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Cancer Stem Cells - Relevance to Clinical Transplantation

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Abstract

Purpose of Review—Despite blood or marrow transplantation (BMT) being arguably the most active modality against hematologic malignancies, relapses remain the major reason for failure. Many cancers have now been shown to harbor cells that are phenotypically and biologically similar to normal cells with self-renewal capacity; these so-called cancer stem cells (CSCs) typically constitute only a small fraction of the total tumor burden, but are hypothesized to be responsible for relapse after conventional-dose therapy. Here, we review whether CSCs may have relevance to BMT.

Recent Findings—CSCs appear to be relatively resistant to standard anticancer therapies *in vitro*. The often dramatic responses induced by chemotherapy in most hematologic malignancies are likely a consequence of their impressive activity against the bulk tumor cells. Although the clinical importance of CSCs remains unproven, new evidence suggests that the limited durability of many of these responses reflect resistant CSCs. It is possible that CSCs are also relatively resistant to both high-dose myeloablative conditioning and allogeneic graft-versus-tumor effects. Data on the ability of most hematologic CSCs to circulate even early in the natural history of a malignancy, also raises concerns about contamination of autografts contributing to relapse.

Summary—Emerging data for the first time suggest CSCs may be responsible for relapse, even after BMT. However, BMT may be a particularly compelling setting to test CSC-targeting strategies, because it provides the most effective clinical debulking of hematologic malignancies and because CSC-targeting strategies may also enhance allogeneic antitumor immunity.

Keywords

Cancer stem cells; transplantation; leukemia; lymphoma; multiple myeloma

Introduction

Carl Nordling first hypothesized the multi-hit mutation theory of carcinogenesis in 1953 [1]. In this model, further refined by Ashley [2], Knudson [3], and Nowell [4], inherited mutations and/or environmental carcinogens lead to the development of pre-malignant cells. Such cells further accumulate mutations until one cell reaches a critical genetic or epigenetic state that confers a growth and/or survival advantage over its normal counterparts. Over time, if it can evade the immune system, this abnormal cancer-initiating cell would give rise to a malignant tumor.

Such a cancer-initiating cell would need to survive long enough to accumulate the 3 - 7 genetic mutations Ashley [2] postulated were necessary to generate cancer. Moreover, this

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cell must already manifest proliferative capacity or, alternatively, develop it anew as a consequence of the genetic mutation(s). Nowell hypothesized their inherent longevity and extensive proliferative capacity make tissue stem cells ideal candidate cancer-initiating cells [4]. In contrast, most terminally differentiated cells are short-lived and have only a limited number of divisions remaining in their differentiation program. Accordingly, such cells could only acquire the multiple genetic mutations required for malignant tumor growth if the essential mutations occurred simultaneously or in rapid succession (e.g., as in the generation of induced pluripotent stem cells). However, longevity and extensive proliferative capacity are not traits restricted to classical tissue stem cells. To some degree, hematopoietic progenitors generated by hematopoietic stem cells (HSCs) retain these properties. Moreover, memory lymphocytes are long-lived and self-renewing in order to maintain life-long immunity.

Most tissue-specific stem cells and other normal self-renewing cells, such as memory lymphocytes, generate differentiated progeny. Tumors derived from such transformed cells might therefore be expected to consist of a heterogeneous population of cells that includes the differentiated progeny of the original cell, mimicking to an extent the hierarchical structure of the normal tissue of origin. Accordingly, putative cancer-initiating cells possessing self-renewal and at least some differentiation potential, two of the defining features of normal stem cells, naturally came to be called cancer stem cells (CSCs). Although the CSC model would explain why only a minority of cells from most malignancies are clonogenic *in vitro* and *in vivo*, it is also conceptually possible that the low clonogenicity is the result of all cells within a cancer retaining the capacity to proliferate, but only at a low rate. Which of these two scenarios accounts for the low clonogenicity of most cancers, has been debated for years. The first clinical evidence supporting the CSC concept was published more than 40 years ago, when Fialkow *et al* demonstrated clonal hematopoiesis involving both erythroid and myeloid lineages in patients with chronic myeloid leukemia (CML) [5].

