Cardiovascular diseases

According to the World Health Organization (WHO) latest statistics that currently analyze and monitor the diseases with the highest percentage of morbidity are alarming. Number of people who die as a result of cardiovascular diseases will increase to 23.3 million in the year 2030.

Atherosclerosis is a one of most common diseases of large and medium-sized muscular arteries. It is characterized by number of symptoms that can be distinguished eg. endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall. This buildup results in plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities of blood flow and diminished oxygen supply to target organs. Modern treatments have reduced the number of deaths from atherosclerosis-related diseases. These treatments also have improved the quality of life for people who have these diseases. However, atherosclerosis remains a common health problem and is still a major burden on humanity. This means that the search for new therapeutical agents is necessary.

Role of inflammation in CVD

Inflammation is a regular reaction of human organism on wounds, pathogens causing infections but also plays an important role in atherosclerosis. Inflammation participates importantly in host defenses against infectious agents and injury, but it also contributes to the pathophysiology of atherosclerosis. Recruitment of blood leukocytes to the injured vascular endothelium characterizes the initiation and progression of atherosclerosis and involves many inflammatory mediators, modulated by cells of both innate and adaptive immunity. Identifying the triggers for inflammation and unraveling the details of inflammatory pathways should aid the development of novel strategies to predict disease susceptibility, target and monitor therapies, and ultimately lead to new approaches for the prevention and treatment of atherosclerosis. Cytokines and growth factors play very important part in immune response of human organism. They take part in signaling and activation of protein in immune cells which is mediator of genes transcription in nucleus. Particularly important are proteins from STAT family (signal transducers and activators of transcription, 7 proteins) and IRF (interferon regulatory factors, 9 proteins). This homologous and multi-domain proteins participate in regulation of basic cell functions: growth, development, differentiation and cell apoptosis, immune response and inflammation. Apart from cytokines and growth factors also oncogenes and presence of pathogens may activate those processes. Abnormalities in activation of STAT- and IRF-dependent pathways appear in many diseases like: autoimmune diseases, cardiovascular diseases, asthma and allergies, development and progression of tumors. Inhibition of STATs and IRFs that take an important part in development and progression of CVDs (STAT1, 2, 3; IRF1 and 8) represent interesting therapeutic targets.

STAT proteins

STAT proteins are activated by signals from interferons (IFN), interleukins (IL) and growth factors like EGF or PDGF. Moreover, Src and ABL oncoproteins are also STAT activators. STAT family consists of seven proteins: STAT1-4, 5A, 5B and 6. Structurally they are composed of 5 domains: N-terminal, 'coiled-coil', DNA-binding, SH2 and C-terminal transactivation domain. STAT activation is induced by phosphorylation of tyrosine residue in transactivation domain of the protein. It leads to cascade of signaling pathways including STAT-STAT dimerization through the reciprocal interaction of pTyr-SH2 domain, migration of dimers to the nucleus, DNA binding and induction of the target genes transcription in the nucleus. STAT proteins are involved in the regulation of fundamental cellular processes, including growth, development, differentiation and apoptosis, immune response and inflammation.

IRF proteins

IRF proteins are modulators of the body`s defense mechanisms against pathogens including innate and adaptive immunity. IRF transcription factors are a family of nine homologous proteins (IRF1-9) with a multi-domain structure. Every IRF has a conserved N-terminal DNA-binding domain (DBD). Each IRF-DBD has the fold of a 'helix-turn-helix' and recognizes a DNA sequence, which is a consensus sequence that binds IRF (IBCS). C-terminal regions of IRFs, with the exception of IRF1 and IRF2, have IRF association domains (IAD). They are responsible for interactions with other IRFs (homo- and heterodimerization), and with other proteins as well, e.g. STAT1 and STAT2. Interferon regulatory factors are primarily related to the innate response of the immune system that is dependent on pattern-recognition receptors (PRR). They also participate in: development of immune cells, control of the growth and survival of cells and processes of oncogenesis.

Conducted basic research and its importance

Cardiovascular diseases are common life-threatening conditions closely associated with our lifestyle. Therefore it is of great importance to broaden our knowledge on the specificity of the activity of STAT and IRFs and their selective inhibition without affecting the rest of proteins. More commitment should be put to a holistic approach that combines experimental research involving investigation of bio-physico-chemical nature of tested mechanism or processes using tools given by bioinformatics and theoretical chemistry. In this project we propose an innovative comparative study. A combined structure-function analysis of STAT and IRF at the level of inhibition: *in silico* using developed 3D models, *in vitro* in endothelial cells and monocytes and *in vivo* on an experimental model of atherosclerosis will bring new information into the existing state of knowledge about the inflammation in CVDs. The study of inhibition of STAT proteins will allow for the improvement of already existing methods and development of new mechanisms to manipulate their activity. Similarly, in case of family of the IRF proteins investigation of mechanisms of action will set a new direction influencing on abnormal activity of pro-inflammatory pathways. Based on comparative virtual screening we will find new inhibitors for potential therapeutic targets for diseases of the cardiovascular system - STAT1, 2, 3; IRF1 and 8, to be tested in cellular models *in vitro* and *in vivo*, that we have developed in the Department of Human Molecular Genetics, Faculty of Biology, Adam Mickiewicz University in Poznan and in collaboration with international and national research partners.