Mechanisms of Communication between Senescent cells and NK cells

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Abstract

NK-cell-mediated immune surveillance of senescent cells is one component of the coordinated process whereby cellular senescence limits the extent of liver fibrosis and facilitates wound repair. Recent studies also suggest that senescent cell recognition and clearance by immune cells promotes tumor regression in established tumors. Our results demonstrate that senescent cells are preferentially recognized and killed by NK cells. We show that DNA damage-induced senescent fibroblasts specifically upregulate the NKG2D immune ligands MICA, ULBP1 and ULBP2. Furthermore, we demonstrate that ERK signaling contributes to this immune ligand upregulation, independent of p53 and NFκB. Importantly, the upregulation of MICA and ULBP2 on the cell surface of senescent cells is pivotal for the NK-mediated recognition, since interference with the receptor-ligands interactions inhibits the NK-mediated clearance both *in vitro* and *in vivo* to limit liver fibrosis and facilitate tissue repair. Lastly, we demonstrate that the granule exocytosis pathway, but not the death receptor pathway, is necessary for the specific killing of senescent fibroblasts and stellate cells by NK cells and participates in the clearance of senescent activated HSCs to limit liver fibrosis. We suggest that this pathway bias is mediated by the upregulation of Dcr2, a decoy receptor for the death ligand TRAIL, by senescent cells. Therefore, NK-cell-mediated recognition of senescent cells via NKG2D ligands and killing through NKG2D signaling and the granule exocytosis pathway contributes to immune surveillance of senescent cells *in vitro* and *in vivo*.