Extramedullary Hematopoiesis Niche in the Spleen

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Abstract

Hematopoiesis is a process in which the Hematopoietic stem cells (HSC's) differentiate to give rise to all lineages of blood cells. In normal adults, HSC's reside in the bone marrow (BM) and their cell niche (microenvironment) in the BM is well-studied in the literature. However, when the BM microenvironment is stressed or diseased, Hematopoiesis takes place in other hematopoietic organs. One of the primary hemic organs is the spleen, yet the mechanisms and microenvironments of the spleen that regulate hematopoiesis and HSC's are not well investigated. By synthesizing articles from the literature, and comparing the spleen hematopoiesis niche to the bone marrow niche, this review will shed light on some of the factors and aspects that mediate hematopoiesis in the spleen microenvironments. It is important to understand how hematopoiesis operates in the spleen as it will provide insights into understanding hematological diseases and some prospective treatments.

Introduction

A hematopoietic stem cell (HSC) is a blood stem cell that has the ability to develop and differentiate into all the blood cell lineages' including white and red blood cells [1]. Almost all blood cells possess a short life cycle; thus, the HSC's are constantly dividing to replenish the blood cell supply. HSC's are found in the bone marrow (BM) and the peripheral blood [6]. Hematopoiesis, the differentiation process of HSC's, normally takes place in the adult bone marrow. However, there are some cases where the bone marrow microenvironment is unable to support hematopoiesis due to bone disease, bone marrow disease, or immune response [4]. In all cases, the BM environment that mediates this process is stressed and therefore, the HSC's migrate to other hematopoiesis supporting organs such as the liver and the spleen.

Extramedullary hematopoiesis (EMH) is a term used to describe the occurrence of hematopoiesis outside of the bone marrow. Several studies suggest that the primary organ of EMH is the spleen [3, 9]. When the bone marrow HSC niche is disturbed, Most HSC's mobilize to the spleen to undergo hematopoiesis [3]. It is accepted that the microenvironment in the spleen can support the splenic hematopoiesis, therefore replenish blood cells and support the function of HSC's. However, the micro environmental factors and niche cells that support this process in the spleen are not fully investigated. In this review, several aspects of the spleen niche and niche factors will be discussed and compared to the bone marrow niche in hope to provide insights on understanding how the splenic niche regulate HSC's and hematopoiesis.

The Hematopoietic stem cell niche in the Bone Marrow

The HSC's microenvironment in the bone marrow is a distinct niche that is well studied and defined in the literature [4]. The HSC's reside in several niches (spaces) in the bone marrow that supports their self-renewal ability as well as differentiation. The microenvironment in the BM regulates the fate

of the HSC's through controlled cell signaling pathways. There are several distinct cells in the bone marrow that contribute to the HSC's regulation [9]. These cells include Stromal stem cells (connective tissue cells), Osteoblasts (mineralized bone cells), endothelial cells (vascular cells), and Mesenchymal stem cells (multipotent stromal cells). The most important two types of cells are the Osteoblasts and endothelial cells as they maintain the production of several chemokines (signaling proteins) that contribute quiescence and maintenance of the HSC's [3]. CXCL12 is a crucial chemokine that is produced by osteoblasts and stromal cells; it is important in keeping the HSC's in their quiescence stage as well as signaling them to mobilize to the spleen in the case of induced Extramedullary hematopoiesis [2, 5]. In addition to Osteoblasts, the vascularized bone marrow niche, that is primarily made of endothelial cells, contributes to the management of the HSC's niche by playing a role in supporting HSC self-renewal and expansion capacity through producing another chemokine known as Stem Cell Factor (SCF).

