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PLENARY PAPER

Comment on Guzman et al, page 4163

The long and winding road may be getting shorter

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Guzman and collegues demonstrate that it is possible to specifically target leukemic stem/progenitor cells with the naturally occurring small molecule parthenolide. These findings open new avenues for the treatment of hematological malignancies.

The field of stem cell biology has recently provided new insights on the pathogenesis, self-renewal, and spreading of both solid cancers and hematologic malignancies. It is of great practical interest to better understand the role of these putative cancer stem cells, for obvious therapeutic and follow-up management purposes.[1-3] In this issue of *Blood*, Guzman and colleagues show, through standard colony-forming unit (CFU) in vitro assays, that $CD34^+CD38^-$ human leukemic stem/progenitor cells (HLSCs), obtained from different patients affected by acute and blast crisis chronic myeloid leukemia (AML and bcCML), are more prone to parthenolide-induced apoptosis than the normal counterparts (human hemopoietic stem cells [HSCs]) with remarkable specificity. Moreover, the authors demonstrated, with reconstitution studies in mice, that HLSCs are exquisitely sensitive to the action of the small molecule parthenolide in vivo, underscoring the pivotal role of HLSCs in the establishment of acute leukemia in vivo. In fact, parthenolide efficiently inhibited the engraftment of the human leukemic cell population in the bone marrow of sublethally irradiated nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice reconstituted by primary human cells obtained from leukemic progenitors. The ability of parthenolide to kill HLSCs while sparing normal HSCs is of particular relevance also in consideration of the fact that cytosine arabinoside (Ara-C), one of the most widely employed drugs in the treatment of AML, is much less specific than parthenolide for AML cells and in particular for the HLSC fraction. Consistently, Guzman and colleagues demonstrated that Ara-C is significantly more toxic to normal HSCs. In an attempt to gain insights on the mechanism of action of parthenolide, Guzman and collegues showed that nuclear factor κB (NF-κB) inhibition, p53 activation/phosphorylation, and induction of reactive oxygen intermediates concur in variable fashion to the effects of the drug on HLSCs. Although the mechanism of action of parthenolide requires further investigation, manipulation of these intracellular pathways might lead to potentiation of the antineoplastic activity of parthenolide. It is also suggested that parthenolide might synergize with tumor necrosis factor (TNF)–related apoptosis inducing ligand (TRAIL)[4] in inducing AML cytotoxicity. Although this possibility is particularly attractive considering the relatively low toxicity of TRAIL on normal HSCs and its therapeutic potential for the combined treatment of hematologic malignancies,[5] it remains to be demonstrated whether HLSCs express the death receptors TRAIL-R1 and/or TRAIL-R2. Although the low solubility in water and poor pharmacologic properties of parthenolide represent a major concern for its therapeutic use, Guzman and colleagues cite unpublished data demonstrating substantial improvement by medicinal chemistry of the molecule, with maintenance of the antitumor properties in several parthenolide analogues. Through this newborn field of cancer stem cell chemotherapy, the long road to a less toxic and more efficient and specific therapy toward AML can now be attained. Further studies will help in translating these very promising findings into clinical practice. ■

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GENE THERAPY

Comment on Thrasher et al, page 4255

Old before its time: age-related thymic dysfunction may preclude efficacy of gene therapy in older SCID-X1 patients

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Gene therapy can not be reserved as a "salvage therapy" in SCID-X1 patients failing bone marrow transplantation.