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Hematopoiesis: a Brief Overview

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REVIEW

Abstract

Hematopoiesis represents the continuous process of formation of all the blood cells, that occurs throughout life, starting from the hematopoietic stem cells (HSCs). Multiple studies have proved that this process is structured in two stages, the primitive wave and the definitive one, resulting in the production of all blood cell types: erythrocytes, neutrophils, eosinophils, basophils, monocytes, lymphocytes and platelets. The objective of this Review is to present the general aspects of this process for a better understanding, including the molecules that influence lineage-specific differentiation, hematopoiesis being one of the most important elements in maintaining one's body homeostasis. This Review describes hematopoiesis, from the beginning, starting with HSCs, throughout fetal development and adult life, including the niches of formation and maturation of hematopoietic stem cells and the factors that influence all the proliferation and differentiation processes. The niches of formation represent local microenvironments of bone marrow tissue which participate in the maintenance, functioning and quiescence of hematopoietic stem cells. The factors that control all the processes of proliferation and differentiation are represented by transcription factors, physical cell-cell interactions and cytokines; they are either produced locally, in the bone marrow, or they can be transported to this, through the blood, being produced elsewhere. The study of hematopoiesis, stem cell plasticity and control mechanisms, offers the opening for interesting approaches for the investigation and treatment of various malignant, inflammatory, and degenerative pathological processes.

Keywords: Blood cells, hematopoiesis, hematopoietic stem cells

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INTRODUCTION

Hematopoiesis is the process of continuous formation of blood cells that occurs throughout life (Hoggatt and Pelus, 2013; Kliegman, 2020) and the most important elements of this process are represented by the hematopoietic stem cells (HSCs) (Durand and Dzierzak, 2005; Tavian et al., 2010). The term hematopoiesis refers to erythropoiesis, leukopoiesis and thrombopoiesis, involving the production of all blood cell types (Kawahara, 2007) through a complex series of proliferation and differentiation processes (Durand and Dzierzak, 2005; Tavian et al., 2010). Hematopoietic stem cells are nonspecific cellular precursors that allow the renewal of mature blood cells: erythrocytes, neutrophils, eosinophils, basophils, monocytes, lymphocytes and platelets (Weiss and Wardrop, 2010). Mature blood cells are localized in the bone marrow of adult animals, though their origin is embryonic (Boisset and Robin, 2011). The hematopoiesis process is structured in two stages: the primitive wave, which is transient and determines the production of embryonic erythrocytes and macrophages, and the definitive wave, in which hematopoietic stem cells capable of differentiation into any blood cell type are produced (Galloway and Zon, 2003;

Bertrand et al., 2007). Subsequently HSCs differentiation, the following unipotent progenitors specific to a cell line appear: common lymphoid progenitor, erythroid-megakaryocyte progenitor cell and granulocyte-monocyte progenitor (Quelen, 2011). These progenitors then generate the precursor of each bloodline, and those will undergo processes of maturation and differentiation, resulting mature blood cells (Quelen, 2011).

HSCs proliferation and differentiation are dependent on certain factors such as: transcription factor, cell-cell interactions and certain cytokines (Kaplan et al., 2007). Cytokines can be divided into two classes: lineage-nonspecific factors that influence the development of multipotent early progenitors and lineage-specific factors that act on cells already engaged in a particular lineage (Metcalf, 1998; Robb, 2007).

HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells (HSCs) represent the main elements of hematopoiesis (Tavian et al., 2010). These unspecialized cellular precursors, through a complex series of proliferation and differentiation processes, have the capacity to produce all types of blood cells: erythrocytes, thrombocytes, neutrophiles, eosinophiles, basophiles, monocytes and lymphocytes (Durand and Dzierzak, 2005; Weiss and Wardrop, 2010). All these processes depend on the body's homeostasis, the apoptotic rate of the progenitors and mature cells being influenced by it (Smith, 2003).

