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The Importance of Altered Hematopoietic Microenvironmental Regulation in Chronic Myeloproliferative Disorders

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Abstract

Normal hematopoiesis depends on critical interactions that occur between stem cells and their microenvironment. This microenvironment is a complex meshwork composed of growth factors, stromal cells, and the extracellular matrix. Pluripotent Stem Cells (PSCs) are the stem cells which present in Chronic Myeloproliferative Disorders (CMPD) to have self-renewal capacity and towards differentiated cells in blood cells lineages. When the process of these stem cells become deregulated, neoplasm can result with possibly several mutations as well as the alterations in the control of growth factors and meanwhile disrupt the normal HSC function and blood cell production. Thus, these interactions must important in the pathogenesis and clinical expression of hematopoietic malignancies in humans. Here, I review the leukemic hematopoietic microenvironment and the genetic alterations as well.

Keywords: Chronic myeloproliferative; Stem cells; Blood cell; Hematopoietic malignancies

Introduction

Bone Marrow (BM) has an organized and structured architecture in which close relationships exist between a regulatory microenvironment and primitive hematopoietic cells. BM niche is a specific microenvironment for all stem cells that includes HSCs, MSCs and the other cells. In fact, BM is a specific environment for receive any kind of support from several sources including: Fibroblasts, osteoblasts, adipocytes, endothelial and reticular cells and Mesenchymal Stem Cells (MSCs) as well (Figure 1).

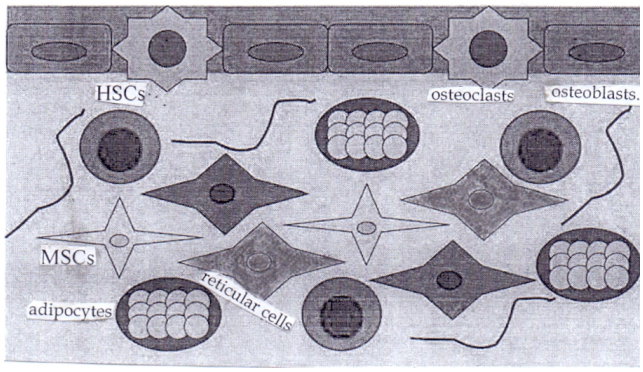

Figure 1: Normal bone marrow niche cells model.

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In this niche, the control of hematopoietic stem cells proliferation is very important for the regulation of hematopoietic cells production; that means self-renewal, differentiation and maturation can be controlled by cell-cell interactions in the hematopoietic microenvironment, cytokines and others. Normality, HSCs can divide to transient amplifying Multipotent (MPPs) and restricted progenitor cells that proliferate and differentiate to mature blood cells [1-3]. In fact, there is a balance control between HSCs and more differentiated cells in the period of self-renewal of these stem cells and limited differentiated progeny as well. After the imbalance control of the cells, these cells may be transformed that resulting in high proliferation of blasts and/or more differentiated and maturated cells and change to a neoplasm growth. Leukemia is the consequence an accumulation of the immature blast cells that fail the functional differentiated cells and molecular alterations occur in the cells as well that resulting in leukemia disease. Also, a block in terminal differentiation and defective apoptosis leading the accumulation of blasts and clinical features (Figure 2) [4,5].

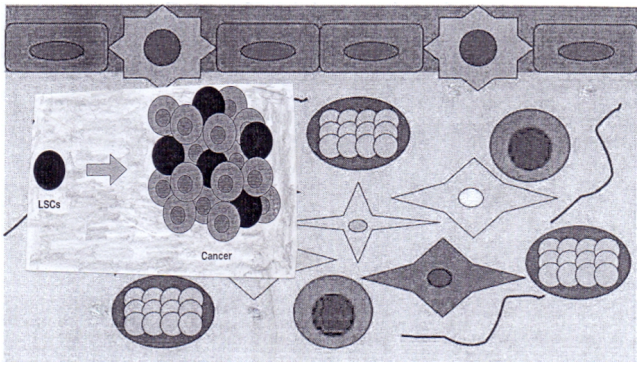

Figure 2: Leukemic bone marrow niche cells model.

As we know, Leukemic Stem Cells (LSCs) infiltrate in a bone marrow and interfere with HSCs differentiation pathways and normal microenvironment hemostasis [6-12]. Leukemic microenvironment supports a site for homing of leukemia cells that plays in growth and

leukemia progression [13,14]. In other words leukemic microenvironment disrupts the normal niche of hematopoietic cells of bone marrow which create a malignant microenvironment or leukemic niche. Thus, leukemia includes multiple genetic and epigenetic alterations that the changes may be disrupted in the hematopoietic cells differentiation pathways which resulting normal cells to abnormal differentiation, maturation and high proliferation of cells. Anyhow, the interactions between malignant cells and their microenvironment should be responsible in part of the complexity of malignancy [15-30].

