Aging is a complicated biological process leading to progressive deterioration of physiological function and increased vulnerability to death and diseases. Recently much progress has been done in our understanding the nature of this process. It was demonstrated that aging at the cellular level – cellular senescence, significantly influence the lifespan and healthspan. Cellular senescence is a stress induced program that leads to irreversible cell cycle arrest accompanied by a set of distinct phenotypical and functional changes. Importantly the features of senescent cells evolve with time, leading to progression from early senescent cells into late/deep senescent cells, that accumulates and remain for long time in the tissues of the organism. However, our knowledge about these changes and its relevance is limited. One of the most important features of senescent cells, called *Senescence Associated Secretory Phenotype* (SASP), is their ability to secret a number of biologically active factors. Moreover senescent cells release increased number of senescence associated extracellular vesicles (sen-EVs) that play important role in the intercellular communication. Thus by releasing both soluble and vesicular components of SASP senescent cells actively modulate the tissue microenvironment but also act systemically by creating low grade inflammation state. Importantly, the level of secreted SASP factors can be modified. We hypothesis that one of the processes that can actively influence senescent cells secretion is autophagy. It was demonstrated that, depending on the cellular context, autophagy can facilitate or counteract senescence; however its role in the modulating phenotype of already senescent cells has not been studied.

Atherosclerosis is one of the most common age-related diseases. It involves the formation of lesions in the arteries called atherosclerotic plaques. Progression of this disease leads to the development of unstable plaques and plaque rupture that could cause a sudden thrombotic occlusion. During plaque maturation vascular smooth muscle cells (VSMCs) undergo senescence and accumulate in the fibrous cap of plaques. Factors secreted by senescent VSMCs facilitate plaque destabilization by driving plaque inflammation and matrix degradation. Thus investigation of the regulatory mechanisms of SASP can help us to counteract the detrimental role of senescent VSMCs in atherosclerosis.

The general aim of the proposal is to comprehensively characterized the state of deep senescent VSMCs on the level of gene expression, protein composition and secretory phenotype (SASP) and to analyze the role of autophagy regulation on extracellular vesicles and soluble factors secretion by senescent VSMCs at different stages of this process (early versus deep senescence).

We believe that comprehensive characterization of late senescent cells will allow to define the unique molecules or signaling pathways that support the survival and metabolic activity of late/deep senescent cells relevant for development of age and age-related diseases. Recently, an idea of selective elimination of senescent cells using senolytic compounds has gain much interest as a strategy to ‘treat’ age-related diseases. Importantly, elimination of senescent cells is not always necessary in order to limit their harmful effect. Most studies emphasize the importance of factors secreted by senescent cells in the pro-aging activity of these cells. Therefore, unraveling the role of autophagy in the regulation of SASP including EVs open the new possibilities of influencing the senescence phenotype and by this mean also the development of some age-related diseases.