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Multi-Role of Cancer Stem Cell in Children Acute Lymphoblastic Leukemia

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1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignant proliferation of lymphoid precursor cells in the bone marrow blood. It is an age related tumor, with a peak between the ages of 2 and 10 and a second peak after the age of 5. Among children younger than 15 years, ALL represents 23% of cancer that was diagnosed. The children aged 2 to 3 years were a sharp peak in ALL incidence (>80 per million per year). The rates of the ALL among children aged 8 to 10 years incidence decreasing to 20 per million. Moreover, there has been a gradual increase in the incidence of ALL in the past 25 years.

With the development of the medicine, considerable advances have been made in the treatment of childhood ALL. In the 1980's, relapsed ALL was regarded as an incurable disease. However, about 85% of childhoods ALL can hope to achieve a second remission over the last years. Meanwhile, around 40% of these can hope to achieve long term cure. On the other hand, despite optimal therapy, long term survival rate still limited to 30–40% of patients and about 15-20% children will sustain relapse. Because of the high relapse rate, refractoriness to conventional treatment protocols, the incidence of chemotherapy-related deaths, the complete remission rate, numerous challenges remained in the management of ALL, especially the children with relapsed ALL. Also, the disease mechanism is multi-factorial and involves in different genetic and environmental factors. So, ALL is still a problem that clinic must face up to. However, the emergency of cancer stem cell seems give us a new direction for deeper recognize this disease.

Despite the clone origin of many cancers, a notable characteristic of primary tumors is a marked degree of cellular heterogeneity. The hypothesis that human cancers comprise a heterogeneous population of cells that differ in marker expression, morphology, proliferation, and tumorigenicity has existed for over a century. Every tumor can be viewed as an abnormal organ that harbors a stem cell compartment. Emerging evidence has confirmed that the capacity of a tumor to grow and propagate depends on a small subset of cells within the tumor, which are most specifically referred to as “cancer stem cells” (CSCs), but have also been referred to as “progenitor cells” or “tumor initiating cells” (TICs) to distinguish them from the rest of the neoplastic cells that are unable to regenerate tumors. CSCs are defined to be a distinct population but variable subpopulation of the total tumor mass with stem cell characteristics that are essential for the initiation, development of human cancers, multi-drug resistance and metastases.

In the last two decades, with the wide spread utilization of fluorescence activated cell sorting (FACS) or magnetic activated cell sorting (MACS), the application of these technology to isolate and characterize of distinct cell populations of hematopoietic stem (HSC) or progenitor cell populations has become available. Using the same methodologies that employed to characterize normal hematopoietic stem cells, Cancer stem cells were first identified in haematopoietic malignancies and later in a broad spectrum of solid tumors including those of the breast, pancreatic, colon and brain. So, the malignant stem cell population that has been identified from ALL have been analyzed in most detail. These leukemia initiating, or leukemia stem cells (LSC) reside at the apex of a hierarchy of malignant cells that is analogous to the hierarchy found in normal hematopoietic. Thus, a hierarchical development structure for the leukemic population can be envisaged that originates from the malignant stem cell and is similar to normal hematopoietic processes. Importantly, these subpopulation of leukemic stem cells maintain the key stem cells properties of self-renewal, extensive proliferative potential and differentiate potential, highly resistant to chemo- and radio-therapy, driven metastasis, especially special organ metastases.

Apart from the method of FACS, LSCs may be sorted by various other characteristics. With the characteristic of limit less self-renewal in vitro, LSCs can be enriched in spheres when these cells are cultured in serum-free medium supplemented with the basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), B27, insulin, and transferrin. With the characteristic of expressing ABC transporters, these cells are able to pump the fluorescent dye hoechst-33342 out of the cell, namely identify unlabelled “side population” (SP) which highly enriched in stem cells.

With the deeper study of cancer stem cell, the role of it in ALL was believed to be more and more important. These functions include the following aspects.