In adults, HSCs are located in the bone marrow; however, they do not originate from this tissue, being produced during embryonic life, with mesodermal origin (Boisset and Robin, 2011). The first hematopoietic stem cells appear in the extraembryonic tissues, first in the yolk sac, then in the allantois and placenta. Subsequently, the process of hematopoiesis continues in the embryonic tissue, in the aorta-gonad-mesonephros (AGM) region following the gradual population of the embryonic liver, thymus and spleen. At the end of the fetal development period, the hematogenous bone marrow will represent the main site of definitive hematopoiesis and to a reduced extent, the spleen (Rieger and Schroeder, 2012).

Researchers like McCulloch and Till (1960) conducted experiments involving bone marrow transplantation in previously irradiated mice, demonstrating for the first time the two specific properties of stem cells: self-renewal and differentiation (Germain et al., 2006).

Due to their ability to self-renew, hematopoietic stem cells give rise to two daughter cells, by mitotic division: a daughter cell identical to the parent one, resulting a new HSC (Seita and Weissman, 2010; Weiss and Wardrop, 2010), and a daughter cell programmed to differentiate into a particular cell type (Weiss and Wardrop, 2010). This process of asymmetric cell division allows the stem cell background to be maintained, while ensuring the renewal of blood cells (Weiss and Wardrop, 2010).

The second characteristic of hematopoietic stem cells is their multipotent nature, which consists in the ability to differentiate in all cell types in a given line (Jaenisch and Young, 2008; Weiss and Wardrop, 2010), being able to generate all blood cell types (Seita and Weissman, 2010; Weiss and Wardrop, 2010).

In studies conducted by Lagasse et al. (2000), Goodell et al. (2001), Orlic et al. (2001), Hess et al. (2002) it was suggested that hematopoietic stem cells are also capable of differentiating into nonhematopoietic cell types, including hepatocytes, myocytes, epidermal cells, neurons and others. Moreover, it has been shown that stem cells in the brain, muscles, or other tissues have been able to produce hematopoietic cells (Howell et al., 2002).

PRIMITIVE AND DEFINITIVE HEMATOPOIESIS

The process of hematopoiesis begins in the embryonic stage and continues throughout the life of animals (Jagannathan - Bogdan and Zon, 2013). It is structured in two stages; the primitive wave and the definitive one, the difference between this two being both the cell types produced and the site of their formation (Galloway and Zon, 2003; Bertrand et al., 2007; Jagannathan - Bogdan and Zon, 2013).

Primitive hematopoiesis is a transient process that determines the production of embryonic erythrocytes (nucleated erythrocytes) and macrophages, cells responsible for oxygenation and remodeling of growing embryonic tissues (Palis and Yoder, 2001; Galloway and Zon, 2003; Bertrand et al., 2007; Jagannathan - Bogdan and Zon, 2013); this process occurs at the level of the yolk sac (Weiss and Wardrop, 2010).

The second wave, definitive hematopoiesis, lasts the whole life of the animals, and it consists in the production of HSCs, cells capable of differentiating into any type of blood cell, the place of their formation being in the first phase the fetal liver, followed by the thymus, spleen and later the hematogenous marrow (Galloway and Zon, 2003; Bertrand et al., 2007; Weiss and Wardrop, 2010).

Although yolk sac progenitors are thought to be capable of differentiating into any blood cell lineage, depending on the stimulating factors, studies on avian chimeras have shown that these cells are only transient, with definitive cells being produced at the embryonic level; these aspects were also found in studies on mammalian embryos (Palis and Yoder, 2001).

In the case of all studied species, it was demonstrated that hematopoiesis begins in the yolk sac, namely at the

level of its blood islands. They are formed first in the process of organogenesis, followed by the second site of hematopoietic cell genesis represented by the AGM, a structure that is the place of generation of the majority of hematopoietic progenitors. From this level, precursors populate the fetal liver in humans and mice, while in birds its counterpart, the para-aortic foci. After proper organ development, the thymus, spleen and bone marrow (humans and mice), plus the bursa of Fabricius in birds, become the definitive sites of hematopoiesis (Table 1).