Identifying and characterizing hematologic malignancy CSCs

The stem cell origin of CML was confirmed nearly 20 years ago when several groups, using characteristics known to define normal HSCs, identified and isolated CML cells capable of expansion *ex vivo* [6]. Dick and colleagues extended these observations, showing cells with a HSC phenotype isolated from CML patients would generate leukemia *in vivo* in NOD/SCID mice [7]. The expression patterns of CML stem cells have also been shown to closely resemble those of normal HSCs [8*]. Thus, there is now universal agreement that the cancer-initiating event in CML, the Philadelphia (Ph) chromosome, occurs in an early hematopoietic cell if not the HSC itself.

Acute myeloid leukemia (AML) was the first cancer in which malignant cells with the ability to recapitulate the disease in NOD/SCID mice were identified [7,9,10]. These NOD/SCID engrafting leukemia cells also possessed self-renewal capacity and shared many phenotypic features with HSCs. Although leukemia stem cells (LSCs) from AML are the best characterized CSCs, the exact surface phenotype of LSCs continues to be a subject of debate [11**], perhaps because of the heterogeneity of AML.

The first modern use of the term cancer or tumor stem cells was probably by Bergsagel and Valeriote [12], who found that only a minority of mouse multiple myeloma cells were capable of clonogenic growth. Subsequent studies by Salmon and Hamburger confirmed these findings with clinical myeloma specimens, revealing a cloning efficiency ranging from approximately 1:1000-1:100,000 cells [13]. Insufficient tools existed at the time to distinguish whether this low clonogenic potential was the result of proliferative capacity

exclusively restricted to a small subset of cancer cells or by all cancer cells retaining the capacity to proliferate but only at a low rate. Work from our laboratory found that the cancer-initiating cells in myeloma are found within the phenotypic memory B-lymphocyte population, with the $CD138^{+}$ plasma cells representing terminally differentiated progeny of the malignant myeloma B cells. These myeloma $CD138^{neg}$ CSCs expressed CD19, CD20, and the memory B cell marker CD27, as well as high levels of the stem cell marker aldehyde dehydrogenase (ALDH) [14,15].

Recent data suggest the CSC concept may also apply to lymphomas. Hodgkin and Reed-Sternberg (HRS) cells, the hallmark of classical Hodgkin lymphoma (HL), belong to the B lymphoid lineage. However, they are unlike any normal cells of that lineage, and their limited proliferative potential belies the clinical aggressiveness of the disease. More than twenty years ago, Newcom *et al* identified a small population of phenotypic B cells that appeared to be responsible for the propagation of HRS cells within a HL cell line [16]. Our group recently confirmed these findings in several HL cell lines, and showed these cells also expressed ALDH and the memory B cell marker CD27 [17]. Moreover, clonotypic memory B cells with high levels of ALDH could be isolated from the peripheral blood of most newly-diagnosed HL patients, regardless of stage; importantly, these B cells and the patients' HRS cells exhibited identical clonal immunoglobulin gene rearrangements [17]. Using a similar isolation strategy, clonotypic $CD19^{+}CD5^{+}ALDH^{high}$ B cells were identified in human mantle cell lymphoma (MCL) cell lines, as well as in patients with newly-diagnosed MCL.[18*]. These MCL cells were also found to be relatively quiescent and resistant to many classical chemotherapeutic agents used to treat this lymphoma.

The Paradox of Response and Survival: The Dandelion Phenomenon

Therapeutic advances over the past three decades now allow most hematologic malignancy patients to achieve major clinical responses. Although the responses can clearly decrease side effects and improve quality of life, most patients still eventually relapse and die of their disease. Moreover, there are numerous examples in which complete clinical responses do not produce improved survivals. Indolent lymphoma patients who achieved complete remissions with conventional-dose therapies in the pre-rituximab era did not experience a survival advantage over similar patients treated with a "watch and wait" approach [19]. In multiple myeloma, neither the magnitude nor the kinetics of clinical response impacted survival in some studies [20]. Even the most intensive therapy for myeloma, BMT [21,22], provided no overall survival advantage in the national intergroup trial [23] or in two recent meta-analyses [24,25].

