Title: Analysis of the effects of proteotoxic stress on cholesterol homeostasis and its associations with cardiovascular disease and cancer risk.

Cardiovascular diseases resulting from atherosclerosis and cancer are the leading cause of death worldwide. It is widely accepted that high blood levels of cholesterol (especially low-density lipoprotein fraction, LDL, so-called “bad cholesterol”) are responsible for the development of atherosclerosis. Therefore, pharmacological reduction of cholesterol levels in the blood is recommended. To achieve this, one can block cholesterol synthesis (using statins), inhibit its absorption in the intestines, or increase the uptake of cholesterol from the blood by cells containing the LDL receptor (LDLR), mainly in the liver. In the studies conducted so far, we have noticed that increasing body temperature can lead to an increase in the number of LDLR receptors and this is directly dependent on the HSF1 protein. HSF1 is a major transcription factor activated by various forms of proteotoxic stress (i.e. causing protein damage in the cell). Our observation suggests that activation of HSF1 (occurring, for example, during fever or hyperthermia) could lower the level of cholesterol in the circulation and counteract atherosclerosis, and therefore would be beneficial for the body. The results available in the literature on the involvement of HSF1 in the development of atherosclerosis are inconclusive. This may be due to the fact that some of them were obtained using a mouse model of atherosclerosis, in which the animals lack the gene encoding the LDL receptor (*Ldlr* knockout). On the other hand, it is known that excessive HSF1 activity in tumors may result in a worse prognosis for the patient. At the same time, reduced serum lipid (and therefore cholesterol) levels are associated with an increased risk of cancer. Although cardiovascular disease and cancer share some common risk factors and are often comorbidities, there are few studies explaining the interrelationships between them, in particular the influence of heat shock and HSF1 on their development.

In our studies, we plan to create an experimental mouse model with a knockout of the *Apoe* gene (in these mice, aortic atherosclerosis develops as a result of a high-fat diet), a knockout of the *Hsf1* gene, and a double knockout (*Apoe* and *Hsf1*). Using this model and human cancer cell lines with normal HSF1 levels and without HSF1, we intend to characterize the expression of LDLR induced by heat shock. We also intend to study the effect of LDLR changes on processes related to atherosclerosis development, such as the ability of cells to uptake cholesterol, blood cholesterol levels, inflammatory cytokine profile, and the ability of macrophages to take up oxidized LDL. By inducing atherosclerosis development with a high-fat diet, we will examine the impact of HSF1 deficiency on the development of atherosclerosis in mice, blood lipid and cytokine profiles, and macrophage function. Then, using a mouse model of melanoma, we will investigate how HSF1 and concomitant atherosclerosis affect cancer development.

The proposed project should clarify the hypothetical role of proteotoxic stress and HSF1 in the development of atherosclerosis (or, more precisely, whether the lack of HSF1 will promote its development). We assume that we will be able to determine which inflammatory processes accompany the development of atherosclerosis and which of them are dependent on HSF1. We will also clarify whether a diet high in fat, leading to atherosclerosis, can promote tumor growth and what role HSF1 plays in this process.