Extramedullary hematopoiesis in the spleen

Although during development, the HSC migrate from the liver to the spleen at E14 and then to the bone marrow at E17, the spleen does not seem to play an important role in hematopoiesis during development [9]. However, The spleen is commonplace for the process of Extramedullary hematopoiesis (EMH)[5, 10]. It is the primary site for hematopoiesis in the cases of lethal radiation, pregnancy, and abnormal/injured microenvironments that result from diseased bones and bone marrow [2, 5]. The splenic microenvironments and the function of HSC's in the spleen are not well studied, but a new study conducted by Yohei Morita and his colleagues revealed that there are similarities in function in both HSC's in the spleen and bone marrow. The Characterization study of the HSC's in the spleen has also shown a difference in the cell cycle for the HSC's in the bone marrow and the spleen [7]. The splenic HSC's have a lower cell cycle compared to the HSC in the bone marrow. In addition, the Hematopoiesis

in the bone marrow is higher in frequency than in the spleen. The differences between the two different niches are expected since they both contain different cells to support HSC's.

It is also known that the stromal cells of hematopoietic organs also support the process of malignant and abnormal hematopoiesis. Both the spleen and bone marrow stroma are known to support the growth of liquid tumors such as leukemia [8]. Shaked and his teams investigated the role of the spleen in providing a fertile environment for the growth of malignant HSC's. Their study provided evidence that the spleen produces inflammatory factors that contribute to the progression of Friend disease (murine leukemia virus)[8]. Not only that, but it was also observed that the number of endothelial cells in the infected spleens increased to support the malignant hematopoiesis. This suggests that the endothelial cells are a common factor between both the bone marrow and the spleen niches for HSC's in both malignant and normal hematopoiesis. However, the chemokines produced by the spleen were different than those of their counterparts in the bone marrow [8].

The spleen niche factors and the regulation of hematopoiesis

The factors contributing to the hematopoiesis in the spleen are well known and studied in the literature. However, the spleen hematopoiesis niche remains a mystery that needs to be solved. Several studies were conducted to investigate specific aspects of the splenic niche and its effect on hematopoiesis, however, there has not been a comprehensive study that explored all factors contributing to hematopoiesis in the spleen. It is known that osteoblasts produce CXCL12 in the bone marrow to maintain the dormancy of the HSC's, however; there are no osteoblasts in the spleen to produce CXCL12. A team of researchers led by Dr. Inra performed several experiments where they induced the EMH in the spleen to study the spleen hematopoiesis niche factors. The study found that the red pulp of the spleen was the region where hematopoiesis took place [2]. This region of the spleen was found to be rich in endothelial cells that produced SCF as the endothelial cells in the bone marrow niche [2]. It was

also found that HSC's in the spleen resided next to endothelial cells and specific stromal cells that are known as Tcf21+ stromal cells[2]. These cells were found to produce CXCL12 in the spleen as their counterparts, the osteoblasts.

In addition to these cells signaling factors, the spleen architecture is also important in maintaining hematopoiesis in the spleen. Pbx homeoproteins are important factors in the development of the spleen [11]. The defect of this family results in abnormal spleens that are pale in color and hypoplastic in structure [11]. Dr. Zewdu and his team tested the function of HSC's and EMH in experimental mice that lacked one or two of the Pbx gene family. The results exposed that the spleen structure is crucial in the EMH process [11]. The splenic HSC progenitors differed from the progenitors produced in the bone marrow. It was demonstrated that the loss of a member of the Pbx family results in altered hematopoiesis in the splenic environment as there were splenic defects in the HSC's in the fetal stage which later resulted in a limited expansion of HSC in both in-vitro and in-vivo assays [11].

Conclusion

Extramedullary hematopoiesis is an important positive feedback loop that takes place in the case of physiological disorders or conditions. Its occurrence is primarily in the spleen, yet there have not been enough investigations regarding this topic. And although there are several studies on the topic of splenic hematopoiesis, such studies are rare and new in the literature. In addition, each study only focuses on one aspect of the spleen microenvironment and its relation to hematopoiesis and therefore, a complete understanding of the spleen HSC niche is not completely studied. It is imperative to conduct more studies relating to the hematopoiesis in the spleen as it is an important phenomenon that happens in the case of leukemia, chemotherapies, and pregnancies. Such fundamental studies are a key in understanding multiple hematological diseases and could eventually lead to the discovery of new treatments.

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