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Meeting abstract

STAT1 Ser727 – key regulator for NK cell-mediated cytotoxicity and tumor surveillance

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The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling cascade plays an important role in hematopoiesis. A constitutive activation of this pathway is found in a broad variety of diverse human and murine leukemias and lymphomas. Whereas STAT3 and STAT5 accelerate and initiate tumor formation, STAT1 is generally considered a tumor suppressor. As shown by Kovacic *et al.* [1], STAT1 accelerates leukemia formation by up-regulation of MHC class I on leukemic cells allowing them to escape natural killer (NK) cell-mediated lysis. In the present study we investigate the role of the STAT1 serine727 phosphorylation site for leukemia initiation and progression. After retroviral leukemia induction $STAT1^{S727A}$ knock-in mice show enhanced disease latency compared to wild type (WT) mice. Upon injection of B16 melanoma cells, numbers of lung metastases were increased in $STAT1^{-/-}$ recipients, but significantly reduced in $STAT1^{S727A}$ mice when compared to WT mice. This indicates that the effect of $STAT1^{S727A}$ may not be cell-intrinsic but rather results from altered interactions with the host immune system. Clearance of leukemic and B16 cells is mainly mediated by NK cells. Therefore, differences in NK cells might explain our *in viv*o data. As determined in a [^{3}H]thymidine incorporation assay, $STAT1^{S727A}$ NK cells showed enhanced proliferation rates compared to WT cells. Moreover, in a classical [^{51}Cr]-release assay $STAT1^{S727A}$ NK cells were able to lyse leukemic cells more efficiently than WT NK cells. NK cells can be divided into different functional subsets according to cell surface expression of DX5, Mac-1 and CD27. *Ex vivo* fluorescence-activated cell sorting (FACS)-based analysis revealed a distinct expression pattern in $STAT1^{S727A}$ NK cells (Mac-1^+, $DX5^+$, $CD27^+$), that is characteristic for a "pre-activated" NK cell phenotype [2] and is found in $STAT1^{S727A}$ mice in spite of the absence of any activating stimulus. These experiments indicate that phosphorylation of STAT1 serine727 in NK cells is relevant for activation, cytolytic function and as a consequence for their ability to eradicate tumor cells *in vivo*.

References

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