Suicide is painless

Helen E. Heslop  Baylor College of Medicine

In this issue of Blood, Berger and colleagues show that transducing adoptively transferred T cells with a suicide gene that should only be used in case of toxicity, leads instead to involuntary eradication of the transduced cells by a broad CD4 and CD8 immune response directed to the transgene products.

Adoptive transfer of donor T cells has many potential applications after allogeneic stem cell transplantation, and is used to treat relapsed malignancy and viral infections. Unfortunately, alloreactive T lymphocytes in the infused population can proliferate in vivo, and since these cells may persist for months or years, the resulting graft-versus-host disease can be highly problematic. A suicide gene that can be used in vivo to destroy unwanted donor T cells would therefore increase the safety and broaden the application of this immunotherapy. Several systems have been used to introduce prodrug-metabolizing genes into T lymphocytes so that the cells are killed when the appropriate agent is administered. Initial studies focused on the thymidine kinase gene (TK), which is derived from herpes simplex virus and renders transduced cells sensitive to produgs such as ganciclovir. There have been conflicting data on the value of this approach. An initial report in patients with HIV revealed a major limitation of this strategy with the development of a cytotoxic T lymphocyte (CTL) response specific for the TK transgene.1 Subsequent studies of TK in allogeneic transplant recipients have shown variable results, with some investigators finding that the system works as designed, while others demonstrated only short-term persistence.2,3

In this issue of Blood, Berger and colleagues report on 3 allogeneic transplant recipients who received donor T cells as therapy for relapse. The cells were transduced with a construct encoding TK and also hygromycin (HY), used as a selectable marker. Both transgenes produced an immune response and the authors’ detailed analysis identified multiple epitopes as the immune targets (see figure). Since multiple epitopes could be recognized, modification to remove immunogenic sequences will not be possible, and as the Tk-Hy–specific immune response contains memory cells, it will persist long term. Although the results differ from those of the Milan group who used a vector encoding TK and the nerve growth factor receptor (NGFR),2 the current study confirms that both Tk and Hy are potentially immunogenic even in immunosuppressed patients after transplantation, and emphasizes the need for nonimmunogenic suicide genes.

One means of attaining such an end may be to develop a suicide strategy which uses human rather than gene products derived from bacteria or viruses. A strategy relying on novel artificial death switches based on chemical inducers of dimerization (CID) and endogenous proapoptotic molecules has been described.4,5 In this approach, human apoptosis molecules can be linked to FK506 binding proteins that contain a binding site for a CID. Administration of this drug then results in the formation of a complex of 2 apoptosis–fusion molecules, which leads to their activation and thus apoptosis. Recent reports show that both fas and caspase 9 molecules can be used in this way, although caspase 9 may kill a higher percentage of transduced cells, including those that have unregulated inhibitors of the apoptosis pathway.4,5 With such all-human systems, suicide may become a directed rather than an involuntary phenomenon.

REFERENCES
Comment on Chandra et al, page 2501

ROS: double-edged sword for leukemic cells

Neil E. Kay  Mayo Clinic

There is increasing evidence that chemotherapeutic drugs can work via acceleration of reactive oxygen species in human malignancy.

In this issue of Blood, Chandra and colleagues describe the activity of the unique molecule adaphostin, a tyrphostin kinase inhibitor, to kill imatinib mesylate (IM)–resistant cell lines through the generation and/or up-regulation of oxidative stress within these cells. Importantly, adaphostin was able to kill IM-resistant cell lines and even primary blood cells from IM-resistant chronic myelogenous leukemia (CML). This work is of great clinical potential and interest since IM resistance is so frequent in Philadelphia chromosome–positive (Ph+/H11001) acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML) blast crisis.1 This latter clinical observation prompted work on generation and study of second-generation drugs that target the abl kinase. There are now several small-molecule inhibitors of p210Bcr/abl that are showing some clinical benefit but still cannot overcome drug-resistant patients who harbor the T315I mutation site.2 The T315I mutation site has been linked to poor clinical responses, whether to higher-dose IM or to second-generation inhibitors such as AMN107. Enter adaphostin, also originally thought to be an agent that would work primarily by inhibiting the substrate of the Bcr/abl kinase.3 However, this agent is also known to cause an elevation of reactive oxygen species (ROS), and can induce DNA single-strand breaks and DNA damage responses. Consistent with this Bcr/abl-independent mechanism, adaphostin has been found to result in the induction of apoptosis and/or killing of chronic lymphocytic leukemia (CLL) lymphocytes and acute myeloid leukemia (AML) blasts.4,5 In those studies, the antioxidant N-acetylcysteine (NAC) was shown to protect leukemic cells from the lethal impact of adaphostin providing further evidence for the importance of ROS.

Chandra and colleague’s report now extends the spectrum of adaphostin killing of leukemic cells to IM-resistant leukemic lymphoid and myeloid cells. In Chandra et al’s work, both NAC and Trolox (water-soluble vitamin E) protects these cells from apoptosis or other functional damage and provides further evidence for the importance of ROS in adaphostin cytotoxicity. Their report also shows that adaphostin can induce down-regulation of both wild-type (WT) and mutant Bcr/abl protein but independent of ROS generation. Does this mean that the former activity can still contribute to IM-resistant cell killing? We agree with the investigators that their findings strongly encourage further studies of unique agents that work by the up-regulation of ROS. Encouragingly, earlier studies by this group have shown relative selectivity of this drug for leukemic and not normal cells.5,6 As is the case with important scientific works, many other related questions arise, including:
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