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POSTER ABSTRACTS

203.LYMPHOCYTES AND ACQUIRED OR CONGENITAL IMMUNODEFICIENCY DISORDERS

Crosstalk between NFAT and NFκB Signaling Regulates NK Cell Immunosurveillance

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One of the major transcriptional regulators in lymphoid cells is NFAT (Nuclear Factor of Activated T Cells), controlling lymphocyte development and activity. The role of NFAT signaling is well defined in T cells, the cytotoxic lymphocytes of the adaptive immunity. However, surprisingly little is known regarding the relevance of this transcription factor family in NK cells as effector cells of the innate immunity. Available data indicate that NFAT activity is dispensable for development of NK cells, whereas effects of the immunosuppressive drugs cyclosporin A and tacrolimus, that inhibit calcineurin and consecutively NFAT, implicate an involvement of the NFAT family in NK cell function. We here employed different genetic mouse models and functional analyses to unravel the role of NFAT1 (NFATc2) and NFAT2 (NFATc1) in NK cell reactivity.
In vitro knockout (KO) of NFAT1 (NFATc2) or NFAT2 (NFATc1) enhanced NK cell degranulation and resulted in increased production of granzyme B and perforin upon stimulation of activating receptors like NK1.1 or Nkp46 or upon co-culture with different leukemia and solid tumor cells. In line, cytotoxicity assays revealed increased lysis of YAC-1 and B16F10 tumor cells by both NFAT1- and NFAT2-deficient NK cells as compared to wildtype (WT) controls. The inhibitory effect of NFAT transcription factors on NK cell effector function could also be confirmed *in vivo* by employing WT and NFAT KO animals in syngeneic B16F10 melanoma, RMA-S lymphoma and LL/2-luc lung carcinoma models, which revealed a significantly reduced tumor burden in NFAT1 and NFAT2 KO mice. Furthermore, we detected higher numbers of tumor infiltrating NK cells in NFAT KO mice, which suggested improved NK cell migration and homing to the tumor side. Comparative analyses with single NFAT as well as NFAT1+NFAT2 double KO and WT animals further confirmed the inhibitory effect of NFAT1 and NFAT2 and pointed to additive effects of NFAT1 and NFAT2 in NK cell tumor immunosurveillance. Proteomics analysis of NK cells from the different NFAT KO strains revealed altered expression of molecules which are regulating chemokine receptor expression as well as a decreased expression of NFκB inhibitory molecules, like NFKBIB (NFKB inhibitor beta) Commd6 (COMM domain containing 6). NFκB signaling was shown to regulate granzyme B and perforin synthesis and expression. Thus, we suggest that NFAT1 and NFAT2 inhibit NFκB signaling in NK cells, and NFAT1 and NFAT2 KO reinforce NFκB induced granzyme B and perforin expression and thereby increase NK cell cytotoxicity.
Taken together, our results identify NFAT as a negative regulator of NK cell function. In addition, we provide the first evidence for a direct functional involvement of NFAT1 and NFAT2 in NK cell antitumor reactivity by regulation tumor infiltration and cytotoxicity of NK cell.

Disclosures No relevant conflicts of interest to declare.

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