EFFECTS OF THE STAT3 INHIBITORS ON SENESCENT TUMOR CELLS

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Background Cellular senescence is the process of cell proliferation arrest. Premature cellular senescence can be induced by chemotherapy, irradiation and, under certain circumstances, by cytokines. Senescent cells produce a number of secreted proteins and growth factors that may either stimulate or inhibit cell proliferation. One of the major cytokines that play a role in regulation of cellular senescence is IL-6. IL-6/STAT3 signaling pathway represent decisive regulatory factors in cellular senescence. The objective of this study was to compare the effects of the STAT3 inhibitors on senescent and proliferative tumour cells. Further, the therapeutic potential of the STAT3 inhibitors was evaluated using murine tumour models.

Materials and Methods In vitro, as well as in vivo experiments were performed using TC-1 (model for HPV16-associated tumours) TRAMP-C2 (prostate cancer) cell lines. C57Bl/6NCtrl mice, 7–8 weeks old, were obtained from Velaz (Prague, Czech Republic). Experimental protocols were approved by the Institutional Animal Care Committee of the Institute of Molecular Genetics (Prague, Czech Republic). STAT3 inhibitors, namely STATTIC, BP-102 (synthesised at the University of Hradec Kralove) and MassArray, Pierre-Fabre, Novartis, Merck MSD, Roche. C.U.

Results We have previously demonstrated that docetaxel-induced senescence in the TC-1 and TRAMP-C2 murine tumour cell lines, which was proved by in vitro (detection of increased p21 expression, positive beta-galactosidase staining, and the typical SASP capable to induce ‘bystander’ senescence), and in vivo experiments, using C57BL/6 mice [1]. Both TC-1 and TRAMP-C2 cells displayed elevated IL-6 secretion and activated STAT3 signaling pathway. Therefore, we tested efficacy of the STAT3 inhibitors on these cell lines. Cytotoxic and STAT3 phosphorylation inhibitory effects of the inhibitors were observed in both proliferating and senescent cells. Antitumor effects of selected inhibitors were evaluated.

Conclusions Collectively, STAT3 is an attractive target for therapeutic approaches in cancer treatment and we can assume that inhibition of the STAT3 pathway can be used for elimination of the pernicious effects of the senescent cells.