Discussion

There is a serious question in this statement. As we know, BCR-ABL fusion proteins can transform hematopoietic progenitor cells *in vitro*. Furthermore, lethal reconstituting of irradiated mice with the gene encoding the p210 BCR-ABL1 and its bone marrow cells infected with retrovirus can lead to induction of CMPD resembling CML in 50% of the mice. The question is ''why only 50%?" Thus we can say, first, the mechanism or transition of CMPD from non-malignant to malignant state is still unclear and second, in normal individuals the messenger RNA for BCR-ABL1 fusion gene may be detected which can be a challenging factor for this rearrangement [15-18,21,25]. Furthermore, in CML, BCR/ABL1 oncogene can be detected in several progenitor cells, indicating that the origin cell is in an HSCs with potential of multi lineage differentiation [6-8]. In fact, involvement of an earlier hematopoietic progenitor that have differentiation for the lymphoid as well as the myeloid, erythroid, and the megakaryocytic series. But as we know the mechanism of normal suppression in leukemia is complex. In many patients with hyper cellular marrows, at least in part of physical replacement of normal marrow precursors by leukemic cells. Thus, we can say these changes are very important for the function of disease. Also, some studies stated that a change in the adhesive properties of malignant cells compared with non-malignant cells is important in the processing of these disorders. In CML early proliferative progenitors have been shown to be defective in their ability to bind to stromal monolayers. In this regard, there is an intrinsic abnormality in the capacity of primitive hematopoietic progenitors in CML to interact with stromal elements. Moreover, CML long term hematopoietic stem cell (CML LTHSC) reduced homing and retention in bone marrow, resulting from increased G-CSF production by leukemic cells. Altered cytokine expression in CML bone marrow was associated with selective impairment of normal LTHSC growth and a growth advantage to CML LTHSC. Furthermore, In CML both leukemic and non-leukemic stem cells preferentially reside in the Osteoblastic (OB) niche and MSCs playing a critical role in their regulation. Similarly in certain of the CMPD and leukemias, bone marrow fibroblasts can proliferative in such excess that they dominate the marrow contribute to bone marrow failure. In Polycythemia Vera (PV) marrow, we have two distinct population precursor cells that indicate the coexistence in malignant and nonmalignant population of hematopoietic these cells. We can say, PV progression a significant decline in the frequency of normal clone and increase in neoplastic clone [19]. Moreover, in PV an intrinsic defect in the HSC can be occurred and we can state in PV, any cell defect or any alteration in cellular function may occur and is not restricted to cytokine receptor signal transduction only. As we know: 1): JAK2 V617F is the basis for many of the characteristics of PV, however, it cannot solely account for the entire PV phenotype and is probably not the initiating lesion in the three CMPDs. But there are some problems such as [20]: First, some PV patients with clonal disease may be lack this mutation. Second, familial PV can occur without this mutation, in spite of the expression in other family members. Third, some clonal malignant cells express JAK2 V617F. Forth, JAK2 V617F may also be present in idiopathic erythrocytosis patients. Fifth, the JAK2 V617F can be followed by another mutation. Sixth, acute leukemia may occur in a JAK2 V617F negative progenitor cell. Finally, not every patient with PV expresses the mutation, while patients without PV do. 2): First, in PV with JAK2 V617F mutation or without it, the erythrocyte production is autonomous with *in vitro* colonies of erythroid that growing in lacking erythropoietin. Why? Second, PV with JAK2 V617F mutation that shared with about 50% of Essential Thrombocythemia (ET) or Primary Myelofibrosis (PMF). In this regard, we have three kind of diseases with same mutation that a main role in the diseases [22,23]. Why? 3): In CMPD advancement, HSCs with LSCs virtues secrete high levels of pro inflammatory cytokines that increase the production of leukemic cells. The leukemic cells effect on MSCs to high production directly that changed OBCs into ruin hematopoiesis, support LSC function and help to fibrosis in the bone marrow [22-24]. 4): In CMPD, in the molecular analysis detected many similarities but a number of these analysis, have some unexpected importance differences, Why? [20-22,26-34].

Conclusion

We know about the relation between abnormal niches and their specific molecules as well as the microenvironment. In fact, malignant hematopoietic disorders can occupy enough of the medullary space to cause global marrow failure. There-fore, first, leukemia is a malignant disease with multistep changes including genetic alterations(one step of leukemia). Second, microenvironment abnormalities in interaction between stromal cells and hematopoietic progenitors must important in these events. Also we can say, all these changes should be useful in the diagnosis and treatment of these diseases. Thus, we must a better understanding concerning hematopoietic microenvironment and to give a more activated role for HSCs niche in the malignant diseases. Researchers can provide more useful information in HSCs and their functions, in addition in molecular analysis in BM cells and attention to their results in similarities, differences as well as unknown, uncommon, or random genetic changes and also on final outcome with or without bone marrow transplantation as well, in models and humans. In fact, genetic abnormalities cannot be responsible to all the questions, and I believe the first and second points with each other can help to response to many of questions in CMPD.

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