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Meeting abstract

Evaluation of Stat5 as a potential drug target in *bcr/abl*-induced leukemias

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The Stat5 transcription factors Stat5a and Stat5b have been implicated in lymphoid development and transformation. Using the complete Stat5 knockout mice, we have previously shown that *Stat5a/b*$^{null/null}$ cells were resistant to transformation and leukemia development induced by Abelson oncogenes, whereas *Stat5a/b*$^{\Delta N/\Delta N}$ cells readily transformed. So far, these findings showed distinct susceptibility to Abelson-induced transformation of *Stat5a/b*$^{\Delta N/\Delta N}$ and *Stat5a/b*$^{null/null}$ mice and defined Stat5 as key regulator of initial transformation. In this study, we tested whether Stat5a/b is also essential for the maintenance of a transformed state. Therefore we developed a system, where Stat5a/b could be deleted at will. Abelson-transformed B lymphoid cells were generated from *Stat5a/b*$^{fl/fl}$ gene targeted mice that had been crossed with Mx-Cre transgenic animals. These leukemic *Stat5a/b*$^{fl/fl}$*MxCre* cells were then used to test effects of Stat5a/b ablation *in vitro* and *in vivo*. *In vitro*, Stat5a/b deletion resulted in a cell cycle arrest followed by apoptosis. Nine days after deletion, no viable cells could be detected. In line with that, a down-regulation of Stat5 target genes mediating G1/S transition within the cell cycle and viability, such as cyclin D2 and cyclin D3, c-myc and bcl-x_L was found. When leukemic *Stat5a/b*$^{fl/fl}$*MxCre* cells were injected into wild type or immuno-compromised mice leukemia rapidly developed. Again, deletion of Stat5a/b *in vivo* within the leukemic cells significantly counteracted disease progression as indicated by an increase of leukemia latency from 16 to 49 days. Eventually, all animals succumbed to a Stat5a/b-positive leukemia indicating that a few residual cells escaped deletion. Moreover, p53 abruption or overexpression of the oncogene did not alter the susceptibility to Stat5 loss of established leukemic cell lines. Taken together our data define a key role for Stat5a/b not only for lymphoid development but also for lymphoid transformation. Stat5a/b is necessary for the initial transformation as well as for leukemia progression. This absolute necessity for the proliferation and viability of Abelson-transformed cells puts Stat5a/b into the spotlight of new therapeutic strategies for the treatment of *bcr/abl*-induced leukemias.