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Short Communication

Another Description of Hematopoietic Stem Cell and Its Hematopoietic Microenvironment in Normal State and Leukemia Disease

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ABSTRACT

Hematopoietic stem cells (HSCs) were first identified in 1961 by Till and McCulloch which less than 0.01% in the Bone Marrow (BM) cells. We know these are multi-potent stem cells defined by their ability to self-renewal, differentiation and maintenance of all blood cell types in hematological system during the entire life time of the organism. In fact, adult Hematopoietic Stem Cells (HSCs) are thecells capable of self-renewal and remain component in the process of hematopoiesis which, together with the cells that makeup the bone marrow stromal environment and other factors ,which means there is a balance between processes such as self-renewal, proliferation and differentiation of the cells versus apoptosis and cell cycle arrest in HSCs.

Keywords: Hematopoietic Stem Cells (HSCs); Leukemia

INTRODUCTION

Genetic molecular analysis on leukemia cell has provided the basic knowledge of pathogenesis and prognosis in acute and chronic leukemia. Molecular mechanism of leukemia resulted from aberrant of proto- oncogene expression and chromosome translocation leading to gene fusion promotes more active of kinase and also increases gene transcription. For example, Acute Lymphoblastic Leukemia (ALL) in children is a heterogenous disease with different subtypes based on their intracellular and molecular features this condition will influence the treatment response and risk for relapse. Thus, a good early stratification is needed to achieve outcome. Nowadays, genetic and molecular analyses have been widely used in practice to support the clinical criteria which have been used. Moreover, the leukemic cells can be immunophenotyped by using monoclonal antibodies to define the specific lineage and to determine the level of differentiation. So, firstly, Flow-cytometric can assist in the identification of immature and abnormal cells as well. In flow cytometry, identification of blasts relies on the demonstration of expression of immature antigens by a population having appropriate CD45 expression and light scatter characteristics. Although it is the overall immunophenotype that allows identification of blasts, antigens commonly used for blast identification include CD34,CD117, CD133, and Terminal Deoxy-Nucleotidyl Transferase (TdT). Secondly, blasts identified by immunophenotyping do not always directly correspond to blasts as identified by morphology. This is true because leukemic populations, similar to normal populations, consist of a maturational continuum and there is not perfect concordance between specific antigenic changes and the arbitrary morphologic changes that distinguish blasts from more differentiated cells. Moreover, in some types of leukemia, for example in the precursors in early neutrophilic lineage (promyelocytes) and monocytic series (promonocytes) are intentionally included in morphologic blast counts, because any blast can be important in the diagnosis of leukemia patient. Nevertheless, co-expression of other non-lymphoid markers is common on the lymphoblasts in both precursor-B and precursor-T ALL and does not necessarily indicate bi-lineal potential. The myeloid markers, CD13 and CD33, are the most frequently expressed. The morphological recognition of lymphoblasts in the blood and bone marrow and their phenotypic characterization are of major importance to the correct diagnosis and classification of ALL. Thus, these require careful evaluation of well-prepared peripheral blood and bone marrow aspirate smears, and phenotypic analysis of the blasts are with cytochemical studies and by flow cytometry or immunohistochemistry with an appropriate panel of surface and cytoplasmic markers [1-6].

DISCUSSION

When the process of blood cell production is unbalanced, leading to an exacerbated and uncontrolled proliferation of blood progenitor cells, so leukemia may develop. We can say, normally many of the different types of signals that are exchanged between stem cells and niche cells and some of signaling pathways that control stem cell

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maintenance, self-renewal and differentiation as well. In other words, regulation of proliferation and differentiation of HSC is controlled by firstly the gene expression in the cell and secondly the Bone Marrow (BM) microenvironment in the composition of external signals. So internal signals regulate the expression of gene while the external signals can be mediated by cell-cell interactions, etc which may promote proliferation, differentiation, migration and apoptosis. Also, some studied confirmed the central role of osteoblastic lineage cells in HSCs regulation which is emerging as an essential component of HSCs maintenance and hematopoietic recovery from injury. Furthermore, for supporting HSC expansion, the liver is also the main site for hematopoietic differentiation in fetus, providing a microenvironment both for myelo- erythroid and B- lymphoid differentiation which both endothelial and stromal cells as well as developing hepatocytes, probably provide cues toward the hematopoietic microenvironment in HSC support [7-11].

Also, while functional HSCs are dormant clearly, but they can reply to extrinsic signaling in injury and in stress too. Likewise, Bone Marrow (BM) stroma is a key element of hematopoiesis which is a rare population includes non hematopoietic skeletal progenitor cells as named Stromal Cells (SC) that closely associated with the vasculature. Furthermore, Mesenchymal Stem Cells (MSCs) play an important role in niche cells particularly in providing the specialized bone marrow microenvironment for HSCs and other hematopoietic progenitor cells. Also, for supporting HSC expansion, the liver can be the main site for hematopoietic differentiation in fetus, providing a microenvironment both for myelo- erythroid differentiation [7-15].

