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Review article

Why Is Importance the Reprogramming and Remodeling In Malignant Hematopoietic Microenvironment and Its Hematopoietic Stem Cells Too

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Abstract:

Hematopoietic microenvironment or niche keeps stem cells in multi-potent/ uni-potent state which prevents precocious differentiation. The niche employs a variety of factors includes growth factors, cytokines and cell adhesion molecules too. In this section, we try to have a better understanding about the role of hematopoietic stem cells, niche and hematopoiesis as well as we demonstrate that leukemia induced reprogramming initially and then remodeling of the bone marrow (BM) microenvironment which can be a major part of leukemogenesis and is a potential prognostic parameter in malignant hematopoietic disease as well.

Keywords: Hematopoietic microenvironment; stem cells; leukemogenesis

Introduction:

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 other words, HSC niche consists of complex components including heterogeneous cell populations, growth factors and extracellular matrix molecules which is essential to regulate in the survival, quiescence, migration, differentiation and maturation of the stem cells [1-3, 25].

Discussion:

We have focused on the cells in BM niche includes mesenchymal stem cells(MSCs), endothelial cells(ECs) and osteoblasts which suggesting that the fate of stem cells is determined by their interaction with the microenvironment they reside in. Also, at least two different hematopoietic microenvironments exit in the bone marrow includes the endosteal niche and the perivascular niche and two key factors for HSC maintenance are CXCL12 and stem cell factor as well. Actually, hematopoietic stem cell (HSC) niche has two practical hypothesis as follows: 1) cell population's characterization and also the factors which produced by them. 2) How the niche is modified at hematological disorders like leukemia and dysplasia and its knowledge too. Stem cells in turn may contribute to niche integrity and function as well, because stem cells regulated by niche cells and non-cellular components together generally and also the stem cell niche defined as the local tissue microenvironment which houses and maintains stem cells. But we must know how stem cell are precisely balanced in self-renewal and differentiation? Also, are many cancers the stem cell diseases? In addition, the relationships between dys-regulation of stem cell niche and human diseases and aging can provide some good strategies in clinical applications. 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 [5-8,25-27]. In fact, acute leukemia is a heterogeneous clonal disorder of hematopoietic progenitor cells characterized by proliferation of stem cell as such progenitor cell in bone marrow patients, and so identified a subpopulation of leukemic cells called leukemic stem cells(LSCs). As LSCs share stem cell properties such as a normal HSC and regulated in BM environment as well. In other words, supposedly LSC is transplanted, so go to influence on normal stem cell niche and causing alteration in the regulation of hematopoietic microenvironment, viz create an abnormal BM niche to usurp the transplanted normal HSC into LSC and thus create a tumor niche gradually. So, an abnormality in the BM environment and specific dysfunction of HSC niche could play a critical in initiation, progression

and response of disease in the malignancy. Murine models demonstrated that disruption of BM environment can initiate myeloproliferative neoplasms (MPN). Molecular changes in MPN expanded osteoblastic lineage cells (OBSc) that promote MPN development by favoring myeloid differentiation and maturation and increase of leukemic myeloid cells as well. Then, create a remodel BM microenvironment gradually which leukemic myeloid cells directly stimulate MSCs to altered OBCs by overproduce functionally. This position demonstrated the BM remodels go to transformed HSCs that drives myeloid differentiation and a self-reinforcing leukemic niche too that spoils normal hematopoiesis, favor LSC function and usually change to BM fibrosis [3-6, 11-14]. Moreover, in another example of hematopoietic diseases, such differential retention of remodel BM could explain clonal dominance which the transformed HSCs have impair functions like myelodysplastic syndrome(MDS) and BM failure syndromes as well. Thus, the concept of the niche allows for the unique frame of reference when remembering hematopoietic pathologies initiation and also interactions of malignant cells with BM microenvironment. For example, MDS cells can alter MSCs and then they promote clonal expansion and so MSC play an important role in the disease, namely MDS clone alters its hematopoietic microenvironment and suppresses normal BM function or its residual. Indeed, primitive subsets of MSCs play a dominant role in the self-renewal and maintenance of HSCs which provide a different niche environment for leukemic stem cell, leading to leukemic relapse heterogeneous kinetics in any distinct stromal environment. In the patients, it is believable that a lack of primary MSCs(P-MSC) in marrow environment would preclude the maintenance of LSC which help to remaining of complete remission and also if the P-MSCs or osteoblastic cells be in high levels, so it would be supported at the maintenance as well as self-renewal of LSCs in a distinct manner.

