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Modulation of tumour directed B cell responses by NK cells

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Background and aim

Spontaneous natural killer cell (NK cell) activity against malignant cells is important for development of tumour directed Th1 biased and cytotoxic T cell (CTL) responses (Kelly *et al*., *Nature* 2002; Geldhof *et al*, *Blood* 2002) resulting in protection from tumour growth in mouse models. Aim of our investigations was to study the significance of NK cell activity on tumour directed B cell immunity.

Material and methods

Tumour directed B-cell responses were studied in C57Bl/6 mice, NK cells depleted in the experimental group by i.v. injection of anti-ASGM1 antibodies. Mice were immunized human IMR5-75 neuroblastoma cells and tumour specific antibody responses measured by flow cytometry and GD2 specific ELISA.

Results

Spontaneous murine NK activity against the IMR5-75 tumor model as a requested condition for analysing NK cells impact on adaptive responses were demonstrated in SCID mice lacking T- and B-cells, but having functional intact NK cells. Single subcutaneous injections of 3.45–4.0 × 10^7 IMR5-75 cells induced growth of tumor nodules in only 3/10 mice, but in 10/10 NK depleted mice (P < 0.000), demonstrating spontaneous murine NK activity against IMR5-75 cells. 4/4 C57Bl/6 mice immunized with irradiated IMR5-75 cells for two weeks developed significant global serum IgG responses (titer: 2 × 1:160, 2 × 1:320) against the immunizing cells (flow cytometry), while NK depleted control animals revealed only poor responsiveness (titer < 1:40; P = 0.003). Interestingly IgG responses in NK depleted mice after three weeks of immunisation were similar to the controls., This may reflect a delayed B cell answer in NK depleted mice. Dissection of IgG1 and IgG2a isotype specific responses demonstrated a strong impairment in Th1 biased IgG2a track and surprisingly in contrast a "compensatory" enforced Th2 oriented IgG1 response. ELISA based antibody measurement against the tumor specific GD2 ganglioside confirmed the flow cytometry data and demonstrated anti-GD2 responses only in NK depleted animals and only from the Th2 oriented IgG1 isotype. Dissection of GD2 specific IgG1 and IgG2a responses in 8 F004/C57 hybrid mice immunised with the GD2 expressing small cell lung cancer cell line H69 confirmed the Th2 biased GD2 specific B cell response in NK depleted mice as an independent control experiment.

Conclusions

Our data demonstrate an important NK cell regulatory function on the development of tumour directed B cell responses. Since Th1 biased IgG production results in antibodies with higher affinity (IgG1 and IgG3 in humans) for Fc-gamma-receptors than Th2 responses impairment of tumor directed ADCC will be a consequence. Tumour vaccination strategies will have to pay attention on the NK cell status of patients e.g. after chemo- or radiotherapy.