2. Cancer stem cell may the origination of children Acute lymphoblastic leukemia

The development of the tumour is always believed to be the result of a succession of epigenetic/genetic alterations and selection steps which leading to the emergence of cells accumulating

survival and proliferation advantages. In the primary tumour, selection is proposed to take place continuously which giving rise to heterogeneity that simply reflects the coexistence of cell populations evolving independently and displaying distinct oncogenic potentials. The environment that the tumor exists was thought to be an important factor that impacts the selection procedure. The theory above mentioned denominates the cancer research one century and might be sufficient to interpret the cell diversity observed in tumors. However, it fails to explain how individual disseminated cancer cells escaping from primary tumours yield secondary tumours with similar diversity. An alternative model assumes that primary and secondary tumours arise from cancer cells displaying both self-renewal and differentiation capabilities, namely cancer stem cell. Recently, it became apparent that the different subpopulations have different degrees of proliferative and self-renewing abilities and only a small subpopulation can regenerate all the other tumor cell subpopulations of the original tumor when injected into immuno-compromised mice. This model seems not exclusive of the above theory, but more suitable to explain the origination of the tumor.

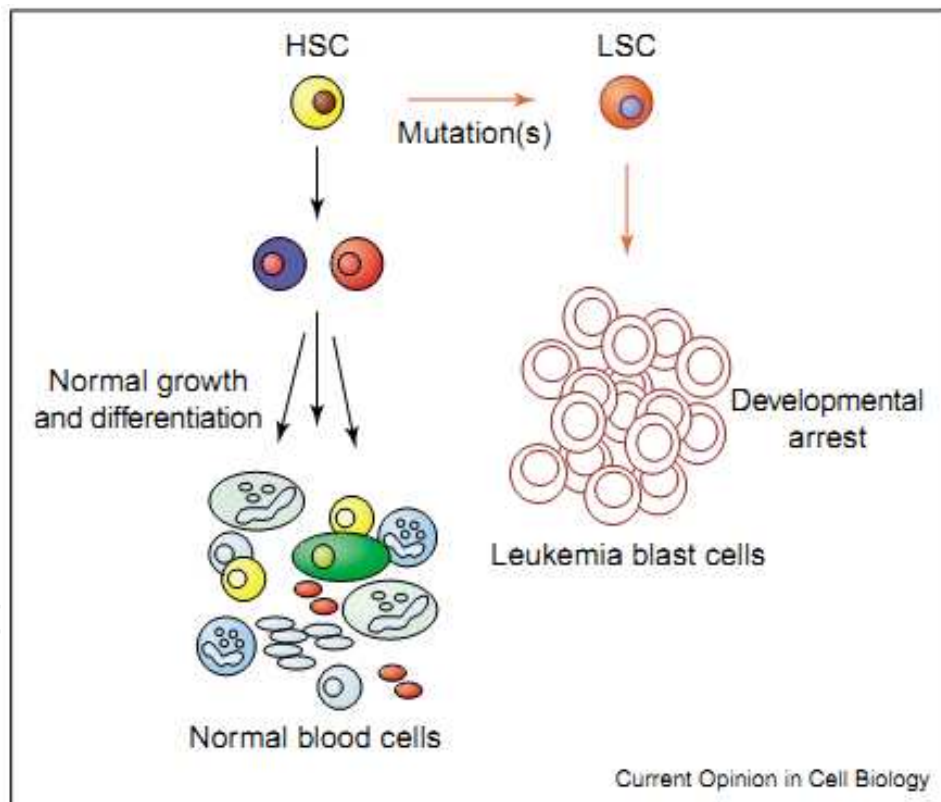


Figure 1. Craig T Jordan. Cancer stem cell biology: from leukemia to solid tumors. *Current Opinion in Cell Biology* 2004, 16:708–712.

At present, on the basis of expression of a particular cell surface marker, Cancer stem cells that sorted by FACE in children ALL are suggested to be have the most superior ability to form a new tumour in an in vivo xenograft assay and great ability to form cell spheres namely clonogenic when plated at low density in non-adherent culture. These two models were beloved to be the golden

standard to test whether the cells own the characteristic of stemness. Meanwhile, it demonstrated that the Leukemic stem cells may be the origination of children ALL.