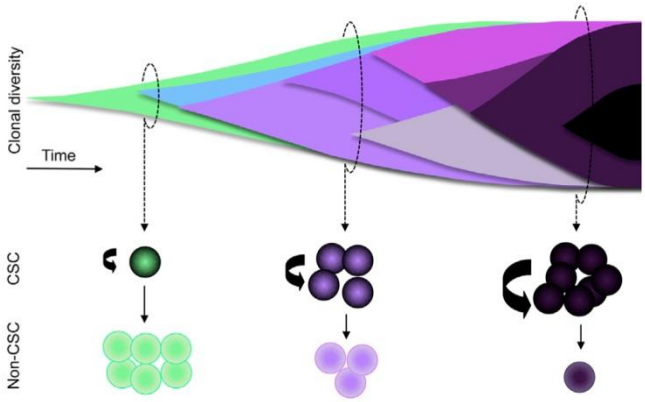

Figure 1: *Cancer stem cells (CSCs) and clonal evolution model as well. it is important to know about the diversity of leukemic disease phenotypes which increased proliferation induced by some fusion genes on the mutant clone that results in diverse clonal evolution which can increase a tendency to leukemic 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 are sharing in development and progression as well .Genetic mutation accumulate can be detected and sub-clones evolve in parallel which CSC concept about homogenous sub-clones is not warranted because the cancer cells are self- renew mostly vs. Non CSC progeny.*

In other words, the BM stromal changes pattern can predict to go into a high risk relapse and wholly it means the BM is ruined and the hematopoietic microenvironment is completely changed to abnormality. During the malignancy development, relapse and death can occur mostly. Now, the question is here, what is the role of cancer stem cell (CSC), (figure 1)? Or what is reprogramming malignant cell? We know in MPN, pluripotent stem cell (PSC) can be involved, so induced pluripotent stem cell (iPSC) is a powerful tool for modeling key aspects of human disease. Indeed, iPSC from primary leukemic cells have been generated from chronic hematological malignancies like chronic myelocytic leukemia (CML), etc, but not reported for acute myeloid leukemia(AML) or acute lymphoblastic leukemia(ALL) to date, whereas iPSC has been generated from normal human myeloid, B and T cells too, and our data demonstrated that despite of multiple combinations of reprogramming factors could not be reprogrammed to pluripotency, but there are some challenges in reprogramming primary cancer cells, for example reprogramming process with human stromal cells to AML blasts may be possible [9-13,17-20]. So, if we want to explain the cellular and molecular interactions in the HSC niche, we have two major practical motivations including:1) one the identification of key molecule is the production, maintenance and expansion of HSC. In this regard, the identification of particular microenvironments and factors which contribute to maintaining stem-ness in vivo is required for the maintenance of hematopoietic progenitor's different types that can make the selective ex vivo different lineages generation possibly. 2) Another point is the identification of changes in the BM niche directly for the leukemia development. So it is expected that different malignancies will induce to set the specific abnormalities which dependence on its niche (figure 1). Now, we expect to go into an aggressive stage in accumulated mutations with relatively cell autonomous and less sensitive to regulation of hematopoietic microenvironment. Actually, in this stage, upset in HSC is occurred and the niche is ruined relatively and then destruction will complete, or relapse is started [11, 12, 15-18]. Hence, if we try to understanding of stem-ness properties and the 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 their microenvironment, as well as tumor fitness allowing the malignant cells to balance survival pressures imposed by treatment which probably can go to diversity in more effective therapies [14,21-24]. For example, polycythemia vera (PV) marrow have two distinct populations of erythroid progenitor cells which indicating the coexistence of a malignant and nonmalignant population of hematopoietic progenitor cells. We can say, PV progression to be associated with a significant decreasing in the frequency of normal colony forming cells and also increasing preponderance of the malignant clone which should be an autonomous clone with genetic abnormality generally or even without it. Additionally, the transformed hematopoietic progenitor cells demonstrate clonal dominance and prevent the proliferation of normal hematopoietic progenitor cells by an unknown mechanisms. Some researchers have

examined about hematopoietic defect in PV which could be accounted for by genetic changing of cytokine receptors expressed by affected hematopoietic cells. Moreover, HSC of PV has an intrinsic defect which the stem cell defect alters a number of cellular functions and is not restricted to cytokine receptor signal transduction. On the other hand, some researchers observed a more complex remodeling of the clone in response to erythropoietin(EPO), actually the action of EPO on erythroid progenitors is known, but its direct action on hematopoietic stem and progenitor cells(HSPCs) is possible too [4,9,17], viz EPO does action on multi-potent progenitor (MPP) independent of the niche as well as modulates fate or varying in nature by remodeling at the clonal arrangement of MPP store (figure 2), which also could be one of the factors underlying the adverse side effects development during use of long term EPO in the therapy and high EPO levels with hematopoietic malignancy as well (9,17,26-27).

