The JAK-STAT pathway is a rapid signaling pathway downstream of cytokine and growth factor receptors, required to change gene regulation [1]. JAKs activate one or several members of the seven STAT transcription factors, and they control cell growth, survival, and differentiation, but they also drive different cancer types.

Scientific merit comes from new STAT1 findings using WT or Stat1-deleted mice analyzing hematopoiesis before and after chemotherapeutic drug application (Fig. 1). The team of Wolfgang Doppler and colleagues [2] focused on basic and preclinical cancer research questions and consequences for the hematopoietic system upon anthracycline treatment. This work will be placed in context below, but we highlight first the JAK-STAT pathway in association with cancer research.

The JAK-STAT pathway gained increased attention in the last years as a result of persistent activation found in all cancer types. An essential role for STAT1 in differentiated myeloid cell types, such as erythrocytes or megakaryocytes [8, 9], and in type I IFN-induced hematopoietic stem cell activation and cycling [10] was demonstrated. No obvious defects in B lymphopoiesis were described to date. It was so far poorly characterized that STAT1 is also required for normal hematopoietic cell development and maintenance of homeostasis, and a role especially upon hematopoietic challenge, e.g., after chemotherapy, has now been reported by Datta et al. [2]. A role for STAT1 upon response to various chemotherapeutic drugs was recognized early in human cancer cell line studies, but in vivo animal studies with genetic loss of Stat1 proving this concept were lacking. The approach being taken by Datta et al. [2] involved cohorts of mice exposed to doxorubicin treatment. Competitive bone marrow transplantation, detailed immunophenotyping, flow cytometry, and immunohistochemistry of B cells in lymphoid organs were carried out. Doxorubicin treatment triggers strong myelosuppression in mice, but the authors extend on doxorubicin impact on blood cells with detailed immunophenotyping and functional analysis. They found a profound general hematopoietic defect in mice devoid of Stat1, particularly evident in decreased common lymphoid progenitor numbers or toxicity, therein upon doxorubicin treatment. It will be interesting to test other chemotherapeutic regimens in the presence or absence of Stat1. Datta and colleagues [2] discovered in their work a new role for STAT1 signaling for B lymphopoiesis under steady-state conditions and myeloblation. STAT1 deficiency mildly increased myelopoiesis, but particularly, B lymphoid development was blunted and depended on STAT1 during normal hematopoiesis or upon chemotherapeutic

Abbreviations: BCL=B cell lymphoma, JAK=Janus kinase, TYK=tyrosine kinase, U-STAT=untyrosine phosphorylated state of STAT

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challenge. Primary transplants allowed for an insight into a potential STAT1-mediated mechanism after chemotherapy in early hematopoiesis. Impaired hematopoietic progenitor cell fitness was associated with reduced Stat1 (a known STAT1/3 target gene) expression that correlated with STAT1 expression status. The authors evaluated recovery of myeloid and lymphoid populations after doxorubicin treatment, and they studied the splenic architecture after a recovery time of 30 days from doxorubicin treatment. Immunostaining for the T and B cell zones revealed differences in the number of B cell replenishment, which is an indicator for reduced immune cell function after doxorubicin treatment in the absence of STAT1. Thus, peripheral lymphoid organs are delayed significantly for B cell repopulation, in contrast to T cell replenishment, after chemotherapeutic intervention. The authors also measured IL-7-dependent colony numbers, and they controlled total and tyrosine phosphorylation of STAT1/3 in B220-sorted bone marrow cells, without or with IL-7 or IFN-γ stimulation. A prominent role for IL-7 was excluded by showing selective activation of STAT5, but not STAT1, upon IL-7 stimulation. Furthermore, the absence of STAT1 neither influenced IL-7-mediated STAT5 phosphorylation nor STAT3 and STAT5 protein expression.

The data suggest that particularly B cell immune function will be disturbed or delayed after hematopoietic reconstitution in a situation of chemotherapy upon STAT1 deficiency (Fig. 1). As predicted from the studies described here with a knockout transgenic, diminished STAT1 abundance, as found in inborn errors of human STAT1 [3], could also have consequences for lymphoid repopulation in transplant patients. Furthermore, this basic research work could have implications for treatment, where it is known that the levels for STAT1 expression vary strongly among individual cancers. It was shown recently that STAT1 expression levels are a prognostic marker for colorectal cancer progression [11]. There, STAT1 controls STAT3 oncogenic activity, as it can make homo- or heterodimers. In addition, STAT1 can interact with other STAT family members in small (STAT2, STAT4) or large (STAT3, STAT4, STAT5A/B) DNA-binding complexes via oligomerization. Cross-talk of STAT1 with other transcription factors that are activated by cytotoxic drugs, such as NF-κB, might also be involved in the regulation of cell fate [12]. Overall, high susceptibility of STAT1-deficient animals to tumor onset and spontaneous breast cancer development was reported. Whether that might also be influenced by diminished B cell function upon STAT1 loss is questionable, as anti-tumorigenic activities of B cells remain to be defined. However, the situation for onset and progression of BCL and leukemia might be different and depend more on STAT1 levels. This leaves room and need

Figure 1. Diminished B lymphopoiesis upon loss of STAT1 during chemotherapy recovery. Chemotherapy affects the common lymphoid progenitor pool in WT mice having the STAT1 protein (Stat1+/+) or lacking it via knockout of Stat1 (Stat1−/−). STAT1 loss causes a low number of B cell progenitors or increased toxicity in B cells upon doxorubicin treatment (chemical structure of the chemotherapeutic anthracycline is shown above). Red arrows illustrate normal recovery of cell numbers after systemic doxorubicin treatment; blue arrows indicate diminished recovery.
for future research on STAT1 signaling during drug treatment of various cancers.

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DISCLOSURES

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REFERENCES


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