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Immune modulation by molecular cancer targets and targeted therapies

Rationale for novel combination strategies

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Following our recent observation that alterations of the Natural Killer (NK) cell compartment in the presence of BCR-ABLinduced myeloproliferation fail to revert under targeted therapy, we discuss by what mechanisms oncogenic molecular pathways and their pharmacological inhibition may interfere with immune functions. Rational combinations of molecularly targeted and immunological strategies may provide a means for more effective cancer targeting.

Natural killer (NK) cells are attractive effector cells of therapeutic antitumor immune activation, since they have potent cytolytic effector function and can amplify adaptive immune responses by interacting with various immune effector and antigenpresenting cells. Functional and immunogenetic studies suggest that autologous NK cells contribute to immune surveillance of both leukemias and solid tumors.[1,2] Conversely, suppression of NK-cell mediated effector function can contribute to tumor escape from immune control.

In our recent article published in *Leukemia*,[3] we have reported that the NK cell compartment is impaired in chronic myelogenous leukemia (CML). We have identified profound quantitative and functional NK cell defects in patients with newly diagnosed CML. These aberrations were mimicked in a mouse model of CML-like myeloproliferation induced by BCR-ABL expression in hematopoietic stem cells. Thus, the disease-driving aberrant tyrosine kinase activity appears to be involved in NK cell dysfunction. Since NK cells in CML are not part of the malignant clone, we concluded that the malignant environment is likely responsible for the observed alterations.

Remarkably, targeted therapy with imatinib failed to restore NK cell function even in patients achieving molecular remissions. This raises the question to what extent and in what way the drug may interfere with the immune system.

Imatinib is the most prominent example for a new generation of anticancer drugs. Progress in understanding the molecular architecture and functional circuits of cancer cells has led to clinical evaluation of agents that selectively target relevant signaling pathways. By inhibiting the aberrant BCR-ABL tyrosine kinase, imatinib has revolutionized the treatment of CML.[4] Development of molecularly targeted drugs has focused on their direct effects on disease-driving and disease-related pathways in tumor cells. More recently, there is an increasing awareness of the significance of the surrounding nonmalignant stroma for tumor development and sustenance. Stroma besides fibroblasts and cells of vascular structures includes various components of the immune system, and evidence is now accumulating that targeted drugs can modulate immune functions in a complex manner. Besides imatinib and the follow-up compounds dasatinib and nilotinib, various inhibitors of receptor-induced and intracellular pathways (e.g., AKT/mTOR) as well as drugs that target epigenetic transcriptional control were found to exert differential effects on individual immune cell subpopulations and antigen-specific effector cells.

These observations are not unexpected, since molecular targeting is not cancerspecific. Pathways involved in oncogenic receptor and intracellular tyrosine kinase signaling are also important for the functionality, proliferation and survival of immune effector cells.[5] Moreover, drugs generally interact with more than one pathway. E.g. imatinib is also active against c-KIT and platelet-derived growth factor receptor (PDGFR), and the newer tyrosine kinase inhibitors have even broader activity. Therefore, systemic treatment with molecularly targeted agents acts not only on the tumor cells, but also affects various other cell types (**Fig. 1**). Imatinib again, by its interaction with the c-KIT receptor, was shown to interfere with the licensing of c-KITexpressing DCs to activate resting NK cells in vivo.[6]

Recent evidence further illustrates that therapeutic inhibition of oncogenic pathways can affect tumor host interactions by altering the immunogenicity and immunomodulatory function of targeted tumor cells. The efficacy of imatinib in a mouse model of gastrointestinal stroma tumors (GIST) critically depended on $CD8^+$ T cells, suggesting that the drug in this model acts at least in part by amplifying a preexisting T cell response.[7] Inhibition of oncogenic Kit expression in GIST cells resulted in reduced expression of the immunomodulatory molecule IDO, subsequent activation of intratumoral $CD8^+$ T cells and apoptosis of regulatory T cells

