ImmunoTools *special* Award 2021

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Effects of hyperactive STAT5B on Natural Killer Cells

Signal transducer and activator of transcription 5B (STAT5B) is a member of the Janus kinase (JAK)-STAT signaling pathway and an important regulator of development, survival, and function of innate lymphocytes, including natural killer (NK) cells. The activating STAT5B^{N642H} mutation has been found in patients with different hematopoietic malignancies, including aggressive forms of NK cell lymphomas/leukemias. We are currently investigating whether STAT5B^{N642H} acts as an oncogenic driver in NK cells with the aim to gain a better understanding of oncogenic mechanisms involved in NK cell transformation. This knowledge is important to guide the development of models to study rare but aggressive NK cell malignancies and to develop new treatment options. We generated a mouse model in which STAT5B^{N642H} expression is restricted to the NK (NKp46-positive) cell lineage. NK cell-specific STAT5B^{N642H} expression increased the number of NK cells in young and aged mice, but no signs of a malignant disease have been detected so far. These current data suggest that STAT5B^{N642H} on its own might not be able to transform NK cells in contrast to other cell types, as previously shown with a *Vav1* promoter-driven transgenic mouse model expressing STAT5B^{N642H} in the whole hematopoietic system. Aging experiments will be continued to investigate an oncogenic potential of mutant STAT5B in NK cells at a later timepoint. In addition, we are currently investigating how enhanced STAT5B signaling impacts NK cell functionality. STAT5B deficiency is associated with defects in NK cells, including decreased effector functions. Thus, we hypothesized that enhanced STAT5B signaling might boost NK cell activity. Surprisingly, we observed that enhanced STAT5B signaling, by overexpression of non-mutant and more prominently of the STAT5B^{N642H} mutant, decreased the expansion capacity and cytotoxic activity of NK cells *in vitro* upon IL-2 culture. In future experiments, we aim to further explore this phenomenon and gain further insights into the underlying mechanisms of how hyperactive STAT5B signaling drives NK cell dysfunction. The selected reagents from ImmunoTools would be extremely helpful to advance our research, contributing to a better understanding of the complex regulation of NK cell activities. Furthermore, we aim to explore whether a STAT5-driven NK cell dysfunction can also be observed in human NK cells. This knowledge is important as NK cells are being pursued as immunotherapeutic tools and cytokines that activate STAT5 are employed to expand and activate NK cells in different clinical trials.

The murine and human cytokines from ImmunoTools (rm-IL15, rm-IL-21, rh-IL-12, rh-IL15, rh-IL-21 (marked in yellow below)) would offer great help to further investigate the effects of hyperactive STAT5B on NK cell functionality under different culture conditions. In addition, the selected antibodies for flow cytometry (CD56-FITC, CD57-PE, CD69-PE, CD3-PerCP, CD25-APC (marked in yellow below)) are important tools that we would need to analyze human NK cells.

ImmunoTools *special* AWARD for **Klara Klein** includes 10 reagents

FITC - conjugated anti-human CD56

PE - conjugated anti-human CD57, CD69

PerCP - conjugated anti-human CD3

APC - conjugated anti-human CD25

recombinant human rh IL-12, rh IL-15, rh IL-21

recombinant mouse rm IL-15, rm IL-21

DETAILS more AWARDS