THE IMPACT OF KIR-GENE EXPRESSION ON NK CELLS MEDIATED KILLING OF MULTIPLE MYELOMA CELLS IN VITRO
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Multiple myeloma (MM) is an incurable plasma cell malignancy. Natural killer (NK) cells have demonstrated anti-MM activity in allogeneic transplants and donor lymphocyte infusions and may provide a more effective therapy for MM. Responsible for the anti-myeloma effect of NK cell against MM cells is the interaction between Killer cell immunoglobulin-like receptors (KIRs) against different human leukocyte antigens (HLAs), like HLA-Cw, on the target cells. The most important inhibiting KIRs KIR2DL2 and KIR2DL3 binding to HLA-Cw group C1 and KIR2DL1 binding to C2, control the NK cell mediated killing of target cells, if their corresponding C1 or C2 is absent or present on these cells. We used the KHYG-1 cell line as a model for human NK cells in vitro. As target cells we used the MM cell lines MOLP-8 (C1/C2), KMS-12-BM (C1/C1) and RPMI-8226 (C1/C2) and the acute myeloid leukemia (AML) cell line OCI-M1 (C2/C2). To demonstrate the effectiveness KHYG-1 against these target cells, we manipulated the expression of KIR2DL1 and KIR2DL3 by siRNA mediated silencing or gene transfer. The down- or up-regulated KIR expression mediated cytotoxicity of KHYG-1 against MM cells was identified in LDH release, flow cytometry cytotoxicity (7-AAD) and chromium release assays. We could show that as expected, down-regulation of one of the both inhibiting KIRs above, directed decrement and up-regulation of one of these KIRs directed modulation of KHYG-1 (NK cell) mediated MM (leukemia) cell killing. (Manipulated) NK cell lines, like KHYG-1, may offer a more effective therapy for multiple myeloma in future.