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Meeting abstract

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Unexpected role of STAT1 serine727 for NK cell function

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Background

Natural killer (NK) cells are important key players of the innate immune system and provide immediate defense against viral infection and tumor transformation. Therefore, their potential in cancer immunotherapy has grown prominently in the last years [1]. As is known from the literature, the Signal Transducer and Activator of Transcription 1 (STAT1) plays an important role for NK cell function, since STAT1-deficient mice display impaired basal NK cytolytic activity *in vitro* and are unable to reject transplanted tumors *in vivo* [2]. STAT1 mediates signals downstream of interferons and gets activated by phosphorylation of several tyrosine and serine residues. In particular phosphorylation of S727 is considered a prerequisite for the full-fledged activation of STAT1 [3]. The aim of this project is to investigate the role of STAT1-S727 in NK cell-mediated cytotoxicity and tumor surveillance.

Methods

The analysis of STAT1$^{-/-}$, STAT1-S727A and wild-type mice includes the preparation of primary splenic NK cells and their investigation regarding proliferation ([^{3}H]thymidine-incorporation), cytotoxicity (standard [^{51}Cr]-release) and cytokine production (ELISA, multi-plex bead arrays). *In vivo* tumor models are employed using NK-sensitive tumor cell lines (v-abl^{+} leukemia, B16 melanoma, 4T1 breast cancer).

Results

Wild-type NK cells from untreated healthy mice display basal phosphorylation on STAT1-S727 *in vivo*. Surprisingly, disruption of this phosphorylation site by mutating serine727 to alanine (STAT1-S727A) significantly enhances NK cell cytotoxicity towards various target cells *in vitro* compared to wild-type. Moreover, we demonstrate that STAT1-S727A mice do not only display delayed leukemia onset but also lower susceptibility to intravenously administered B16 (melanoma) and 4T1 (metastasizing breast cancer) cells compared to STAT1$^{-/-}$ and wild-type mice.

Conclusion

Obviating the phosphorylation of STAT1-S727 seems to increase NK cell cytotoxicity *in vitro* and *in vivo*. As an ultimate goal we aim to find the underlying mechanism(s) and upstream regulator(s), since loosening the brake on NK cell functions could represent a potential novel strategy in cancer therapy.

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