The MICA-129Met/Val dimorphism affects plasma membrane expression and shedding of the NKG2D ligand MICA.

Abstract:

The MHC class I chain-related molecule A (MICA) is a ligand for the activating natural killer (NK) cell receptor NKG2D. A polymorphism causing a valine to methionine exchange at position 129 affects binding to NKG2D, cytotoxicity, interferon-? release by NK cells and activation of CD8(+) T cells. It is known that tumors can escape NKG2D-mediated immune surveillance by proteolytic shedding of MICA. Therefore, we investigated whether this polymorphism affects plasma membrane expression (pmMICA) and shedding of MICA. Expression of pmMICA was higher in a panel of tumor (n = 16, P = 0.0699) and melanoma cell lines (n = 13, P = 0.0429) carrying the MICA-129Val/Val genotype. MICA-129Val homozygous melanoma cell lines released more soluble MICA (sMICA) by shedding (P = 0.0015). MICA-129Met or MICA-129Val isoforms differing only in this amino acid were expressed in the MICA-negative melanoma cell line Malme, and clones with similar pmMICA expression intensity were selected. The MICA-129Met clones released more sMICA (P = 0.0006), and a higher proportion of the MICA-129Met than the MICA-129Val variant was retained in intracellular compartments (P = 0.0199). The MICA-129Met clones also expressed more MICA messenger RNA (P = 0.0047). The latter phenotype was
also observed in mouse L cells transfected with the MICA expression constructs (P = 0.0212). In conclusion, the MICA-129Met/Val dimorphism affects the expression density of MICA on the plasma membrane. More of the MICA-129Met variants were retained intracellularly. If expressed at the cell surface, the MICA-129Met isoform was more susceptible to shedding. Both processes appear to limit the cell surface expression of MICA-129Met variants that have a high binding avidity to NKG2D.