The Leukemic stem cells (LSCs) appear to retain many characteristics of normal hematopoietic stem cells (HSCs). This observation indicates that the malignant stem cell population can arise in two possible ways. One possibility is that normal HSCs are the direct target of mutations that cause conversion to an LSCs phenotype. Alternatively, more differentiated cell types might acquire mutations that confer stem-cell-like properties on cells that typically would not display stem cell characteristics. Normal stem cells intrinsically possess three hallmark features: first, the potential to undergo self-renewal; second, the potential to undergo extensive proliferation; third, the potential to differentiate into multiple distinct cell types. Like normal stem cells, LSCs own the ability of asymmetric division and symmetric division. Leukemic stem cells undergo symmetric division and expand the stem cell compartment. Conversely, via asymmetric division, CSCs give rise to the variety of differentiated cells in the tumor mass. They are stringently defined by functional attributes including the ability to instigate, maintain and serially propagate leukemia *in vivo* while retaining capacity to differentiate into committed progeny that lack these properties.

So, LSCs not only sustain the tumor but maintain the number of cancer stem cell in the tumor tissue. One contribution to our understanding of tumor initiation and growth comes from considering the developmental biology of stem cell systems.

3. Cancer stem cells are the main factor of drug resistance and relapse

Subsequent studies have further refined the immunophenotype of ALL stem cells and substantially added to our understanding of their biology. One of the most important characteristics of cancer stem cells is highly resistant to chemo- and radio-therapy. Because of the resistant to chemo- and radio-therapy, cancer stem cells further led to the relapse of the tumor. With the deeper research, it had made out of that resistance could depend on certain features that LSCs share with normal stem cells. First, this property concerns cell proliferation. A lot of research showed that ALL stem cells reside mostly in a quiescent cell cycle state in the absence of specific stimulation from the microenvironment which is analogous to their normal hematopoietic stem cell counterparts. This observation has a great significance in understanding the role of cancer stem cells in drug resistance. Because most therapeutic agents which rely on cycling cells in order to cause lethal cellular damage approaches to leukemia are directed towards actively cycling populations. The quiescent nature of LSCs indicates that standard chemotherapy drugs will not generally be effective against ALL stem cells. Notably, while treatment of ALL children with the drug that specially targets actively cycling sub-populations, it has been highly effective for inducing remission. However, because of the existence of the quiescent cells, the patients would recur in the short time. This evidence indicates the disease is suppressed rather than eradicated. For example, 5-FU which is special for the S stage have obvious effect in the patient who was first diagnosed of ALL. However, once the drug was retreated, the tumor may relapse. FACS analysis displayed that the existence cells mostly display the stemness cell characteristic. So, most

chemotherapeutic agents, especially those special for the cycle population agents were cytostatic but not cytotoxic to the LSCs. This result supported the concept that ablation of the LSC is necessary to completely destroy the tumor population permanently. On the other hand, new therapy agent desperately needed to be explored to promote the quiescent LSCs into the active state. Second, the second key property of LSCs is their abnormal expression of certain pumps which are absent in their compartment of non-LSC. These proteins included ATP-binding cassette (ABC) transporters super family, multidrug resistance-associated protein (MRP) family, breast cancer resistance protein (BCRP), lung resistance protein (LRP) and so on. They are promiscuous transporters of both hydrophobic and hydrophilic compounds and can help the cell extruding several drugs out of the cells. The exact physiological role of these pumps is not yet fully understood, but it is known that they are involved in cellular protection against exogenous products and in resistance to hypoxic stress, mediated by an increased ability to consume hydrogen peroxide and a reduced accumulation of toxic metabolites. So, with the help of these abnormal proteins, LSCs can display the great ability to promptly eliminate or degrade toxic compounds even though the concentration of the drug at a very high level. Once the treatment stopped, LSCs may self-renewal and differentiate into multiple distinct cell types which led to the relapse. Third, the most important key property is resistance to apoptosis, which can be limited to CSC initially, is often rapidly acquired also by the bulk of tumor cells at relapse, perhaps due to the genetic instability which distinguishes tumor from normal cells. Activation of programmed cell death or apoptosis is a promising strategy for the treatment of cancer, and the balance between anti-apoptotic and pro-apoptotic members is a key factor in the regulation of cell death. In order to maintain the progenitor pool from which differentiated cells derive, cancer stem cells are programmed to be long-lived. For this purpose, cancer stem cells activate some protective mechanisms that protect them from senescence and/or cellular stress. These mechanisms include: (I) The current results showed that cancer stem cells expressed high levels of the anti-apoptotic protein such as Bcl-2, and low levels of the pro-apoptotic protein caspase 3, compared to non cancer stem cells. Enhancement of their anti-apoptosis ability means that tumor cells survival becomes more dependent on anti-apoptotic-pathway activation, and standard therapeutic approaches may thus fail to kill cancer stem cells; (II) activation of some self-renewal pathways, such as TGF- β , Sonic Hedgehog (SHH), Wnt/ β -catenin or BMI-1; (III) generation of auto-crine loops through the production of growth factors like epidermal growth factor (EGF), basic fibroblast growth factor (bFGF); and (IV) enhanced capability to repair DNA damage after genotoxic stress. As a consequence of this, chemotherapy invariably causes bone marrow toxicity due to its effects on trans-amplifying, progenitor and even more differentiated cells, whereas tumors may initially regress but subsequently become completely resistant to chemotherapy. By these natures, it was easy found that CSCs are biologically distinct from other cancer cell types. Moreover, certain natural properties of CSCs are likely to increase their resistance to standard chemotherapy agents. So, if cancer therapies do not effectively target the CSC population during initial treatment, then relapse may occur as a consequence of CSC driven tumor expansion. This is almost certainly the case in many instances of ALL, where standard drugs are unlikely to target the LSCs population effectively. Therefore, in developing new cancer therapeutics, analyses that directly assess toxicity towards tumor stem cells are an important priority.

