Vascular endothelium play a pivotal role in maintain homeostasis and its dysfunction is described in various diseases. However is not clear whether dysregulation of endothelial cell functions is the cause of the disease or the result of the pathology. However, studies of recent years indicate that disturbances in epigenetic regulation of biological process could contribute to the dysfunction of endothelium.

The concept of epigenetics assumes regulation of gene activity that is not caused by changes in DNA sequence. MicroRNAs (miRNAs, miRs) are endogenous noncoding RNAs which are responsible for suppress activity of genes. The way of the down-regulation depends on the sequence complementary of the miRNA and the target mRNA. In the case of perfect sequence complementary between the miRNA and mRNA, the mRNA will be degraded. In other cases the effective translation of mRNAs will be inhibited by different induced mechanisms resulting in gene expressional down-regulation. In this way microRNAs play a key role in the majority of biological processes and their expression is also tightly regulated. Both the deregulation of genes controlled by miRNAs and the altered miRNA expression have been linked to many disorder, including cancer, cardiovascular and metabolic diseases. However, the precise mechanism in which microRNA participate in pathogenesis of the disease is still unclear. Up to date, most studies focused on obtaining the profile of differentially expressed microRNA in disease affected tissue or in patients' serum. One of this research was performed by us in terms of aortic aneurysms. Our study revealed 10 miR candidates, significantly elevated in aneurysmal thoracic aorta compared to non-aneurysmal aortic tissue. Three of these (has-miR-21-5p, has-miR-126-3p and has-miR-191-3p) seems to be important in terms of endothelial dysfunction, however for all of these microRNAs lack is a comprehensive study, which would indicate molecular functions of these molecules in endothelial cells.

One of the approach for functional analyze of miRNA-mRNA pairs is cell cultures followed by transfection with microRNA mimics or microRNA inhibitors, which allows to establish the role of particular miRNAs. Difference in gene expression mediated by transfection with synthetic molecules provides evidence that the miRNA is involved in regulation of that selected gene. Up to date, mostly low-throughput approach for assess the differential expression are used. However, development of new RNA sequencing technologies in recent years led to quantify the difference in gene expression in wide-genome scale. Thus we would like to perform a study in in which we will transfected endothelial cells with mRNA mimics and miRNA inhibitors followed by RNA sequencing of whole transcriptome. This led us to assess the epigenetic regulation of whole transcriptome. The next step will be associated with bioinformatics analysis in order to indicate the pathways which are deregulated by overexpression of miR-21-5p, miR-126-3p or miR-191 and could contribute to endothelial dysfunction.

Results which will be obtained in proposed study allow us to construct a whole model of regulation of gene expression in endothelial cells mediated by previously selected microRNA. In addition we will be able to indicate pathways which could be a target for novel therapies for diseases associated with endothelial dysfunction. Lack of effective treatment for these pathologies is a huge economic problem because cardiovascular diseases are the leading global cause of death. Because of that is important to find a novel methods of therapies and the only way to obtain this goal is to find pathways which are dysregulated in endothelial diseases. Moreover, finding a novel biomarkers which could be helpful in early diagnosis or monitor the disease are also important. In the future proteins encoded by differentially expressed genes could be assess as potential biomarker of the disease, however at this step it is only a basic research.