

Structure analysis and identification of templates degraded by Regnase-1.

Regnase-1 called also MCPIP1 protein was described in 2006 as a transcription factor, responsible for control of genes expression coding for proteins involved in programmed cell death and apoptosis. Further studies showed that MCPIP1 function is different. Two independently working groups: one supervised by prof. J. Jura from Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, the other one supervised by prof. S. Akira from University of Osaka, published data showing, that MCPIP1 acts as RNase controlling half-time of transcripts coding for important mediators of inflammation, thus has critical role in regulation of inflammatory processes.

Inflammatory processes are the response of cells to tissue damage caused by different factors: physical, chemical, mechanical or biological (such as pathogens). Inflammation is considered as a local process, when acute phase inflammation is a systemic response of an organism to local inflammation. Acute phase response last from few days to several weeks and have therapeutic impact, as this process leads to restoration of homeostasis. Nevertheless, deregulation of restoration of acute phase reaction by different agents may results in initiation of chronic inflammation which is accompanied by pathological changes and in turn may results in different disorders, such as cardiovascular, neurodegenerative, autoimmune diseases and also cancer.

Inflammatory processes are controlled on different levels. One of them is regulation of stability of transcripts coding for mediators of inflammation, such as cytokines and chemokines. MCPIP1 protein is responsible for degradation of templates encoding these mediators. Moreover, this protein negatively regulates activity of NF κ B, a transcription factor which is one of the key regulators of inflammation. Because data obtained so far show that MCPIP1 has anti-inflammatory properties, its role in termination of inflammatory processes is very substantial. Changes in the amount of this protein or its activity may result in dangerous for health complications and development of immunological disorders or other diseases with inflammatory background.

Because mechanism of MCPIP1 action is not fully solved, the aim of this project will be analysis of biophysical properties of this protein, determination of interaction mechanism of this protein with RNA templates, coding for mediators of differentiation in selected cells (adipocytes, keratinocytes). Moreover, we are planning to obtain crystal structure of MCPIP1 and on the basis of that characterize structure in details. So far such studies were not carried out and they are essential for further experiments leading to identification of expression level modulators for this protein. Obtained so far data are promising that MCPIP1 can be considered as a target in the treatment of autoimmune diseases and cancer. Studying the role of MCPIP1 in development of clear cell renal cell carcinoma, we found that upregulation of this protein results in lower cancer cell survival and diminished metastatic potential.

Studies will be carried out by three experienced scientists and two PhD students who will use obtained data in their PhD thesis. Molecular studies, concerning determination of templates directly bound by MCPIP1, will be conducted under supervision of prof. Jolanta Jura. Biophysical analysis will be carried out under supervision of Dr A. Gorecki. Crystallography studies will be performed under supervision of Dr G. Dubin. Establishment of such scientific group, involving experts in the particular field, will lead to successful results.

Obtained results will be published in prestigious international journals and used in further studies where we focus on identification of specific for MCPIP1 protein level modulators, which will be employed in the treatment of diseases with inflammatory background.