

Cellular senescence is a fundamental and inevitable process concerning all types of cells building tissue and organs, and it is believed that cellular senescence is a cause of aging and age-related diseases. Senescent cells cease to proliferate, but they are metabolically active and therefore can influence their neighborhood. Cells exhaust their proliferative potential as a result of telomere erosion (replicative senescence) or senesce in an accelerated manner as a result of stress (stress induced premature senescence). Senescence concerns both proliferating cells and cells which do not divide in the organism, e.g., post-mitotic cells such as neurons (chronological senescence). Senescence can be induced also in cells which acquired the ability to proliferate endlessly, namely in cancer cells which can be considered as anticancer approach. Senescent cells are characterized by multiple biochemical and morphological changes. One of the most important features of senescent cells is senescence associated secretory phenotype (SASP). Cells which have undergone senescence secrete soluble factors, such as mediators of inflammation and growth factors. By secreting proteins into the extracellular matrix (paracrine manner), senescent cells change the microenvironment and, due to increased inflammation, harm the surrounding cells and accelerate their senescence. The physiological function of cellular senescence is complex. On the one hand, cellular senescence is an anticancer barrier (inhibition of proliferation of damaged cells) and is necessary for tissues regeneration (preventing of scar tissue formation). On the other hand, a long-term presence and excessive number of senescent cells can promote tissue damage and aging. Senescent cells begin to accumulate with age. The percentage of senescent cells varies in different types of tissues. However, even if the number is not very high, the presence of senescent cells can lead to impaired functioning of tissues and organs, because of a chronic low grade inflammation which is one of the features of the aged organism.

Communication between cells plays an important role in senescence. Until recently it has been believed that senescent cells communicate only by a paracrine manner, namely by SASP. However, recent studies have shown that senescent cells can communicate with neighboring cells also in a direct way, namely by forming cytoplasmic bridges (CBs), which are involved in the transfer of proteins from a senescent cell to distant cells. In this manner proteins which normally are not secreted can be transferred between cells. Such manner of communication has been already described for different types of cells, however its role in senescent cells has not yet been examined. The physiological function of such type of communication is not fully understood. The key role in CBs formation play actin and Cdc42. There is no information about the contribution of other proteins interacting with actin and responsible for the establishment of CBs. One of the potentially good candidates to be involved in direct intercellular protein transfer (IPT) could be IQGAP1. This protein has binding domains for both actin and Cdc42, and is involved in fundamental cellular processes, such as reorganization and dynamics of the actin cytoskeleton, cell proliferation, migration, intracellular signaling, cell polarization and also in the formation of cellular protrusions. Therefore, the aim of this proposal is to verify whether IQGAP1 is involved in the formation of CBs in vascular smooth muscle cells. We also plan to analyze the direction of the protein transport by CBs. We are interested the transport is preferentially performed by senescent cells or is senescence-independent. Primary human vascular smooth muscle cells isolated from aorta will be used as an experimental model. Our previous research has shown that this type of cells forms numerous CBs and IQGAP1 has been found in these protrusions. The involvement of IQGAP1 in CBs formation will be analyzed after gene knock-down or introduction of protein with mutated binding domains for actin and Cdc42. The direction of the transport will be analyzed by tracking the flow of a fluorescent protein or a dye from cell to cell.

This proposal could help to understand the mechanism of CBs formation and, at least partially, elucidate the physiological role of such type of communication. Such studies are especially appropriate in vascular smooth muscle cells because they are directly involved in the pathology of atherosclerosis. It has been shown that cells isolated from atherosclerotic plaques are characterized by limited proliferation potential and by the presence of some senescence markers. Obtained results could provide the basis for the further studies of such type of communication of senescent vascular smooth muscle cells with other integral compounds of atherosclerotic plaques such as endothelial and immune cells.