SUMMARY

Cellular senescence is a state of proliferation arrest that can be induced in cancer cells by anticancer therapies. Although this mechanism limits tumor growth, senescent cells remain metabolically active and secrete a variety of pro-inflammatory factors and modulators of the tumor microenvironment, known as senescence-associated secretory phenotype (SASP). The impact of these factors on immune responses is crucial for the efficacy of cancer therapies, yet it remains incompletely understood. In this study, we evaluated the effects of etoposide-induced senescence in bladder cancer HCV29 cells and non-small cell lung cancer A549 cells on interactions with NK-92 cells, as well as the independent influence of SASP on the functionality of this NK cell line.

Our results confirmed the presence of senescence-associated features in the cancer cells, including increased β-galactosidase activity, hypertrophy, G2/M cell cycle arrest, and elevated secretion of IL-8 and VEGF. Analysis of interactions with NK-92 cells revealed that senescence induction in HCV29 and A549 did not enhance their cytotoxicity, despite active NK-92 recruitment, evidenced by multicellular attacks on examined senescent cells. The limited cytotoxicity correlated with reduced expression of NK-activating ligands (ULBP-2/5/6, PVR) and the immunosuppressive effects of SASP, which decreased NK-92 viability and effector activity. This effect was especially evident with medium conditioned by HCV29 cells and correlated with higher concentrations of pro-inflammatory mediators. Notably, this effect was not observed in primary NK cells ($CD56^+$) or PBMCs, indicating its specificity to the NK-92 line.

The heterogeneity of SASP in the studied cancer cell lines reflects its variable capacity to modulate NK-92 viability and effector functions. This is particularly relevant in the context of the increasing use of engineered NK cells in cancer immunotherapy, including NK-92, and may provide a basis for developing novel therapeutic strategies.