Abstract

Senescence is a specific cell state distinquished by cessation of cell division and proliferation and changes in gene expression. Normal cells enter senescence after distinct number of cell divisions or in case of an unrepairable damage. Senescence in cancer cells can be induced by subliminal stress as sublethal treatment with certain drugs. Senescent cancer cells persist in the tissue and may secrete a number of factors and nutrients affecting surrounding cells. Senescence can thus change the response of cancer cells to various apoptogens during cancer therapy. In this study, we focused on the elucidation of presumed differences between normal proliferating and senescent cancer cells in their response to selected apoptogens. Implementing bromodeoxyuridine (BrdU)-mediated replication stress in cancer cells derived from pancreatic (PANC-1) or mesothelioma (H28) tumors, we efficiently forced these cells to acquire senescent phenotype. We document that these senescent cells gain higher resistance to combined TRAIL and homoharringtonine (HHT) treatment and enhance sensitivity to other apoptogens such as FasL, camptothecin and mVES. These cells also showed increased expression of anti-apoptotic protein c-FLIP in senescent cells and changes in the expression of some Bcl-2 family proteins. ShRNA-mediated downregulation of c-FLIP expression sensitized H28 cells to BrdU treatment but it apparently did not affect attenuated sensitivity of senescent H28 shFLIP cells to TRAIL+HHT treatment. We also generated clones of H28 cells inducibly overexpressing two CDK inhibitors, $p21^{CIP1/WAF1}$ and p16. These cells exhibited some markers of senescent cells and became resistant to most apoptogens. However, these cell-cycle arrested cells lack some aspects of senescent phenotype arising probably from DNA damage signaling which precedes senescence. In this work we confirmed and extended some previous findings, gathered new, potentially interesting data on a role of c-FLIP, death receptors, Bcl2 family and cell cycle inhibitors in the communication between cellular senescence and apoptotic signaling and slightly opened door for further discoveries in this so far overlooked field of research.

Keywords: apoptosis, cell death, senescence, death receptors, c-FLIP, $p21^{CIP1/WAF1}$, $p16^{ARF/INK4a}$, cancer cells