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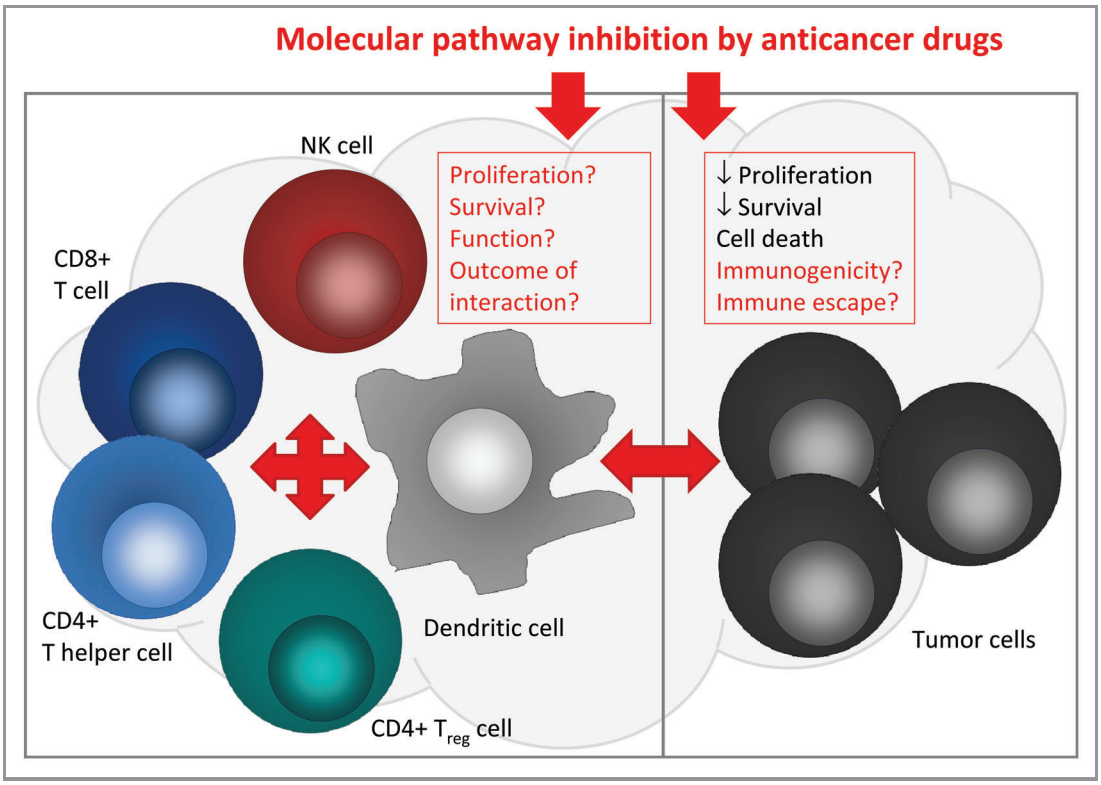

Figure 1. Role of molecular pathway inhibition in tumor host immune interactions. Tumor-host immune interactions within the microenvironment are critical for tumor development and sustained tumor growth. Complex crosstalks between various immune effector cells, antigen-presenting cells and tumor cells yield an integrated outcome toward either antitumor immune activation or tolerance. Oncogenic alterations within molecular pathways in tumor cells as well as therapeutic inhibition of these pathways in tumor cells, along with both on- and off-target effects of targeted drugs in immune cells, interfere with this network, affect functional tumor immune responses, and may be exploited for more effective therapies.

(T_{reg} cells). In CML blasts, by contrast, imatinib was shown to reduce immunogenicity by interfering with the BCR-ABL-induced upregulation of immunogenic antigens and thereby to impair antigen-specific T cell responses.[8]

What is the relevance of interference by molecularly targeted drugs with the tumor-interacting immune functions?

Despite the efficacy of tyrosine kinase inhibitors to induce and maintain remissions, CML patients are rarely cured by these drugs. BCR-ABL expressing leukemic stem cells persist even in the sustained absence of detectable molecular residual disease[9] and may reinitiate leukemic growth. By contrast, immunological graft-vs.-leukemia reactions in the context of allogeneic hematopoietic stem cell transplantation can eradicate the disease. Moreover, in mouse models, an intact immune system was required for sustained tumor regression upon inactivation of disease-driving oncogenes.[10] Thus, molecularly targeted drugs should be selected not only for their direct, on-target antitumor effects, but also for their capacity to interfere with immune escape, activate various components within the immune microenvironment and initiate and maintain potent and sustained anticancer immune responses. This requires detailed studies of the effects of drug treatment on immune effector cells and dissection of the mechanisms by which molecular pathways affect tumor-host immune responses. Moreover, the potential of combined molecular and immune targeting will need to be explored. Preferably, the effects of combination therapies should be studied within the tumor microenvironment where the most relevant tumor-immune interactions are likely to take place. The mouse model that we used in our study closely mimics BCR-ABL-driven myeloproliferation and proved suitable for studying the role of aberrant tyrosine kinase expression in NK cell dysfunction. However, its application to the investigation of tyrosine kinase inhibition on the immune system is limited by differences in clonal origins and target expression between patients and mice. The generation of adequate models for studying these interactions remains a challenge.

We conclude that the effects of molecularly targeted agents on the immune system deserve close attention. Strategies should be explored that target disease-driving pathways in tumor cells while at the same time suppressing immune escape mechanisms, inducing tumor-specific immune activation inside tumors and thereby providing long-term immune control over residual cancer cells.

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