HER-2/neu-mediated regulation of components of the MHC class I antigen-processing pathway.

Abstract: Because of its amplification and/or overexpression in many human tumors, the HER-2/neu proto-oncogene represents an attractive target for T-cell-mediated vaccination strategies. However, overexpression of oncogenes is often associated with defective expression of components of the MHC class I antigen-processing machinery (APM), thereby resulting in an immune escape phenotype of oncogene-transformed cells. To determine whether HER-2/neu influences the MHC class I antigen-processing pathway, the expression pattern of different APM components was examined in murine in vitro models of constitutive and tetracycline-controlled HER-2/neu expression. In comparison with HER-2/neu(-) control cells, HER-2/neu(+) fibroblasts exhibit reduced levels of MHC class I surface antigens that were associated with impaired expression and/or function of the peptide transporter associated with antigen processing, the proteasome subunits low molecular weight protein 2 and low molecular weight protein 10, the proteasome activators PA28alpha and PA28beta, and tapasin. These APM abnormalities resulted in reduced sensitivity to lysis by CTLs. The HER-2/neu-mediated immune escape phenotype could be corrected by IFN-gamma treatment. The clinical relevance of this finding was supported by an inverse correlation...
between HER-2/neu and the peptide transporter associated with antigen-processing protein expression as determined by immunhistochemical analysis of a series of HER-2/neu(-) and HER-2/neu(+) breast cancer specimens. Thus, a functional link between deficient APM component expression and HER-2/neu overexpression is proposed that might influence the design of HER-2/neu-targeted T-cell-based immunotherapeutic strategies.