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 therapeutic agents and strategies 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. Advanced plaques are loaded with macrophages, T lymphocytes, VSMCs, lipids, and cholesterol, and cause myocardial infarction after they may rupture. 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.

IFNγ and STAT proteins

The pro-inflammatory cytokine interferon (IFN)γ is a member of the IFN family, which consists of three types: IFN-I, IFN-II and IFN-III. IFNγ is the sole member of the IFN-II type and vital for both innate and adaptive immunity by activating macrophages, natural killer cells, B cells and vascular endothelial cells and smooth muscle cells (VSMCs). IFNγ is expressed at high levels in atherosclerotic lesions thus playing a crucial role in the pathogenesis of atherosclerosis and regulating the functions and properties of all cell types present in the vessel wall (3). By interacting with its specific receptor, IFNγ activates signal transducer and activator of transcription (STAT) complexes; STATs are a family of transcription factors that regulate the expression of certain immune system genes. As such IFNγ plays a crucial role in the pathology of atherosclerosis through predominant activation of STAT1. Thus, STAT1 homodimers directly activate many pro-inflammatory genes containing the IFNγ activation site (GAS) DNA element. Evidence exists, that IFNγ activates a second STAT-based signaling cascade that entails the formation of STAT1-STAT2 heterodimers in association with interferon regulatory factor (IRF) 9 [known as interferon-stimulated gene factor 3 (ISGF3)], which then promote the expression of a distinct set of ISRE driven genes. Recent discoveries in combination with our preliminary results provide novel evidence to suggest that IFNγ-activated STAT1-complexes orchestrate a platform of cell-type common and specific inflammatory responses in VSMC and MQ that are instrumental in onset and progression of atherosclerotic plaque formation

Conducted basic research and its importance

Using state of the art technologies of contemporary whole-genome approaches of molecular biology such as Next Generation Sequencing (NGS) of RNA (RNA-Seq), Chromatin Immunoprecipitation-sequencing (ChIP-Seq) as well as Assay for Transposase-Accessible Chromatin-sequencing (ATAC-Seq) on cells in culture, together with experiments in atherosclerotic plaques from mice, this project proposes to further characterize these mechanisms and aims at identifying the full spectrum of IFNγ-induced STAT1-dependent VSMC and MQ common and –specific genes. With the proven role of STAT1 in experimental and clinical atherosclerosis, especially in VSMC and MQ, STAT1-target genes represent promising diagnostic markers. As such, this project also plans to characterize a predefined STAT1-target gene "Vascular Inflammation" signature that could serve to monitor and diagnose "plaque-specific" inflammatory responses during disease progression. This may open a promising avenue towards development of targeting and monitoring therapies in the treatment of atherosclerosis.