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How close are we to targeting the leukemia stem cell?

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There are a number of approaches for selective targeting of leukemic stem cells (LSCs). These include targeting stem-cell properties, such as self-renewal, inducing cycling of quiescent LSCs to sensitize them to conventional agents, employing or inducing immune-based mechanisms, and targeting tumor-specific physiology. Agents such as parthenolide inhibit the ability of leukemic stem cells to respond to oxidative stress and make leukemic stem cells and bulk leukemic cells susceptible to cell death, while normal stem cells remain relatively unharmed by these agents. The major mechanism of action of these small molecules appears to revolve around the aberrant glutathione metabolism pathway found in leukemic cells.

Introduction

The question of how close we are to targeting the leukemia stem cell (LSC) has a complicated answer. In the past few years, there has been significant progress in three relevant areas: functional assays, molecular studies, and preclinical models. The functional assays that we use to define leukemia-initiating cells and to evaluate the cells both biologically and from a therapeutic standpoint have become very sophisticated. Molecular studies have been advancing at multiple levels, and preclinical models show intriguing results, though nobody has been able to directly mimic a human patient response in a sophisticated xenograft. Perhaps most importantly and directly, some of the therapeutics emerging from preclinical model systems are showing exciting results.

Two major challenges remain to bringing the targeting of the leukemia stem cell to clinical reality: the cell cycle status of LSCs and the heterogeneity of LSCs. Nearly a decade ago, Guan, Gerhard, and

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Hogge [1] demonstrated that, at least in acute myeloid leukemia (AML), leukemia-initiating cells are predominantly quiescent, which has obvious ramifications for therapeutic targeting. It is also becoming more apparent that the tumor-initiating cell that we are attempting to target is a heterogeneous target. A recent analysis clearly demonstrated heterogeneity of LSCs at a phenotypic level and multiple functional levels within the same patient over time during the course of pathogenesis [2]. And when comparing different patients, the LSCs vary enormously. Furthermore, there has been an enormous amount of debate about what controls heterogeneity and some aspects of tumor-initiating cell potential, cell cycle status, and intrinsic vs extrinsic factors [3]. These two issues are at the core of discussions about drug development and experimental therapeutics. Unfortunately, these issues are rarely taken into consideration when drug development begins.

Approaches for selective targeting of LSCs

Four different approaches exist to selectively target LSCs: target "stem-cell" properties, i.e., self-renewal; induce cycling of quiescent LSCs to make them sensitive to conventional agents; employ/induce immune-based mechanisms; and target tumor-specific physiology. Targeting self-renewal properties of stem cells has worked in certain murine models [4–6], but it has yet to work well in humans. Certain cytokines have been found to induce cycling activity of quiescent murine leukemic stem-cell populations, which can then be targeted with conventional agents [7]. It remains to be seen if those results can be translated to human populations. Other work has shown the activity of anti-CD47 antibodies in eliminating AML cells [8]. Tumor-specific physiology, such as metabolism and epigenetic modifications, can also be targeted.

Targeting stem-cell specific physiology

A number of small molecules selectively target LSCs, possibly by similar mechanisms. Parthenolide, a naturally occurring small molecule, is one of them, and is much less toxic to the normal stem-cell population than other agents [9]. The same properties can be found in several other naturally occurring small molecules, such as 4-hydroxynonenal, a lipid peroxidation product; celastrol and piperlongumine, plant-derived compounds; and prostaglandin J2, which is naturally found in mammals (Fig. 1) [10].

The mechanisms by which these molecules appear to selectively kill leukemia cells revolve around the chemical moiety known as an alpha beta unsaturated carbonyl group. Molecules of this class were rejected by the National Cancer Institute in the 1970s because they are a highly reactive group that is chemically predicted to interact with almost any free thiol group. However, in biological systems, the associated structures of the molecules likely constrain their ability to substantially react with many thiol groups. The alpha beta unsaturated carbonyl group allows these molecules to interact covalently

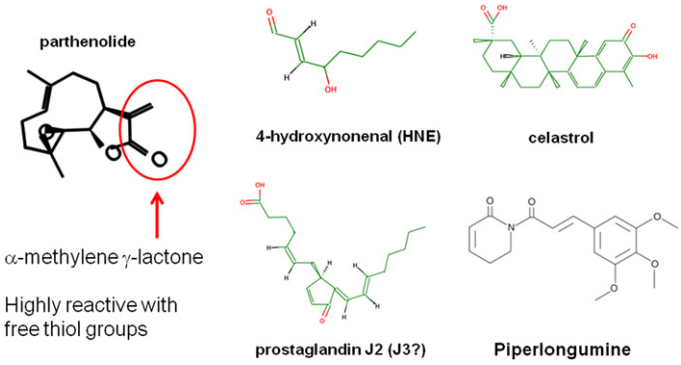

Fig. 1. Naturally occurring small molecules that selectively target leukemia stem cells.