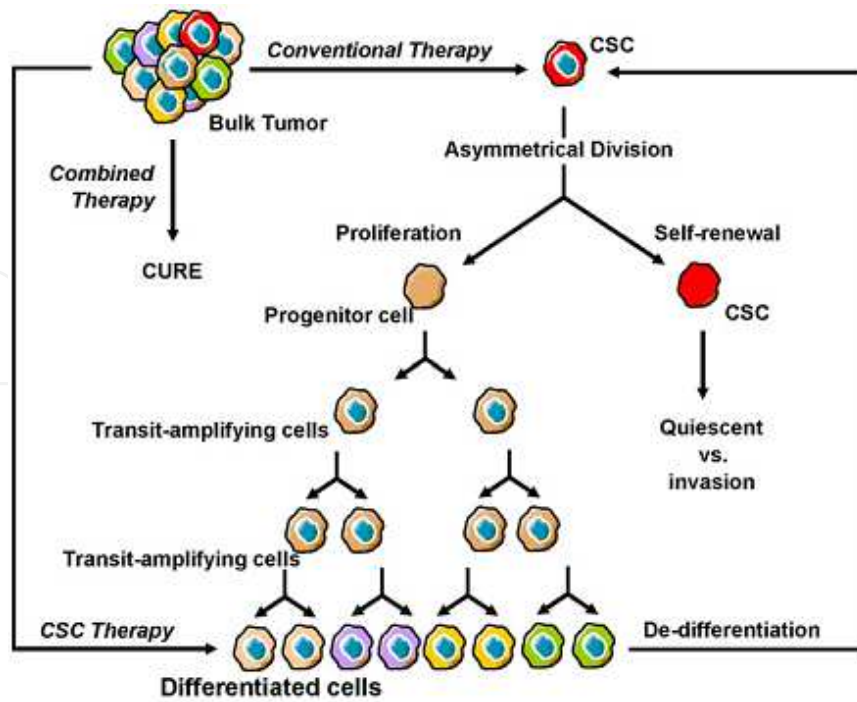


Figure 2. Lara Lacerda, Lajos Pusztai, et al. The role of tumor initiating cells in drug resistance of breast cancer: Implications for future therapeutic approaches. *Drug Resistance Updates*, 2010, 13: 99–108

