Get a grip on immune cells by inhibiting JAKs

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ABSTRACT

JAK inhibitors are approved for myelofibrosis (MF) and polycythemia vera (PV), as they reverse inflammation-associated splenomegaly and symptoms. Notably, JAK inhibitors only marginally affect disease burden. The anti-inflammatory effects of JAK inhibitors affects DC, T and NK cells explaining their therapeutic potential for limitation of cancer-associated inflammation, Graft-versus-Host Disease (GvHD) and autoimmunity.

Myeloproliferative neoplasia (MPN) are clonal hematopoietic diseases characterized by an often uncontrolled hyper-inflammatory response of non-clonal cells finally leading to severe symptom burden. The identification of the gain-of-function mutation V617F in the JAK2 kinase led to a deeper understanding of the molecular pathology of MPN.1 Similar to the constitutively activated tyrosine kinase BCR-ABL in chronic myelogenous leukemia (CML), which nowadays allows CML patients to have an almost identical life expectancy compared to age-matched non-CML individuals, scientists and pharmaceutical industry envisioned a similar targeted therapy approach by inhibiting the constitutively activated JAK2 kinase in Ph-negative MPN. The first drug that entered clinical trials was a JAK1/2 inhibitor called INCB18424 (ruxolitinib), which was subsequently approved for the treatment of primary or secondary MF based on its convincing spleen-reducing and symptom-controlling effects. The fact that the compound is also active in non-JAK2 mutated MF patients already suggested, that it may not be as specific as previously considered in terms of targeting the mutated MPN cell clone. Moreover, only very few selected patients have a clear reduction of clonal disease burden (in these patients probably the clone largely depends on cytokine signaling, which is inhibited by ruxolitinib). However, the drug is associated with a dramatic reduction of pro-inflammatory cytokines, as well as it reverses the catabolic status of MF patients.2,3 These data highlight the potent anti-inflammatory potency of this compound class. Intriguingly, ruxolitinib therapy is also associated with severe infections among which tuberculosis, hepatitis B reactivation, progressive multifocal leukencephalopathy, toxoplasmosis retinitis and EBV-associated aggressive lymphoma (J. Richter/Lund, personal communication, 06/14) are the most relevant ones.4

These clinical observations already suggested that JAK inhibitors may pre-dominantly act via their anti-inflammatory/immunosuppressive properties. In line with this idea, we could demonstrated a significant impact of ruxolitinib on DC and T cell biology not only in vitro but also in vivo in murine models and in MPN patients.5,6 Our most recent data now provide also clear evidence that ruxolitinib affects key characteristics of human NK cells, such as cytokine-induced expansion and killing activity.7 NK cells are known to be of critical importance for the elimination of virus-infected and transformed malignant cells. We observed, that ruxolitinib inhibits cytokine-mediated NK cell activation and differentiation, which results in an immature NK cell phenotype and strongly reduced NK cell frequency. Due to the knowledge that NK cell deficiency leads to a high susceptibility to various infections in patients suffering from immune-defects affecting NK cells, the decreased NK cell frequency and function in ruxolitinib-exposed individuals may help to better understand the susceptibility of those patients for viral infections. However, our data should also be considered when testing ruxolitinib in solid tumors, as NK cells are an important component of cancer immune-surveillance.

In addition, our data also shed a light on an intrinsic immune dysfunction in MPN patients, as a clear NK cell defect could be observed even in MPN patients not exposed to ruxolitinib. Especially, the killing activity of MPN NK cells is reduced compared to what can be induced in NK cells isolated from age-matched healthy individuals.

Our in vivo observations are supported by various in vitro experiments. The potential of cytokine-mediated activation of NK cells is clearly inhibited in the presence of ruxolitinib (as shown by diminished killing, degranulation and IFNγ production as well as reduced induction of CD16, CD69, NKG2D, NKP46 and granzyme B expression), whereas the JAK-independent activation via NKP46 remains unaffected. Interestingly, ruxolitinib also clearly reduced the ability of NK cells to generate lytic synapses with target
cells, which may in addition to the reduced expression levels of the NK cell activation markers at least in part explain their reduced killing capacity. Our data are also of importance when considering a recent paper showing that JAK inhibitors increase susceptibility of tumor cells to NK cell-mediated killing. However, in this report the authors only focused at JAK inhibitory effects on the tumor cell side, whereas the impact of JAK inhibition on the immune-cell side also has to be taken into account, as systemic JAK inhibition may counteract the sensitizing effects on the tumor cell level by impairing NK cell function. Moreover, in the context of allogeneic stem cell transplantation, where ruxolitinib has recently been suggested as a potential therapeutic option for the therapy of steroid-refractory GvHD, the results might also be considered because NK cells are critical for the GvL effect.

In summary, the limitation of the function of various immune cells by ruxolitinib highlights their therapeutic potential for conditions in which tissue damage by uncontrolled immune cell activation is observed, such as in autoimmunity, graft rejection after solid organ and GvHD after allogeneic stem cell transplantation (see Fig. 1). Moreover, in some cancer entities (especially in GI-malignancies), inflammation is an important variable supporting malignant transformation and (in case the disease is already established) also drives epithelial–mesenchymal transition (EMT) and metastasis. This process may also be successfully treated with JAK-inhibitors as anti-inflammatory compounds. First, data from pancreatic cancer patients support a beneficial effect of ruxolitinib as anti-inflammatory therapeutic. However, one may also take into consideration that inhibition of various immune cells by JAK-inhibitors may also inhibit cancer-immune surveillance and fosters disease relapse on the long-run for example, when it is used after allogeneic stem cell transplantation for the treatment of GvHD.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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Figure 1. The figure depicts the pleiotropic immunemodulatory effects of the JAK inhibitor ruxolitinib. Both, positive but also potential side effects of this compound class are shown.
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