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Targeting PI3Kδ
One man's meat is another man's poison

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We have recently uncovered the indispensable role of phosphoinositide-3-kinase δ (PI3Kδ) at different stages of the canonical killing pathway of cytotoxic T lymphocytes (CTLs). The interception of PI3Kδ-conveyed signals has been considered a valuable therapeutic strategy in oncology. However, our observations predict that the benefits of this approach may be limited by a trade-off between direct anticancer effects and an impaired ability of CTLs and NK cells to attack tumor cells.

In our recent article, "PI3Kδ is essential for tumor clearance mediated by cytotoxic T lymphocytes,"[1] we set an example for the preclinical evaluation of anticancer drugs, considering both pharmacological and immunological aspects. We used the power of murine models to study the immunological consequences of the ablation or pharmacological blockage of phosphoinositide-3-kinase δ (PI3Kδ). Our findings can be viewed as a contribution to translational research, as these insights are valuable to anticipate issues that may otherwise be evident only at late stages of clinical development.

PI3Ks constitute central hubs in cellular signaling networks. The main components of the module, namely PI3K, AKT and mTOR, are crucial to support cell survival, adaptation of cell growth to external stimuli and nutrient supply, as well as to suppress apoptosis.[2] Class I PI3Ks are heterodimeric molecules comprising a catalytic and a regulatory subunit. There are four catalytic isoforms of Class I PI3Ks (Class IA p110α, p110β, p110δ and Class IB p110γ). The expression of PI3Kδ is mainly restricted to the hematopoietic system. Hence, PI3Kδ is a prime target for the therapy of hematopoietic malignancies. The safety and therapeutic profile of PI3Kδ inhibitors are currently being investigated in clinical trials. In fact, the first results on the therapy of chronic lymphocytic leukemia are promising.[3]

We have previously documented that PI3Kδ is essential for the function of natural killer (NK) cells.[4] Upon genetic ablation of PI3Kδ, NK cell-mediated tumor surveillance is impaired and PI3Kδ-deficient mice were indeed prone to tumor formation. These findings made us and others[5,6] recognize the dilemma of targeting PI3Ks in cancer: the net effect of a PI3K-targeting intervention depends on how the balance is tilted, i.e., whether the effects on cancer cells or those on the immune system prevail. This conundrum is further highlighted by our recent findings,[1] which demonstrated that PI3Kδ is indispensable for the eponymous activity of cytotoxic T lymphocytes (CTLs). When challenged in vitro, indeed, Pik3cd$^{-/-}$ CTLs did not respond to foreign antigens. These cells also expressed reduced levels of key components of the lytic machinery and displayed a severe degranulation defect. Moreover, PI3Kδ-deficient mice were prone to succumb to tumors that are known to be cleared by CTLs. We therefore concluded that PI3Kδ is highly relevant for tumor surveillance in vivo. These findings further substantiated our concerns about PI3Kδ (**Fig. 1**).

Conclusions and Possible Consequences: The Pain and the Gain

The development of targeted therapies has created the illusion that compounds would always exert their effects with surgical precision. However, the rising field of signal interception-based therapy has already collected an amazing record of unintended consequences, often resulting from pharmacological effects on cells other than the target cell. In hindsight, this is to be expected: most signaling proteins have cell-context dependent roles.

Newly introduced drugs might fail in clinical trials or lose their market authorization, not because they lack efficacy, but owing to unacceptable side effects. In most

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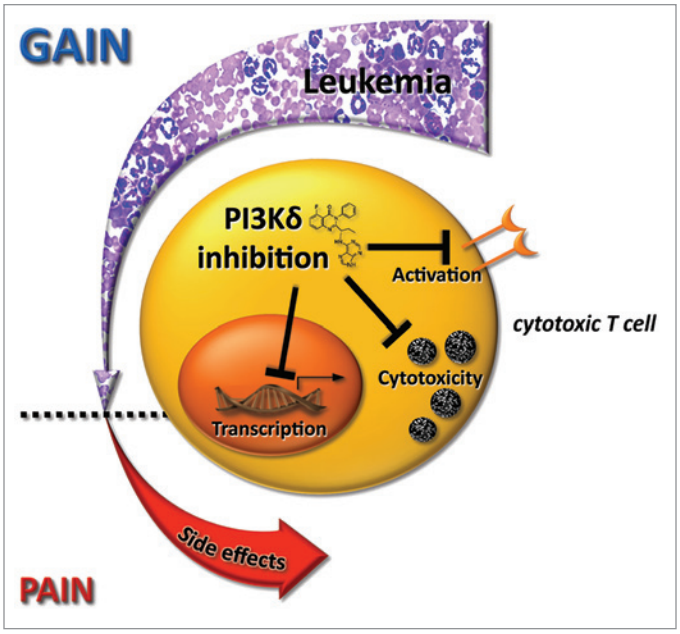

Figure 1. Lack or inhibition of PI3Kδ in cytotoxic T lymphocytes results in impaired activation and cytotoxicity as well as in reduced levels of key components of the lytic machinery. Albeit the inhibition of PI3Kδ in leukemic cells may provide therapeutic benefits, the effects of PI3Kδ inhibition on other cell types must be carefully considered for the development of meaningful anticancer regimens.

instances, this is a direct consequence of precipitant developing programs, which do not anticipate all potential problems.

Both general inhibitors of PI3K and selective inhibitors of PI3Kδ represent first-in-class drugs. Hence, by definition, long-term safety data are not available at the early phases of clinical development. However, input from murine models, such as those used in our studies, is helpful to challenge and continuously re-evaluate the therapeutic working hypothesis. It is possible to look for signs of impaired CTL and NK function, e.g., increased susceptibility to viral infections or tumor development. Finally, new experimental insights can be useful to shape clinical trials and to improve the safety profile of the compounds under development. It is evident that foresight is superior to hindsight, and as patients at risk can be identified ex ante, they should either be excluded from treatment or subjected to very close monitoring.

Under ideal conditions, the concept underlying evidence-based medicine is a virtuous cycle that operates in two directions: insights from basic science are translated into improved therapies through progressively refined and expanded clinical trials. Unexpected side effects drive in vitro and in vivo experiments that allow for an improved understanding of the underlying mechanistic insights.

We are aware that the murine and the human immune system differ to substantial extents. It is therefore not self-evident that the inhibition of PI3Kδ would cause a substantially impaired response of human CTLs and NK cells. Nevertheless, our work points to a number of simple experiments that can be performed during clinical trials to improve patient safety. CTLs can, for instance, be readily harvested from the patient blood prior to and during treatment with PI3Kδ inhibitors. Monitoring their degranulation by recording the change in membrane capacitance in patch clamp recordings admittedly requires sophisticated equipment. However, the expression of proteins of the lytic machinery can readily be monitored with reasonably high sample throughput to cover a large patient population. This and related approaches are likely to detect early signs of impaired cellular defense mechanisms.

Impaired CTL function is an unwarranted side effect of tumor therapy. However, considering the central role of PI3Kδ for CTL function, this opens a new window for the use of PI3Kδ inhibitors in settings in which $CD8^+$ CTLs constitute a therapeutic target, e.g., in transplantation medicine or in the treatment of autoimmune diseases or chronic obstructive pulmonary disease (COPD). This conjecture is supported by a recent study of Ying et al.[7] investigating the therapeutic potential of pharmacological PI3Kδ inactivation in murine models of heart and skin transplantation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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