A hypoxia-induced decrease of either MICA/B or Hsp70 on the membrane of tumor cells mediates immune escape from NK cells.

Recent findings suggest that hypoxia of the tumor microenvironment contributes to immune escape from natural killer (NK) cell-mediated cytotoxicity. Heat shock protein 70 (Hsp70) and the stress-regulated major histocompatibility class I chain-related protein A and B (MICA/B) both serve as ligands for activated NK cells when expressed on the cell surface of tumor cells. Herein, we studied the effects of hypoxia and hypoxia-inducible factor-1? (HIF-1?) on the membrane expression of these NK cell ligands in H1339 with high and MDA-MB-231 tumor cells with low basal HIF-1? levels and its consequences on NK cell-mediated cytotoxicity. We could show that a hypoxia-induced decrease in the membrane expression of MICA/B and Hsp70 on H1339 and MDA-MB-231 cells, respectively, is associated with a reduced sensitivity to NK cell-mediated lysis. A knockdown of HIF-1? revealed that the decreased surface expression of MICA/B under hypoxia is dependent on HIF-1? in H1339 cells with high basal HIF-1? levels. Hypoxia and HIF-1? did not affect the MICA/B expression in MDA-MB-231 cells but reduced the Hsp70 membrane expression which in turn also impaired NK cell recognition. Furthermore, we could show that the hypoxia-induced decrease in membrane Hsp70 is independent of HIF-1? in MDA-MB-231. Our data indicate that hypoxia-induced
downregulation of both NK cell ligands MICA/B and Hsp70 impairs NK cell-mediated cytotoxicity, whereby only MICA/B appears to be regulated by HIF-1?.