The CSC concept would explain not only the low clonogenic capacity of most malignancies, but also why complete treatment responses translate into cures in only a minority of cancer patients: initial responses in cancer represent therapeutic effectiveness against the bulk cancer cells, while rarer resistant CSCs could be responsible for relapse. Putative CSCs have in fact been reported to be relatively resistant to standard anticancer therapies. Myeloma CSCs have been shown to be resistant to most clinically active agents (e.g., dexamethasone, lenalidomide, bortezomib), at least in part by co-opting normal stem cells' intrinsic defense mechanisms such as quiescence, efflux pumps, and detoxifying enzymes [15]. Treatments that eliminate tumor bulk but spare the CSCs could be considered analogous to mowing dandelions; although this will eliminate the visible portion of the weeds, the unseen roots also need to be addressed to prevent regrowth [26,27]. Equally problematic would be treatments that are specific for CSCs. Such a treatment effect is akin to attacking just the root of the dandelion; although this has no immediately discernible effect on the weed, over time the weed should eventually wither and die if its root has been eliminated [26,27].

Controversy

Although cells meeting the definition for CSCs have now been described in many malignancies, there remains healthy skepticism about their true biologic significance [28,29]. Even in leukemia where the CSC concept is perhaps best established, a paucity of data indicates that LSCs are in fact responsible for disease resistance or relapse. This has led some to question whether CSCs may be nothing more than laboratory curiosities, simply reflecting the limitations of NOD/SCID mice for assessing tumorigenic potential [30]. However, despite being considered the gold standard assay for CSCs by many in the field, there is no reason to assume that growth in immunosuppressed mice is a relevant assay for clinically-significant CSCs. Actually, the most clinically relevant cancer cells are not necessarily those that engraft immunodeficient mice, but rather those responsible for relapse. Accordingly, even if every cell in a cancer possessed tumorigenic potential, the more clinically relevant question is probably whether any cell can also be responsible for relapse or only a discreet cell subset. Emerging data in several malignancies now suggest that a discreet subset of phenotypic CSCs may in fact be responsible for relapse.

Clinical Relevance

If CSCs are indeed more resistant to therapy than the bulk tumor cells and thus responsible for relapse, minimal residual disease (MRD) after treatment should be enriched for these cells. Furthermore, the presence of CSCs after therapy should predict recurrence. Indeed, residual breast tumor cell populations persisting after conventional treatment have recently been found to be enriched for breast cells with a CSC phenotype [31]. Similarly, patients with deletion 5q myelodysplastic syndrome (MDS) continue to harbor phenotypically distinct MDS stem cells ($CD34^{+}CD38^{low}CD90^{+}$), even in complete clinical and cytogenetic remission; these cells appear resistant to lenalidomide treatment and thus may account for disease relapse [32**]. Our group also showed that there was a strong and significant association between myeloma CSC numbers and progression-free survival in patients after treatment with high-dose chemotherapy and rituximab [33]. Our recent data also suggest that MRD in AML has a stem cell phenotype [34], and the presence or absence of AML CSCs after therapy correlates with progression-free survival. These data, perhaps for the first time, provide evidence of clinical relevance for CSC's.

CSCs and BMT

Autologous BMT as rescue for dose intensification of standard cytotoxic agents is in general usage for three diseases: multiple myeloma, diffuse large cell lymphoma, and Hodgkin lymphoma. However, autologous BMT is unable to cure multiple myeloma, and its effectiveness in relapsed diffuse large cell lymphoma has significantly lessened in the rituximab era [35**]. These data suggest that even very high doses of chemotherapy may be unable to kill some CSCs [15]. Moreover, we found that CSCs circulate in the blood at surprisingly high levels, even in early stage Hodgkin lymphoma and multiple myeloma [15,17], suggesting that contaminating CSCs within the autograft might also contribute to relapses. It is possible that the ability to circulate is an inherent property of CSCs, co-opted from their normal counterparts that migrate for the purposes of maintaining tissue homeostasis and repair.

Relapse remains the major cause for failure of allogeneic BMT as well. Even the potent allogeneic graft-versus-tumor effect appears to provide limited antitumor benefit for many hematologic malignancies; e.g., despite high complete remission rates, relapse rates remain high after alloBMT for multiple myeloma [36] and advanced myelodysplastic syndromes (MDS) [37]. It is likely that those cancer cells remaining after the BMT conditioning regimen are resistant to immunologic, and well as genotoxic, killing. Although there is

limited work on mechanisms of resistance to immunologic killing, the same anti-apoptotic signals responsible for cytotoxic resistance may also produce resistance to the induction of immunologic apoptosis. Moreover, LSCs like HSCs upregulate the “don’t eat me signal” CD47, presumably as a mechanism to avoid immune-mediated killing [38].

