CANCER SENESCENT CELLS DIFFER FROM THEIR PROLIFERATING COUNTERPARTS IN THEIR RESPONSE TO CELL DEATH-INDUCING AGENTS

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Increasing and persisting incidence of senescence cells has been shown to have detrimental effect on an organism contributing to pro-aging features. Senescence normal as well as cancer cells seems to have modified apoptotic signaling at the level of mitochondria and Bcl-2 family proteins. Within tumour the presence of senescent cells positively support its growth and can even stimulate transformation of surrounding cells. Senescence state of tumour cells can be triggered by chemotherapy or spontaneously induced. Thus, for the effective cancer therapy it would be beneficial to eliminate senescent cancer cells along with the ordinary cancer cells. Current strategies for elimination of senescent (cancer) cells target mitochondria exploiting their intrinsic apoptotic signaling as well as mitochondrial bioenergetics.

Two main senescence induction signalings downstream of initial stimuli employ either p16/pRb or p53/p21 pathways. In our model of senescent cancer cells we used mild and controllable approach employing inducible expression of p16 or p21 in mesotheliomal cancer H28 cells and clonal selection. In addition to the analysis of their growth and bioenergetics profile we aimed to screen and analyze their response to various cell death-inducing agents/drugs including those directly targeting mitochondria.

Though p16- and p21-induced pro-senescence phenotype (growth, cell shape and mitochondrial profiles) differed between p16 and p21 H28 clones they responded similarly to various cell death stimuli. In both p16 and p21 clones we observed an increase of mitochondrial mass and ROS production though to a significant lesser extent in p16-expressing cells. We show that senescent cancer cells are more resistant to ROS- mediated cell death induced by mitochondrially-targeted vitamin E succinate (mitoVES) and interestingly also to TRAIL-induced apoptosis enhanced by homoharringtonine. However and interestigly, they became more sensitive to FasL- and Bcl-2/BcL-XL-targeting drug ABT-737-triggered apoptotic signaling. These data together with their bioenergetics profiling might be instrumental in better understanding (cancer) senescence phenotype and pave a way for more effective cancer therapy.