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Review

Leukemia stem cells: Old concepts and new perspectives

Samanta A. Mariani, Bruno Calabretta *

Department of Cancer Biology and Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107, United States

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ABSTRACT

Myeloid leukemias are heterogeneous malignancies in morphology, immunophenotype, genetic and epigenetic alterations, and response to therapy. This heterogeneity is thought to depend on the accumulation of secondary mutations enhancing proliferation/survival and/or blocking differentiation in a small subset of leukemia-initiating cells capable of self-renewal. This model of clonal evolution is based on xenotransplantation studies demonstrating that leukemia can be initiated and maintained in immunodeficient mice by a small subset of purified leukemic cells immunophenotypically similar to normal hematopoietic stem cells and is known as the leukemia stem cell model. Since its original formulation, many studies have validated the main conclusion of this model. However, recent data from xenotransplantation studies in more severely immunodeficient mice suggest that imunophenotype and behavior of leukemic stem cells is more heterogeneous and "plastic" than originally thought. We will discuss here the evolution of the leukemia stem cell model and its impact for the therapy of patients with myeloid malignancies.

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1. Introduction

The concept that leukemia develops from and is maintained by a small population of transformed stem cells organized hierarchically like its normal counterpart has been among the most important in modern oncology and has prompted a lot of studies attempting to validate or disprove the idea that more common non-hematopoietic malignancies follow a similar hierarchical organization. Whether this concept is correct is not an academic dispute but has profound practical consequences since it implies that leukemia (or cancer) can be permanently cured only if therapies can eliminate leukemic (cancer) stem cells.

* Corresponding author. Tel.: +1 215503 4552; fax: +1 215923 0249.
E-mail address: B_Calabretta@kimmelcancercenter.org (B. Calabretta).

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In its original formulation (Bonnet and Dick, 1997), the leukemia stem cell model was based on the demonstration that a rare population of acute myeloid leukemia (AML) cells immunophenotypically similar to the normal counterpart (the CD34+CD38− subset) was enriched in cells capable of inducing leukemia when injected in non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice. Leukemia that developed in NOD/SCID mice was immunophenotypically heterogeneous and similar to that seen in the original patients and was serially transplanted in secondary recipient mice, consistent with the concept that transformed stem cells, like their normal counterparts, are capable of self-renewal and differentiation.

Subsequent studies confirmed that leukemic stem cells (LSCs) are rare and confined to the CD34+CD38− subset, although additional antigens capable of enriching for leukemia-initiating cells (LICs) in NOD/SCID mice were identified.

Although widely accepted, early critics argued that the use of xenotransplantation assays to functionally assess the repopulating capability of leukemic cells was subjected to several potential problems; for example, some LSC subsets may not escape residual host immunity, or interact appropriately with the bone marrow microenvironment, or respond efficiently to survival and proliferative signals intrinsic to recipient mice.

In the past few years, data on xenotransplantation assays using purified leukemic cell subsets in more immunodepressed mice such as NOD/SCID mice with a targeted deletion of the γ common chain of the interleukin-2 receptor (IL-2R) (NSG mice) which lack residual natural killer (NK) activity and exhibit an improved environment for the functionality of human hematopoietic stem cells (HSCs), has prompted a reassessment of the leukemia stem cell model. In these mice, cells that promote leukemia formation remain exceedingly low; however, they do not appear to be restricted to the CD34+CD38− subset as leukemia-initiating cells (LICs) were identified in the CD34+CD38+ subset as well as in the CD34− fraction (Sarry et al., 2011; Goardon et al., 2011). Moreover, each subset of leukemic cells that promotes the development of leukemia in NSG mice was capable of reconstituting the phenotypic heterogeneity of the original AML sample. The results of these studies do not challenge the notion that leukemia is maintained by a small cohort of self-renewing cells; however, if confirmed by additional studies, they support the conclusion that: (i) self-renewing, LICs reside in primitive as well as more differentiated progenitor cell subsets; and (ii) in addition to be hierarchically organized with primitive LICs giving rise to more differentiated blast cells, antigenically differentiated LICs can undergo "de-differentiation", suggesting that LICs may exhibit some degree of "plasticity".

In the following sections we will discuss how the leukemia stem cell model has evolved over the years and the implications of this model for disease progression and therapy.

2. Xenotransplantation assays with purified AML leukemic subsets: evolution of the leukemia stem cell model

The impetus for assessing whether leukemic subsets can repopulate hematopoietic organs of immunosuppressed recipient mice stems from pioneering experiments demonstrating long-term reconstitution of multi-lineage hematopoiesis in immunodeficient mice co-implanted with small fragments of human fetal thymus and fetal liver (McCune et al., 1988) or with unfractionated human marrow cells (Kamel-Reid and Dick, 1988). Following these and other studies (including those with sorted populations of human cord blood cells) (Dick et al., 1991; Lapidot et al., 1992), engraftment of leukemic cells in immunodeficient mice was obtained first with unfractionated leukemic cells (Lapidot et al., 1994) and subsequently with purified subsets of AML cells, demonstrating that those capable of initiating leukemia in NOD/SCID mice were restricted to the CD34+CD38− subset (Bonnet and Dick, 1997). The latter study also showed that the frequency of LICs was variable but low and that these cells possessed two critical properties typical of the stem cells: they were able to proliferate and differentiate into blast cells identical to those of the original AML sample and to renew themselves as indicated by induction of leukemia, when re-injected in secondary recipients. Collectively, these studies led to the hypothesis that, in the majority of cases, AML originates from and is maintained by transformed stem cells.

The notion that the LICs were confined to the CD34+CD38− subset remained unchallenged for over a decade, but several recent studies have disputed this assumption.

First, Taussig et al. (2008) showed that the apparent inability of AML CD34+CD38+ subsets to induce leukemia in immunodeficient mice was, in part, due to immune-mediated elimination of anti-CD38-labeled cells since pre-treatment of recipient mice with immunosuppressive antibodies restored the leukemia-initiating capability to the CD34+CD38+ fraction of several AML samples.

Second, the same group (Taussing et al., 2010) showed that LICs of AML with mutation of the nucleophosmin gene, which is characterized by low CD34 expression, were confined in approximately one-half of cases to the CD34− fraction. Moreover, LICs were found in more than one subset in a significant number of AML samples and were immunophenotypically unstable upon serial transplantation in mice, further supporting the concept that multiple subsets have leukemia-initiating capacity (Taussing et al., 2010).

Evidence that LICs are not restricted to a distinct "stem cell-like" subset was further strengthened by other important studies (Goardon et al., 2011; Sarry et al., 2011; Eppert et al., 2011).

Goardon and colleagues reported that in most AML samples LICs reside in two populations of hierarchically ordered progenitor subsets, CD34+CD38−CD90−CD45RA+ and CD34+CD38+CD90−CD45RA+ (or "granulocyte–macrophage progenitor (GMP)-like"). The more immature subset (CD34+CD38−CD90−CD45RA+) differentiates in vivo into the more mature "GMP-like" subset while >0.2% of CD34+CD38−CD45RA+ cells are generated upon injection of "GMP-like" cells, consistent with an in vivo immunophenotypic hierarchy whereby more primitive progenitors give rise to more differentiated