The role of NK cell NKG2D in human hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the second-leading cause of cancer-related deaths. NK cells form 30-50% of human intrahepatic lymphocytes. They have a double-edged character in the liver, a uniquely tolerogenic site. HCC may express both soluble and cell-bound NKG2D-ligands (NKG2D-L) but it is unclear whether NK cells perform tumour surveillance of HCC.

We found for the first time that soluble ULBP1 is significantly increased in sera from HCC patients compared to non-malignant liver disease. However, in the same donors, we saw no downregulation of NKG2D on circulating NK cells. By contrast NK cells infiltrating HCC had reduced NKG2D expression compared to those in surrounding liver margins or from livers with non-malignant disease.

Our group has recently defined a population of liver-resident NK cells characterised by a CXCR6+, CD69+, Tbetlo, Eomeshi phenotype. Liver-resident NK cells were consistently found within the tumour-infiltrating population and showed a greater reduction of NKG2D than their non-resident counterparts, suggesting persistent exposure to the tumour environment drives downregulation.

Taken together, these findings indicate that peripheral NK cells are able to maintain NKG2D expression in the face of high concentrations of NKG2D-L whereas NK cells within the tumour milieu are subject to NKG2D down-regulation. To investigate this we co-cultured peripheral and intrahepatic NK cells with even higher concentrations of NKG2D-L than found in patient sera, but did this not down-regulate NKG2D. Instead, PLC/PRF/5 cells, an HCC cell line that expresses high levels of the NKG2D ligand MICA/B, caused NKG2D downregulation on both peripheral and intrahepatic NK cells. These NK cells exhibited reduced cytotoxicity on subsequent challenge. Preliminary experiments suggest this effect may be inhibited by blockade of NKG2D-MICA/B interactions.

Inhibitors of NKG2D engagement by HCC cells may paradoxically maintain anti-tumour immunity, providing novel targets for tumour immunotherapy.