

# Studying of Hematopoietic Microenvironments in Some Hematological Disorders, Including Normal and Malignant Diseases

Ahmad Reza Rahnemoon\*

Department of Hematology, Iran University of Medical Sciences, Tehran, Iran

## ABSTRACT

Hematopoietic neoplasms are known or assumed to be clonal processes arising as the result of genetic errors. But I think some other items should be involved in these neoplasms too. As we know, Hematopoietic Stem Cells (HSCs) are classified as important stem cells due to their ability to differentiate to the cells including the lineages of lymphoid and myeloid cells. Lymphoid cell lineage includes T and B cells while granulocytes, monocytes, erythrocytes, megakaryocytes belong to the lineage of myeloid. Hematopoiesis, is controlled by several complex interactions between genetic processes in blood progenitor cells and bone marrow microenvironment as an important regulator in this matter. Thus, we must understand how malignancy disrupts the normal mechanisms of hematopoiesis which controlling HSC function and blood production? In the past decades, the theoretical concept of a stem cell microenvironment was proposed and its structure is called HSC niche described which the existence of niche includes regulating in function of HSC and its differentiation.

**Keywords:** Hematopoietic diseases; Hematopoietic stem cells (HSCs)

## INTRODUCTION

As the abnormal cells can be arrested in the blast stage of the normal maturation pathway and so we have a clonal chromosomal abnormality that can be detected by cytogenetic or molecular analysis. After the imbalance, the cells may be transformed that resulting in high proliferation of blasts and or more differentiated and matured cells and change to a neoplasm growth. Malignant disorder, is the consequence an accumulation of the immature cells that fail the functional differentiated cells and molecular alterations occur which resulting in malignant disease [1-3].

In some cases the blasts exhibit significant morphological variation, such as nuclear outlines and morphologic variation in chromatin like less homogenous chromatin, nuclei are variable such prominent frequently or not present and sometimes multiple. The cytoplasm is normal or more than enough or abundant but still pale blue. The granules are sometimes present in the blasts which distinguished as myeloblasts. Some other morphological cells in Peripheral Blood (PB) and Bone Marrow (BM) are as follows: nuclear clefts, hand-mirror cell, vacuole cell, smudge cell or some cells are due to an artifact of the preparation which is detectable in the slide film. Conventional morphology is useful and important too for the study of immature cells and some problem or question in the blood and marrow film but is not sufficient to identify differentiation

features. Anyway, the interactions between malignant cells and their microenvironment must be responsible in part of the complexity of malignancy including HSCs situation, progenitor and precursor cells conditions which must be predominant in the disorders [4-12]. Moreover, immunophenotyping and molecular genetics have been suggested to add further for diagnosis accuracy in most cases [13].

## DISCUSSION

In the discussion, three disorders are described in PB and BM smears which change probably to clonal disorders which are as follows:

### Aplastic Anemia

In some disorders like Aplastic Anemia (AA), the alterations of physiological status in stromal microenvironment reported which revealed impair proliferation and differentiation. Also, the defective of hematopoiesis can be resulted from failure of the stromal microenvironment which produces essential growth factors or absence of proper growth receptors as well. Furthermore, the defective production of fibroblast showed decrease CFU-Fibroblast (CFU-F) due to defective micro-environmental stromal fibroblast function which results of additional mitosis due to stromal precursor cell activated to support mesenchymal cells under position of

**Correspondence to:** Ahmad Reza Rahnemoon, Department of Hematology, Iran University of Medical Sciences, Tehran, Iran, Telephone: +989195615992; E-mail: ar.rahnemoon@gmail.com

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stress marrow. Furthermore, MSCs are multi-potent cells capable of multi-potent differentiation with immunosuppressive virtues after the treatment of Bone Marrow Transplantation (BMT). It is defined by pancytopenia with a hypo-cellular bone marrow with no increase in reticulin and without any abnormal infiltrate. Patients with cytopenias are in two or three involved lineages that including chronic moderate Aplastic Anemia (cmAA) with no clinical progression as well as pmAA (progressive moderate AA) with clinical symptoms similar to Severe Aplastic Anemia (SAA) approximately and also should be differentiated with HMDS (Hypo-Cellular Myelodysplastic Syndrome) as well. The assessment of SAA is important in prognostic significance and treatment decisions as well which can begin of challenge in the disease [14-17].

The role of MSCs after its transplantation can be modified the recipient BM microenvironment by paracrine effect or cell-cell mediated reparative function. Thus, this change seems that the success of HSC Transplantation (HSCT) base on the essential role of osteoblastic cells in the regulation of HSC. Some researchers stated after MSC co-injection to establish of HSC in the niche and after the recovery as well, MSCs donor cleared possibly by the immune system and concerning in their animal experiments after transplantation and they suggested the necessary role of MSC transplantation to be only transient. On the other hand, age related Clonal Hematopoiesis (CH) by genetic analysis identified in 1%-3% of patients with non hematologic cancers as well as normal persons that showed an important correlation with age and the high risk persons toward subsequent hematologic malignancy which suggested a common mechanism in relation of genomic aging between healthy elderly and bone marrow failure syndromes [18-19].

