Somatic stem cells and the origin of cancer

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Most human cancers derive from a single cell targeted by genetic and epigenetic alterations that initiate malignant transformation. Progressively, these early cancer cells give rise to different generations of daughter cells that accumulate additional mutations, acting in concert to drive the full neoplastic phenotype. As we have currently deciphered many of the gene pathways disrupted in cancer, our knowledge about the nature of the normal cells susceptible to transformation upon mutation has remained more elusive.

Adult stem cells are those that show long-term replicative potential, together with the capacities of self-renewal and multi-lineage differentiation. These stem cell properties are tightly regulated in normal development, yet their alteration may be a critical issue for tumorigenesis. This concept has arisen from the striking degree of similarity noted between somatic stem cells and cancer cells, including the fundamental abilities to self-renew and differentiate. Given these shared attributes, it has been proposed that cancers are caused by transforming mutations occurring in tissue-specific stem cells.

This hypothesis has been functionally supported by the observation that among all cancer cells within a particular tumor, only a minute cell fraction has the exclusive potential to regenerate the entire tumor cell population. These cells with stem-like properties have been termed cancer stem cells. Cancer stem cells can originate from mutation in normal somatic stem cells that deregulate their physiological programs. Alternatively, mutations may target more committed progenitor cells or even mature cells, which become reprogrammed to acquire stem-like functions in any case, mutated genes should promote expansion of stem/progenitor cells, thus increasing their predisposition to cancer development by expanding self-renewal and pluripotency over their normal tendency towards relative quiescence and proper differentiation.

Key words: cancer stem cells, cancer, leukemia, telomerase, microRNAs.


The ability of the stem cells to produce progeny that expresses different mature phenotypes is called potential or plasticity. Pluripotent embryonic stem cells can give rise to all of the differentiated tissues of the body whereas multipotent somatic stem cells have the capacity to form many but not all different cell types. Some childhood tumors have provided a link between embryonic stem cells and cancer. Both neuroblastoma (which arises from fetal neural crest cells of the sympathetic nervous system) and Wilms tumor (which arises from embryonic cells of the kidney) are caused by mutations occurring in embryonic stem cells, giving rise to tumors composed of a mixture of undifferentiated spindle cells, immature epithelial tubules and more differentiated cells. Similarly, teratocarcinomas are made up of a variety of differentiated cell types as well as of embryonic and fetal tissue cells. Because these normal embryonic cells physiologically differentiate with age and eventually disappear, neuroblastoma, teratocarcinomas and Wilms tumors only affect to young children. However, the majority of cancers occurring in adults are derived from multipotent or pluripotent (somatic) stem cells, some of which have been recently discovered.

Here we review the role of the cancer stem cells identified in different hematopoietic and solid tumors, focusing on the molecular networks that govern their homeostatic programs. We will additionally address emerging new concepts and controversial issues of cancer stem cell biology. Last, the potential implicati
tion of cancer stem cells in the development of lymphoid malignancies will be discussed.

HEMATOPOIETIC STEM CELLS AS TARGETS OF TRANSFORMING MUTATION IN LEUKEMIA

Early bone marrow reconstitution experiments in immunocompromised mice revealed the existence of the hematopoietic stem cells (HSCs). Recently, many tissue-specific stem cells have been identified. Stem cells share the characteristics of unlimited self-renewal, which maintains or expands the stem-cell population, and multi-lineage differentiation, which generates and regenerates tissues. Yet another defining characteristic of stem cells is their limited replication frequency (quiescence) compared to their more proliferative progeny. Although initial evidence for the concept of cancer stem cells also came from early studies, solid experimental analysis have demonstrated their existence only recently. Two pioneering reports showed that despite most of the tumor cells obtained from patient with acute myeloid leukemia (AML) were unable to proliferate extensively, a small subset were capable of transferring the leukemia to immunocompromised mice. These leukemia-initiating stem cells (LSCs) were prospectively identified as having a CD54+CD38- phenotype, resembling normal HSCs. By contrast, CD34+CD38+ leukemic cells were not able to propagate the leukemia. Notably, on each of the morphological and genetic subtypes of AML, only the CD34+CD38- cell population retained the capacity to transfer the leukemia in vivo. These data indicate that AMLs exhibiting different stages of differentiation are originated from a common LSC that shares similar cell-surface markers with normal long-term HSCs. Subsequent studies have characterized in detail the phenotypes of normal HSCs and LSCs. Besides a CD34+CD38- phenotype, both lack expression of the lineage markers CD71 and HLA-DR. Notably, LSCs also lack expression of CD90 and the stem cell factor receptor CD117 (c-Kit) whereas they had high expression of the interleukin-5 alpha receptor CD125. However, despite a common immunophenotype, LSCs are not functionally homogeneous but instead, resemble the normal hematopoiesis, form a hierarchy of cells that differ in their self-renewal potential. The similarities between HSCs and LSCs strongly suggest that HSCs are the source of LSCs when targeted by oncogenic mutations. Nevertheless, these mutations may also target progenitor cells that become de novo leukemia stem-like cells. Additional evidence supports that AML is a progressive model of cancer resulting from mutations in HSCs and their progeny. The t(8;21)q22 is the most frequent chromosomal translocation in AML, resulting in a chimeric gene fusion. In HSCs isolated from patients with AML in complete remission, transcripts were found in a fraction of normal bone marrow HSCs. These cells did not show leukemic properties, and normally differentiated to myeloid and erythroid cells. Consequently, the t(8;21) occurred in normal HSCs suggesting that it was the additional mutations in a subset of HSCs or their progeny which led to leukemia development. A different experimental approach has investigated the transformation capacity of a variety of oncogenes involved in human leukemia when ectopically expressed into the different HSC compartments. Short-lived myeloid progenitors transduced with MLL-ENL or MOZ-TIF2 oncogenic fusions generated AML with similar latencies and characteristics than those observed in long-term HSC models. Notably, this observation was not expanded to BCR-ABL or MLL-ENL gene fusions, which did not transformed committed murine hematopoietic progenitors. According to these data, some but not all oncogenes are capable of mediate similar leukemic transformation in both HSCs and committed progenitors. More recently, Eguchi et al expressed the two variants of the TEL-TRKC fusion gene, which are found in leukemias and solid tumors, into the mouse stem cell compartment. Results showed that the leukemia form of TEL-TRKC enhanced hematopoietic stem cell renewal and originated leukemia whereas the solid tumor variant of TEL-TRKC elicited impairment of hematopoiesis but did not induce cancer. Thus, related oncogenic fusion genes similarly expressed in stem cells may produce diverse cell type-specific developmental impacts. This interesting finding might explain the phenotypic diversity of human leukemia despite having identical chromosomal rearrangements. Functional studies have also been conducted in chronic myeloid leukemia (CML), a disease of HSCs that undergo hierarchical differentiation, thus resulting in a vast majority of differentiated CML blood cells, whereas a rare cell fraction resembling normal HSCs is responsible for disease maintenance. CML cells also have the potential to generate acute leukemias of myeloid and lymphoid lineage during the blast crisis.

In conclusion, the discovery of cancer stem cells and their role in hematopoietic malignancies will be discussed.