Moreover, as per our knowledge HSCs provide homeostatic maintenance of the blood system through their ability to differentiate and generate the hundreds of millions of erythrocytes and leukocytes needed per day. Hence, if we try to make or produce in induced HSCs or HPCs, so there may be more than one way to reprogram cells in the hematopoietic lineage and a next understanding of HSCs biology in leukemia therapy patients. In fact, cell niches play essential roles for self- renewal and differentiation of HSCs *in vivo* and hematopoietic microenvironment show to generate functional hematopoietic stem cells. In this regard, single cell genomics describe to better analyze hematopoiesis in the microenvironment which can provide guidance for promoting HSC expansion and help to prevent hematopoietic malignancy as well. The role of hematopoietic research about single cell studies are important in last decade but we have some complex in the regenerative system. So, it is better to determine the exact role of involved molecules in clonal expansion and implication of invasion for deconstructing the molecular network including the normal situation to abnormal and malignant stem cells as well [16-18].

We know about the diversity of leukemic disease phenotypes which increased proliferation induced by some fusion genes on the mutant clone that results in diverse clonal evolution which can increase a tendency to leukemic transformation but in the follow-up, we understand that the clonal evolution has considerable potential to identify patients at high risk in progression disease ultimately or in other words, clonal evolution means key regulators of the disease in development and progression only. Actually, we know that the clone contains to exhibit unlimited growth potential which explain this growth is exhibited by the most primitive cells, that possess stem-ness virtues like self- renewal, etc. Hence, if we try to understanding of stem-ness properties and most important cells like progenitor and precursor cells as well, so we'll be able to perceive that can drive in sequential rounds of leukemia development. In leukemia, diversity within the cells at the genetic and functional level together with their coexistence with the hematopoietic microenvironment, allowing the leukemic cells to offset survival pressures imposed by treatment. Also, we know about the important role of cytokines in normal and malignant hematopoiesis. In other words, Colony Stimulating Factor- Granulocyte (CSF-G) , CSF- GM (Colony Stimulating Factor- Granulocyte and Monocyte) and CSF-M are critical for granulocyte and monocyte production whereas erythropoietin and thrombopoietin can stimulate erythroid and megakaryocyte series respectively. So the cytokines act on hematopoietic progenitor and precursor cells which localized in the Bone Marrow (BM).

Concerning these points, we try to discuss about "niche concept" in more than 50 years ago till now and we want to explain fundamental differences between bone marrow and spleen microenvironments in supporting hematopoiesis. Studies in last decade, uncovered overlapping niches for HSCs, multi-potent stem cells and other committed stem cells. So HSC and lymphoid niches are importantly composed by a little of endothelial cells and Mesenchymal Progenitor Cells (MPCs) too which create specialized microenvironments that in the situation, the cross-talk can be between hematopoietic stem and progenitor cells with other niche cells and thus we need to clear the mechanisms and magnitude of cross talk between normal and pre-leukemic hematopoietic cells and other kind of leukemias importantly [19-20]. In this way, specialized microenvironment formed by sinusoidal endothelial cells and MPCs is important emphatically. Now, what is the imagine of this microenvironment? My imagination can be like seed and soil, in other words, if a plant goes to a seeding, after the live and grow, its seeds fall on congenital soil and so the seed can be reinterpreted as progenitor cell or cancer stem cells and the soil as host factors, stoma , niche or specialized microenvironment and thus we should be accepted that hematopoietic microenvironment can't be ignored in leukemia genesis and its progression. Furthermore, normal state and leukemia state can be as an "endogenous molecular cellular network" and so that , leukemia disease and its progression, can be regarded as the endogenous molecular cellular network in transition from a normal stable state to a leukemia state [21]. Therefore, any malignancy is an intrinsic state shaped by evolution which the transition from normal to malignant can or can't be arbitrary that need to pass through the critical saddle points. In this capacity and in the network theory as well, both genetic and environmental agents are effective [16-21, 2-4].

In the end, we should know, which niche cells can regulate HSC action mechanism? And we can investigate exactly about the location of endogenous HSCs and the accurate role of perivascular cells as well as other niche cells too. Moreover, it will be important in our studies to determine the role of some cytokines such as SCF, FLT3L, IL-1, IL-6, IL-15 in the upset of pluripotent stem cell or HSCs and its hematopoietic microenvironment in changing from benign state to malignant disease and how can exactly determine the particular manner in changing from pre-leukemia to leukemia as well? And finally, how leukemic transformation might alter the

dependency of Leukemic Stem Cells (LSCs) on their niches for self-renewal and survival correctly?

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