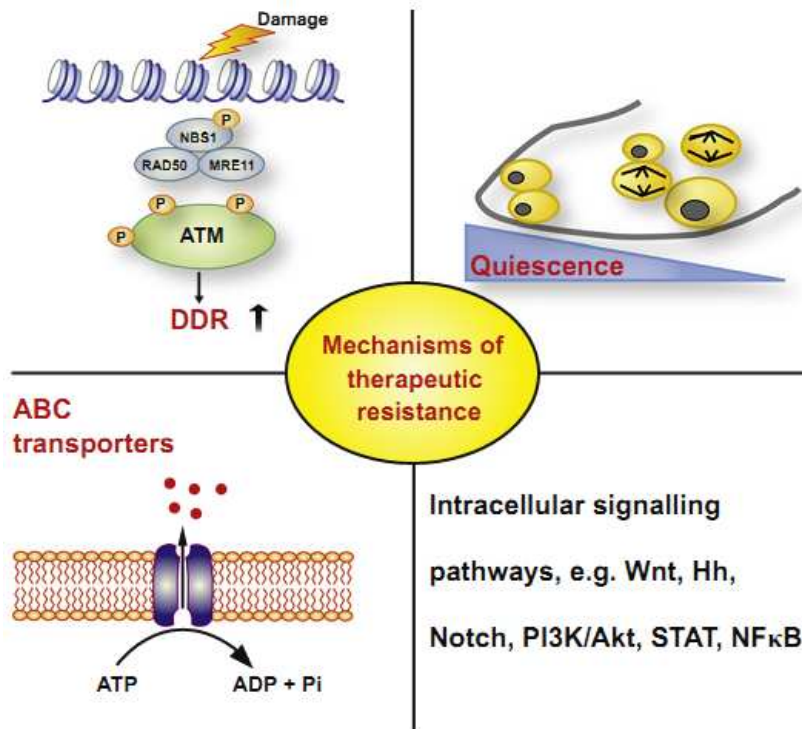


Figure 3. Malcolm R. Alison, Wey-Ran Lin, et al. Cancer stem cells: In the line of fire. *Cancer Treatment Reviews*, 2012, 38: 589–598.

4. LSCs solely are capable of driving tumor metastases

With the deeper research, it was well understanding that the cancer metastasis was viewed as a series of distinct steps that comprise the “invasion-metastasis-cascade” on the biological level [30-31]. The first step, cancer cells in the primary tumor acquire the ability to invade into the surrounding tissue such as the basement membrane. Next, tumor cells must gain access to blood and/or lymphatic vessels, enter into these vessels (intravasation), survive transport through these vessels, and exit from the vasculature (extravasation). Finally, small cell clumps or singly disseminated tumor cells must acquire the ability to survive and proliferate in the microenvironment of a foreign tissue in order to form macroscopic metastases, namely colonization or akinesis.

In the procedure of the tumor metastasis, EMT represents a crucial step and plays important role in mediated invasiveness and metastasis, also is strongly associated with poor clinical outcome in many tumour types [32]. EMT termed epithelio–mesenchymal transformation was first described in a model of chick primitive streak formation. Nowadays, EMT is defined as a biologic process that allows a polarized epithelial cell, which normally interacts with the basement membrane via its basal surface, to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype, which includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and greatly increased production of extracellular matrix components [33-35]. Due to reorganization of epithelial intercellular junctions, EMT weakens cell-cell cohesion. Further-more cell-cell adhesion complexes and their transcriptional repressors are strongly regulated by a number of classical EMT-regulated pathways which including TGF- β , PDGF, Notch, Wnt, many of which also seem to play key role in skeletal metastasis. Moreover, EMT stimulates focal, proteolytic degradation of extracellular matrices, thus favoring invasion of stroma and intravasation. The modification of the cytoskeleton during EMT also contributes to migration. Intermediate filaments of epithelial cells such as cytokeratins are responsible for maintaining cell structure, stiffness and integrity. Apart from invasiveness, EMT also contributes to angiogenesis and intravasation. In addition to stimulating neovascularization, migratory carcinoma cells that have undergone EMT have acquired a number of specific properties that allow them to interact with endothelial cells and to enhance trans-endothelial migration. At last, EMT renders enhanced resistance to apoptotic signals and may contribute to the survival of circulating tumor cells (CTCs) in the hostile bloodstream environment and, eventually formed the second tumor.

