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POSTER PRESENTATION

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P16. Differential susceptibility of human and mouse NK cells to malignant cell-induced abnormalities in autologous combinations: a potential mechanism for the NK cell-based immunotherapy efficacy

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Background

Natural killer (NK) cells are highly effective in controlling tumour growth, in mice, but have no significant effect in humans. The reason(s) of this phenomenon is (are) unclear.

Methods

The effects of cancer cells on NK cells during target-effector cell conjugation was investigated utilising standard immunological methods including flow cytometry, chromium release and enzyme-linked immunosorbent assays while gene expression was evaluated by quantitative reverse transcriptase-polymerase chain reaction.

Results

We found that this phenomenon was associated with the different susceptibility of human and mouse NK cells to autologous tumour cell-induced NK cell abnormalities (NKCA). The latter includes CD16 down-regulation and NK cell depletion. Induction of NKCA by leukaemia and solid tumour cells was influenced neither by IL2 treatment nor by HLA class I antigen expression, but was abrogated by a 10 day culture. Following a 10 day of PBMCs culture, NK cells became resistant to leukaemia and solid tumor cell induced NKCA but maintained their cytotoxic activity. Actinomycin D restored the susceptibility of long term NK (LTNK) cells to NKCA suggesting that the generation of

resistance to NKCA required RNA transcription. TAPI-0, a functional analogue of the tissue inhibitor of metalloproteinases (TIMP) 3 inhibited cancer cell induced NKCA underlying a role for a restricted number of metalloproteinases in the generation of this phenomenon. Finally, we found an association of TIMP3 gene and protein over-expression with the reduced susceptibility of LTNK cells to cancer cell induced NKCA.

Conclusions

This study provides evidence that TIMP3 plays a role in the protection of LTNK cells from cancer cell induced NKCA.

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