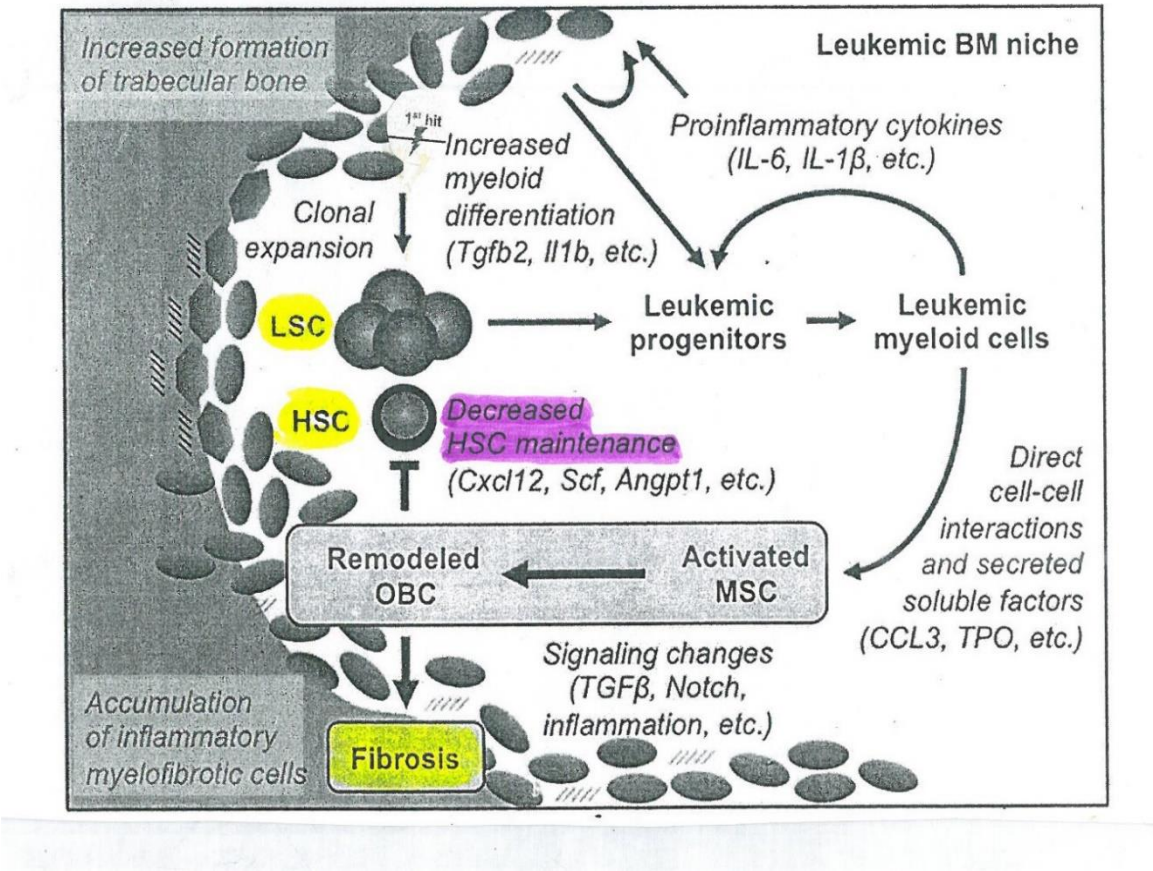

Figure 2: *Remodeling in MPN bone marrow microenvironment from reprograming to an autonomous strengthening leukemic niche.*

In conclusion:

My viewpoints about BM reprogramming to lead to remodeling of hematopoietic microenvironment is as follows: we know the transition from intrinsic normal position to cancer state is not arbitrary but may be accidentally viz typical uncontrolled power and so needs to pass through the critical points including: target cell transformation, heterogeneity of intra-tumor, fusion genes lineage affiliation and developmental effect of malignant specific genetic invasions. In other words we should say the cancer displays mimic features of normal tissue organization with mostly genetic abnormalities such as fusion genes, etc or without them. In this case, after reprogramming, wholly we have abnormal hematopoietic microenvironment or remodeling.in any niche (figure 2). For example, in MPN niche, leukemic myeloid cells stimulate MSCs (activated MSC) to overproduce functionally altered OBCs (remodeled OBC) which can collect in BM as myelofibrotic cells (fibrosis).and in the following of MPN development remodels in BM niche (remodeled BM microenvironment), go to change the normal hematopoiesis , decreased HSC maintenance, clonal dominance which impaired functions of HSCs and finally how the hematopoietic malignant cells created the self-strengthening BM niche cells which should be described fully.

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