### MyeloDysplastic Syndromes (MDS)

These are a diverse group of clonal stem cell disorders which characterized by clonal myelopoiesis with an alternation in proliferation and differentiation. Also the patients have usually macrocytosis and cytopenia due to impaired production in blood cells which including the levels of dysplasia and blast percentage in White Blood Cells (WBCs). Peripheral blood film and bone marrow smear are important in the cases too, because these are quick and easy tests in helping to shed light on the patient with complex position. The disorder depends on the rates of clonal expansion and leukemic evolution. So, the disease can be cured by allogeneic HSC transplantation and stromal cells as remains of patient origin after its procedure, it has been postulated that alterations in MDS stroma must be secondary to interactions with clonal MDS cells and reversible upon their eradication [20].

Regarding this syndrome, we know normal hematopoiesis depends on critical interactions that occur between stem cells and their microenvironment, so we can say; hematopoietic neoplasms are known or assumed to be clonal processes arising as the result of genetic errors. In fact, LSCs results from multiple genetic and epigenetic alterations within hematopoietic stem cells or progenitors that alter the normal position in self renewal, proliferation, differentiation and apoptotic pathway. In fanconi anemia murine model, committed stem cells and progenitors are hypersensitivity to a kind of cytokines versus the malignant clones are resistant which the situation is similar to human position approximately.

### Myeloproliferative Neoplasms (MPN)

These are a hematopoietic clonal disorders and can lead to increase of one or more mature blood cell progenitor which pluripotent stem cell can be involved, or characterized by the high production of myeloid series which including Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) [1-2,16]

The actions can expand our understanding on the effects of leukemic hematopoiesis in the BM microenvironment and the contribution of the endosteal BM niche in pathogenesis of MPN. Also the neoplasm development alters the normal activity of MSCs and their Osteo Blastic lineage Cell (OBC) derivatives, leading to a major remodeling of the endosteal BM niche, which mainly affects normal HSCs, with minimal effects on transformed LSCs. The main fact that LSC maintenance is unaffected by the remodeled OBCs could be, in large part, due to their different requirement in adhesion molecules for homing and retention in the BM compared to normal HSCs. For more understanding, such as in murine models, activation of the normal HSC niche improves recovery from radiation and chemotherapy injury and suppresses CML disease progression, impairing LSC maintenance in a syngeneic model.

In PV marrow, we have two distinct populations in precursor cells which indicate the coexistence in malignant and nonmalignant hematopoietic cells. The progression of disorder is a significant decline in the frequency of normal clone and increase in neoplastic clone. Also, an intrinsic defect in the HSC can be occurred in PV and so, any cell defect or any alteration in cellular function may occur and is not restricted to cytokine receptor signal transduction [21-23].

Some researchers point out if we accept the malignant niche and two distinct precursor cells too as well as the accumulation of more differentiated and matured cells in the disorder, thus we understand the skill and ability of malignant HSCs to covering molecular analysis and the microenvironment controlling in the heterogenous cells too. In MPN, in the molecular analysis detected many similarities but a number of these analysis, have some unexpected importance differences, for example, the BCR-ABL positive ET without any CML morphology in the smears of PB and BM [24-26].

Thus, In this discussion, after the investigation of different types of bone marrow HSC niche in the above cases which might change to malignancy, particularly to leukemia, we have some important questions remain possibly, asfollows:

- How many different types of hematopoietic microenvironment exist in bone marrow and periphery as well?
- How many HSCs are in each niche and what is the role of any niche in hemostasis, in particular after the stress exactly?
- The interactions of HSC and its microenvironment are stable or dynamic?
- How single cells (like HSC) are subverted to drive leukemia with due attention to the significant heterogeneity in normal and malignant HSCs?

Lastly, we have two series from different disorders in the note includes a group with cytopenia and the other group without

cytopenia or with leukocytosis. But these disorders can go to a malignancy in the duration of middle or final stage. Why? On other words, 10% till 20% of acquired aplastic anemia will develop to a clonal disease in the duration of decade. What is the reason? What is the role of somatic driver mutation? What is the niche role in the position? This is my important point in the discussion, In other words: If a deeper understanding occur in the genes function on normal and abnormal hematopoiesis, in the explanation of clonal evolution and the hematopoietic microenvironment comprehension as well, so we can lead to therapeutic targets.

## CONCLUSION

In spite of advances in any kind of malignancy therapy, many patients still fails, resulting in a disease progression. Therefore, we should be understood about it including it is a heterogeneous disease, not genetic and biochemical mechanism only. In other words, it is not a simply bag of homogeneous malignant cells and so we have a various infiltrating endothelial, stromal and other cell types that can influence the function of the tumor as well as hematopoietic system which involved too. But how is mechanism driving at intra-malignant cell? How can learning about damage of stem cell in these disorders? What is the process of clonal selection and adaption in the disorders? In the end, understanding of the mechanism underlying clonal selection of different mutations must help in the exact diagnosis of malignant clonal evolution and in better management of these patients. Furthermore, the knowledge of stem-ness and its role in malignant microenvironment can help to the disease control as well. Meanwhile, the above viewpoints and their comparison with each other and also these questions can help to researchers which solve some problems in the clonal disorders and their niche too.

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