DESCRIPTION FOR THE GENERAL PUBLIC

Cardiovascular diseases, including atherosclerosis and aortic stenosis, are one of the major causes of mortality in developed countries. Aortic stenosis is caused by the reduced aortic valve area by an active process with calcification and degeneration, which leads to impaired blood flow from the left ventricle to the aorta. Atherosclerosis is a chronic disease of the arteries, which most often involves the aorta and medium-sized arteries, and its course, like aortic stenosis, is associated with inflammation. It can also develop, among others, as a result of disorders of lipid and carbohydrate metabolism, which are directly related to the risk of cardiovascular disease.

Many compounds, including nucleotides and nucleosides, play an important role not only inside the cell but also on its surface, activating specific receptors. Their role includes the regulation of inflammatory processes. ATP (adenosine-5'-triphosphate) works mainly pro-inflammatory, while adenosine (the final metabolite of ATP metabolism) is known for its anti-inflammatory properties. The concentration of these compounds is due to enzymes on the cell surface, such as ecto-5'-nucleotidase (CD73). Its main substrate is AMP (adenosine-5'-monophosphate), and its activity leads to the formation of adenosine. CD73 is also less responsible for the metabolism of another nucleotide that appears in the extracellular space - nicotinamide adenine dinucleotide (NAD). In turn, the main enzyme involved in NAD metabolism is the enzyme CD38 (ecto-NADase), which leads to the formation of nicotinamide (NAM) and ADPR (adenosine-5'-diphosphate ribose), from which adenosine can be formed indirectly. ADPR is also responsible for increasing the concentration of calcium in the cell and regulating inflammatory processes.

CD38 is a multifunctional protein, which means that it can serve as an enzyme (responsible for various chemical reactions), as well as an adhesive molecule that helps other cells stick together and contact each other directly. CD38 is also a known marker in the recognition of B lymphocytes and a therapeutic target in the treatment of multiple myeloma. In our studies, we have shown that on the surface of calcified aortic valves from patients with aortic stenosis, there is increased NAD catabolism, in which CD38 has the largest share, while CD73 activity decreases. It has already been observed that in people with a mutation in the gene coding for CD73, leading to a deficit in its activity, scientists have observed an intensified process of calcification of blood vessels. However, few papers have been written that would explain the role of increased CD38 in the development of aortic stenosis and atherosclerosis.

Therefore, the goal of this project will be to investigate the role that CD38 plays in the development of aortic stenosis as well as atherosclerosis on *in vitro, in vivo,* and *ex vivo* models. We will examine the cellular origin of this enzyme and determine the mechanism of its action. During research on cell lines and primary cells that build the aortic wall and the aortic valve, the cells will undergo stimulation to increase or inhibit CD38 activity. We will assess the effect of CD38 on the proper functioning of cells and the participation of this enzyme in the inflammatory process and signaling pathways that bind to them. The obtained results will help in the implementation of planned studies using mice that are animal models of aortic stenosis (CD73-/-) and atherosclerosis (ApoE/LDLr--/--). We will track the lesions and activity of CD38 with mice age, as well as the signaling pathways through which this enzyme works. We will also carry out experiments with treating a group of mice with a specific CD38 inhibitor and assess whether inhibiting its activity limits the development of the disease. The final step will be to assess CD38 activity and its effect on signaling pathways in pathologically altered aortic valves and aortic fragments obtained from patients undergoing aortic valve replacement and Bentall surgery.

The key is to clarify whether the increased activity of CD38 we observe is a result of the development of valve and vessel pathologies, or whether it is CD38 that leads to a disorder in the proper functioning of the cell and the development of cardiovascular diseases. The implementation of the project can significantly contribute to expanding knowledge in the field of the pathophysiology of these disorders. The obtained results may in the future be the basis for an innovative therapeutic strategy.