It has even been proposed that cancer cells adopt stem cell features only upon undergoing EMT. Indeed, induction of EMT in immortalized human mammary epithelial cells resulted in the expression of stem cell markers, and phenotypes associated with CSCs. These findings illustrated a direct link between EMT and gain of properties characteristic for migratory stem cells. So, it can be concluded that LSCs acquired the property of EMT which is essential for the LSCs to form macroscopic metastases

CD44 has been proposed as one such marker. CD44 may play a crucial role in developing of metastasis in ALL, especially metastasis to special organ. Additionally, LSCs may express higher levels of cell-surface receptors than their non-LSCs counterparts so that they may fully

harness the soluble growth factors present at secondary sites, conferring a growth advantage and permitting successful colonization.

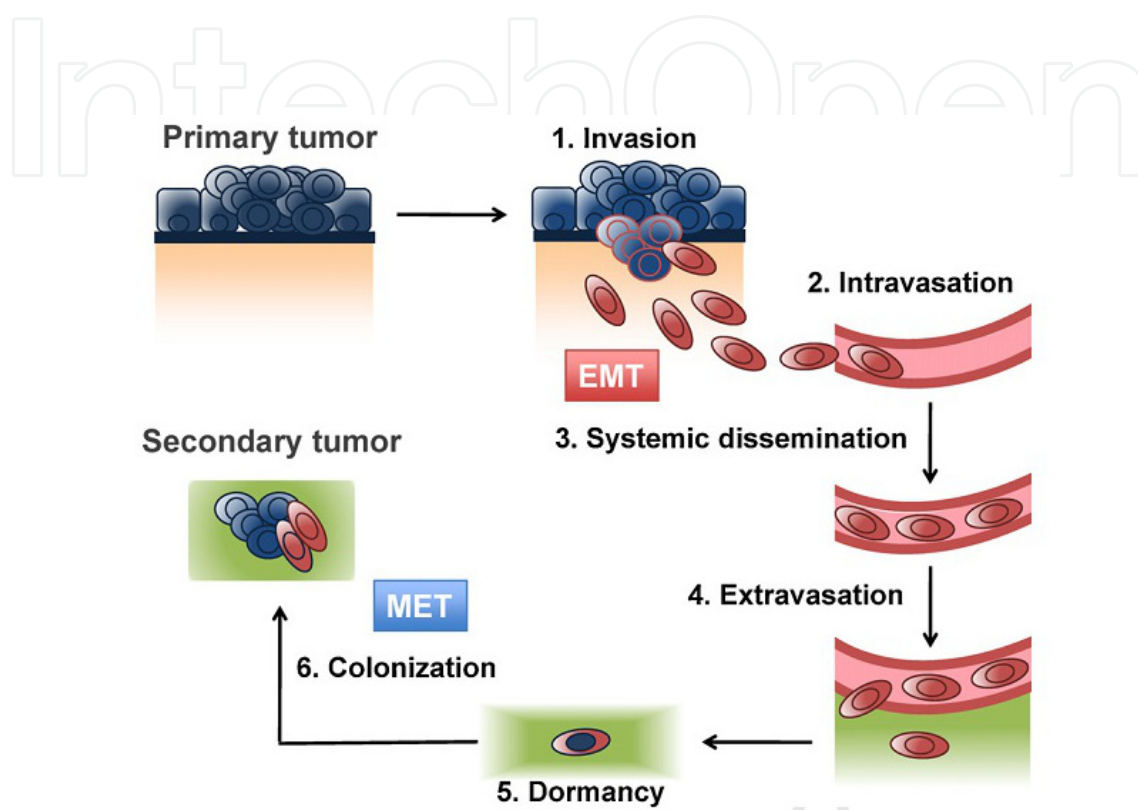


Figure 4. Christina Scheel, Robert A. Weinberg. Cancer stem cells and epithelial–mesenchymal transition: Concepts and molecular links. *Seminars in Cancer Biology*, 2102.

In a world, although LSCs accounting for only a few distinct populations, it is the most important factors that mediated the biology of the ALL. LSCs may play a great role in the origination, drug-resistance and metastases. In the future, LSCs may be the sole target for treatment. A detailed consideration of stem cell biology principles will be useful in better understanding tumor pathogenesis and in designing strategies for more effective therapies.

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