Defective localization with impaired tumor cytotoxicity contributes to the immune escape of NK cells in pancreatic cancer patients

ABSTRACT

Tumor infiltrating lymphocytes (TILs), found in patients with advanced pancreatic ductal adenocarcinoma (PDAC), are shown to correlate with overall survival (OS) rate. Although majority of TILs consist of $CD8^+$/$CD4^+$ T cells, the presence of NK cells and their role in the pathogenesis of PDAC remains elusive. We performed comprehensive analyses of TIL, PBMC, and autologous tumor cells from 80 enrolled resectable PDAC patients to comprehend the NK cell defects within PDAC. Extremely low frequencies of NK cells (< 0.5 %) were found within PDAC tumors, which was attributable not to the low expression of tumor chemokines, but to the lack of chemokine receptor, CXCR2. Forced expression of CXCR2 in patients' NK cells rendered them capable of trafficking into PDAC. Furthermore, NK cells exhibited impaired cell-mediated killing of autologous PDAC cells, primarily due to insufficient ligation of NKG2D and DNAM-1, and failed to proliferate within the hypoxic tumor microenvironment. Importantly, these defects could be overcome by *ex vivo* stimulation of NK cells from such patients. Importantly, when the proliferative capacity of NK cells *in vitro* was used to stratify patients on the basis of cell expansion, patients whose NK cells proliferated < 250-fold experienced significantly lower DFS and OS than those with ≥ 250-fold. *Ex vivo* activation of NK cells restored tumor trafficking and reactivity, hence provided a therapeutic modality while their fold expansion could be a potentially significant prognostic indicator of OS and DFS in such patients.