and that the cells respond to changes in pH and 2,3-diphosphoglycerate. This is encouraging evidence that red blood cells produced from hESCs in vitro are relatively normal and in agreement with work done with hematopoietic stem cells. However, major questions, such as the half-life and the immunogenicity of these cells, must be addressed. Procedures to eliminate undifferentiated cells that could be tumorigenic must also be developed.

The first transfusions in modern times occurred more than 100 years ago, 70 years before the first transplantations because red blood cells are among the simplest cells present in the body. They are easy to harvest and store, do not express the HLA antigens, and do not have a nucleus. They are therefore less immunogenic than most cells and cannot cause tumors. Many of these same characteristics make them an attractive translational target for the hESC field. Importantly, most of the difficulties that are highlighted above apply to the manufacture of other cell types that have therapeutic potential. Therefore, the development of a procedure to manufacture red blood cells from hESCs would pave the way to the production of other cell types.

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The dilemma of anticancer therapy: tumor-specific versus immune effects

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The PI3Kδ isoform is required for both optimal growth of Abelson-transformed leukemia cells and antileukemic NK-cell effectors. Therefore, the simultaneous inhibition of PI3Kδ in tumor and host cells results in therapeutic failure.

Deregulation of the phosphoinositide 3-kinase (PI3K) pathway can occur by activating mutations in growth factor receptors or in the PIK3CA locus coding for PI3Kα, by loss of function of the lipid phosphatase PTEN, by up-regulation of protein kinase B (PKB/Akt), or by the impairment of the tuberous sclerosis complex (TSC1/2). All these events stimulate cancer growth and proliferation and have thus prompted a major interest in therapeutic inhibition of the PI3K pathway. One particular PI3K isoform, PI3Kδ, is selectively expressed in leukocytes and, hence, might constitute a pharmacologic focus for the “targeted” treatment of hematological malignancies.

In an elegant study published in the present issue of Blood, Zebedin and colleagues explore the effect of the PI3Kδ knockout on Abelson virus (cAbl)–induced leukemia in mice. For this, PI3Kδ was either removed from the transformed cells themselves, or from the host environment into which transformed cells were injected. These experiments reveal a formidable contradiction. PI3Kδ deficiency in leukemic cells retarded tumor progression while PI3Kδ deficiency in nonleukemic host cells accelerated the fatal course of leukemia. Intriguingly, the simultaneous removal of PI3Kδ from leukemic cells and the host had no effect on leukemic progression at all. This latter result suggests that complete and selective pharmacologic PI3Kδ inhibition (something that obviously would affect both tumor and host cells) would have no therapeutic benefit on PI3Kδ-overexpressing Bcr/abl-positive human leukemias.

Zebedin et al also show that PI3Kδ−/− mice exhibit an accelerated development of cancers that are usually controlled by natural killer (NK) cells, such as Abelson-transformed cells, Eμ-myel–induced B-cell lymphoma, EL4 thymoma, and B16 melanoma. These PI3Kδ effects were also found on a RAG2−/− background, indicating that they must involve other immune effectors besides B or T lymphocytes. Indeed, PI3Kδ−/− NK cells poorly lysed leukemic cells, correlating with a general defect in exocytosis that affects both degranulation and IFNγ secretion. Although formal proof that accelerated tumor progression must be attributed to this NK defect is elusive, these results make it highly plausible that PI3Kδ–dependent effectors of the innate immune system play a major role in tumor control.

The results by Zebedin et al contribute to a general debate on the mechanisms through which anticancer chemotherapeutics (fail to) act. Accumulating evidence indicates that radiotherapy and some chemotherapeutic agents, in particular anthracyclines, can trigger specific immune responses that result either from immunogenic cancer cell death or from immunostimulatory off-target effects. This anticancer immune response then helps to eliminate residual cancer cells (that failed to be killed by chemotherapy) or maintain micrometastases (or perhaps cancer stem cells) in a stage of dormancy.1

Ideally, anticancer chemotherapeutics should induce a cellular stress response and/or immunogenic cancer cell death that trigger an effective immune response. Genotoxic agents induce NKG2D ligands through an ATM-dependent and Chk1-dependent DNA damage pathway.2 Such NKG2D ligands on the surface of tumor
HO-1 extends to stem cells

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