researchers might lead to the development of tools effective in counteracting negative effects of the retrotransposon activation including neurodegeneration and ageing processes.