

Atherosclerosis is the primary cause of heart disease and stroke. Disorders such as, for example, too high blood glucose levels, accelerate disease progression by premature cellular senescence, particularly endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) senescence. Senescent cells do not proliferate, but neither do they die. Our data demonstrate that these cells modulate their environment and affect other cells by secreting a number of pro-inflammatory cytokines, chemokines and growth factors that may promote the development of atherosclerotic lesions. These factors also recruit cells of the immune system, such as macrophages, which remove senescent cells. But why do some senescent cells accumulate while others are removed from the tissue? What leads to the disturbed clearance and, as a result, accumulation of such cells actively producing a range of pro-inflammatory and pro-atherosclerotic factors? Our preliminary data indicate that this may depend on the senescence trigger. However, the type of tissue, molecules displayed on the surface or secreted by cells, and impaired phagocyte function can also play a role.

Unfortunately, investigation of senescent cells is difficult due to the lack of fully specific and universal markers. These cells are typically defined by the simultaneous detection of several biochemical markers such as senescence-associated protein expression and secretion and DNA damage, although they are not exclusively present in senescent cells. Therefore, there is a need to identify new senescence markers that would uniquely define these cells.

Hyperglycemia, defined as too high blood glucose levels, accelerates atherosclerosis through increased oxidative stress, which among others accelerates cellular senescence. However, it is not fully understood why cellular antioxidant mechanisms fail in atherosclerosis. The transcription factor NFE2L2 (NRF2) is the master transcriptional regulator of cellular redox homeostasis and its activity is tightly regulated by oxidative stress. Our previous work demonstrated a significant role of this protein in post-ischemic angiogenesis, cancer development, and neurological disorders. Importantly, the activity of Nrf2 decreases with age and in diabetes. Deficiency of this factor leads to impaired antioxidant response and decreased phagocytic activity of macrophages.

Accordingly, this project is based on two hypotheses: 1) Hyperglycemia induces specific senescence-related markers in ECs and VSMCs and impairs the recognition and removal of these cells from the vascular wall by macrophages, and 2) Decreased Nrf2 activity in macrophages increases oxidative stress, impairs the function and phagocytic activity of these cells, and contributes to the progression of atherosclerotic plaque. To test these hypotheses, we will develop two specific aims: 1) Determine the effect of hyperglycemia on the transcriptome, proteome and secretome of senescent ECs and VSMCs and their cross-talk with macrophages, and 2) Determine the effect of Nrf2 deficiency on the phenotype and function of macrophages and their role in atherosclerotic plaque development.

We are convinced that the results of this project will improve our understanding of the biology of senescent cells, their role in vascular homeostasis and disease. We believe that the planned broad-spectrum analyses using mouse and human cells and tissues will enable us to identify novel shared features of senescent cells formed under hyperglycemia. In the future, they could be used as biomarkers enabling identification of these cells in diabetes. We are also convinced that this project will help to identify genes and signaling pathways crucial for the interaction of senescent ECs or VSMCs with macrophages and for the disturbed clearing of senescent cells from atherosclerotic plaques. In the future, modification of these key signaling pathways could ameliorate or even stop progression of atherosclerosis.