Although some CSCs may be able to evade high-dose cytotoxic therapy and immunologic graft-versus-tumor effects, allogeneic BMT may be a particularly compelling setting to study novel CSC-targeting approaches. Because BMT provides the most effective clinical debulking of hematologic malignancies, any added antitumor approach should be most effective. Further, the effectiveness of any novel CSC-directed treatment will also be most readily assessed in the setting of optimal clinical debulking. It also appears that many anticancer therapies may interact with the new allogeneic immune system to produce an enhanced antitumor effect. One mechanism of such synergy could be through enhancement of tumor cell recognition by the new immune system [39-41].

Conclusion

Stem cell pathways not only appear to be responsible for CSC resistance to many anticancer agents [15], but they may also lead to the development of novel therapies active across many malignancies. Several signaling pathways that are important for the generation and maintenance of normal stem cells during embryonic development, (e.g, Notch, Wnt, and Hedgehog) [42] and/or postnatally (e.g., telomerase [43]) also appear to be important for the growth of many cancers. In fact, prospective targets shared with normal stem cells may have particularly strong anticancer potential since their conserved expression implies a critical function retained by the CSCs. Preliminary data suggest that inhibition of these pathways, even when they are not mutated or over-expressed, may produce potent antitumor activity across a range of malignancies, possibly because of the key roles these pathways play in stem cell maintenance and growth [44*, 45].

While toxicity is an obvious concern for targets shared with normal stem cells, there are several potential differences between normal stem cells and CSCs that may provide a therapeutic ratio for shared targets. Normal stem cells have normal cell cycle checkpoints that are likely to protect them from cellular damage or crisis. The stage of differentiation at which cancers arise may also provide selectivity for approaches targeting CSCs. Although many cancers may arise from normal cells with stem cell properties, these cells may not be the most primitive tissue stem cells. Accordingly, if a therapy equally eliminated both myeloma CSCs and their normal counterparts, memory B cells, the existence of more primitive normal HSCs should replenish the normal B cell pool.

Differences in the interplay of telomere length and telomerase is another example how a stem cell pathway may provide a therapeutic ratio between CSCs and their normal counterparts [44*]. Normal stem cells require telomerase to prevent telomere shortening, leading to replicative senescence. However, even in the absence of telomerase, normal stem cells can maintain replicative capacity for some period of time because of their relatively long telomeres. Accordingly, telomerase knockout mice show a phenotype only after 4-6 generations [46]. In addition, the major cause of death in dyskeratosis congenita, a congenital disease that results from loss of function mutations in telomerase components, is bone marrow failure but this usually does not manifest until the second or third decade of life [47]. In contrast, uninterrupted telomerase activity may be absolutely required for the maintenance and growth of most malignancies, in order to stabilize the short telomeres that appear to characterize CSCs [48]. In fact, crossing telomerase knock-out mice with *INK4a*$^{-/-}$ [49] or *APC*^{min} [50] mice predisposed to cancer, significantly lowered the development of

cancers in these mice. Thus, the differential in telomere length between normal (long) and cancer (short) stem cells could render telomerase inhibition selectively toxic to cancer.

Although the biologic and clinical relevance of CSCs remains controversial, emerging data are beginning to suggest that resistant CSCs are often responsible for relapse. The BMT setting may provide the optimal platform for testing post-transplant CSC-targeting. BMT not only provides arguably the most effective clinical debulking of hematologic malignancies, but the allogeneic immune system may also potentiate CSC-directed therapies. The use of CSC-targeted therapy in the MRD state after BMT potentially offers a novel approach to improving tumor control.

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Bullet Points

1. Most cancers have been found to have a rare population of cells with stem cell characteristics, but the clinical significance of these cells has been unclear.
2. The cancer stem cell concept, if true, would explain why complete treatment responses translate into cures in only a minority of cancer patients.
3. Emerging evidence in several cancers suggest for the first time that cancer stem cells are responsible for relapse, even after blood and marrow transplantation.
4. BMT may be a particularly compelling setting to test cancer stem cell-targeting strategies, because it provides the most effective clinical debulking of hematologic malignancies and because such strategies may also enhance allogeneic antitumor immunity.