Irradiation-induced up-regulation of HLA-E on macrovascular endothelial cells confers protection against killing by activated natural killer cells.

Abstract:
Apart from the platelet/endothelial cell adhesion molecule 1 (PECAM-1, CD31), endoglin (CD105) and a positive factor VIII-related antigen staining, human primary and immortalized macro- and microvascular endothelial cells (ECs) differ in their cell surface expression of activating and inhibitory ligands for natural killer (NK) cells. Here we comparatively study the effects of irradiation on the phenotype of ECs and their interaction with resting and activated NK cells. Primary macrovascular human umbilical vein endothelial cells (HUVECs) only express UL16 binding protein 2 (ULBP2) and the major histocompatibility complex (MHC) class I chain-related protein MIC-A (MIC-A) as activating signals for NK cells, whereas the corresponding immortalized EA.hy926 EC cell line additionally present ULBP3, membrane heat shock protein 70 (Hsp70), intercellular adhesion molecule ICAM-1 (CD54) and HLA-E. Apart from MIC-B, the immortalized human microvascular endothelial cell line HMEC, resembles the phenotype of EA.hy926. Surprisingly, primary HUVECs are more sensitive to Hsp70 peptide (TKD) plus IL-2 (TKD/IL-2)-activated NK cells than their immortalized EC counterparts. This finding is most likely due to the absence of the inhibitory ligand HLA-E, since the activating ligands are shared among the ECs. The co-culture of HUVECs with activated...
NK cells induces ICAM-1 (CD54) and HLA-E expression on the former which drops to the initial low levels (below 5%) when NK cells are removed. Sublethal irradiation of HUVECs induces similar but less pronounced effects on HUVECs. Along with these findings, irradiation also induces HLA-E expression on macrovascular ECs and this correlates with an increased resistance to killing by activated NK cells. Irradiation had no effect on HLA-E expression on microvascular ECs and the sensitivity of these cells to NK cells remained unaffected. These data emphasize that an irradiation-induced, transient up-regulation of HLA-E on macrovascular ECs might confer protection against NK cell-mediated vascular injury.