Table 1. Primitive and definitive hematopoiesis: their locations. (Adapted from: Cumano and Godin, 2007; Weiss and Wardrop, 2010; Dzierzak and Medvinsky, 1995)

	Initial generation site	Second generation site	Intermediate hematopoietic site	Definitive hematopoietic sites
Human	**YS** (generation, differentiation)	**AGM** (generation)	**FL** (HSC maintenance, expansion, differentiation)	**Thymus** (T cell differentiation) **Spleen** (B cell differentiation) **BM** (HSC maintenance, differentiation)
Mouse	**YS** (generation, differentiation) E7 (Dzierzak and Medvinsky, 1995; Weiss and Wardrop, 2010)	**AGM** (generation) E9 (Dzierzak and Medvinsky, 1995) E8.5 – E11.5 (Weiss and Wardrop, 2010) **Allantois/Placenta**	**FL** (HSC maintenance, expansion, differentiation) E9 – E10 (Dzierzak and Medvinsky, 1995) E12 – E16 (Weiss and Wardrop, 2010)	**Thymus** (T cell differentiation) E13 **Spleen** (B cell differentiation) E15 **BM** (HSC differentiation, maintenance) E16
Avian (chick/quail)	**YS** (generation, differentiation)	**AGM** (generation) **Allantois**	**Para-aortic foci** (HSC maintenance, expansion, differentiation)	**Thymus** (T cell differentiation) **Spleen** (cell differentiation) **Bursa of Fabricius** (B cell differentiation) **BM** (HSC maintenance, differentiation)

Note: YS: yolk sac; E-: post coitum day; AGM: aorta-gonad-mesonephros region; FL: fetal liver; HSC: hematopoietic stem cells; BM: bone marrow

NICHES OF HEMATOPOIETIC STEM CELLS

In the process of fetal development, certain structures such as AGM and embryonic liver are sites of formation and maturation of hematopoietic stem cells, and the final process of cell's formation will take place in the hematogenous bone marrow of the animal, this being the main support microenvironment for the hematopoietic reservoir (Kaplan et al., 2007). These local microenvironments of bone marrow tissue are called niches (Weiss and Wardrop, 2010). They consist of support cells and participate in the maintenance, functioning and quiescence of hematopoietic stem cells (Kaplan et al., 2007; Kiel and Morrison, 2008; Weiss and Wardrop, 2010).

The distribution of cells in these niches is based on cellular characteristics and their stage of differentiation, two types of niches being identified: osteoblastic niche and vascular niche (Wilson and Trumpp, 2006; Kaplan et al., 2007; Kiel and Morrison, 2008; Weiss and Wardrop, 2010). Due to this reason, in the endosteum region are mainly undifferentiated hematopoietic stem cells, while the progenitor's characteristic of each cell line are largely found in the central region of the hematogenous marrow (Kaplan et al., 2007).

The osteoblastic niche is located close to the bone marrow endosteum and consists of mesenchymal stromal cells, including osteoblasts, reticular cells, adipocytes and fibroblasts (Balduino et al., 2004; Kaplan et al., 2007; Kiel and Morrison, 2008; Weiss and Wardrop, 2010). This environment ensures optimal conditions for hematopoietic stem cell survival and has influences on the cell's migration into the bone marrow (Taichman and Emerson, 1998; Kaplan et al., 2007; Kiel and Morrison, 2008; Weiss and Wardrop, 2010). Cellular homeostasis is influenced by

angiopoietin and thrombopoietin. Angiopoietin is a hormone secreted by local osteoblasts, megakaryocytes and other perivascular cells and thrombopoietin is a hormone produced by osteoblasts, liver and kidneys. The main molecule which affects the hematopoietic cell migration is chemokine ligand 12 CXC (CXCL12), a factor also secreted by the osteoblasts and reticular cells (Kiel and Morrison, 2008).

The vascular niche is located near the sinusoidal endothelium, and it contains active hematopoietic stem cells (Arai and Suda, 2007; Kaplan et al., 2007; Weiss and Wardrop, 2010). It is therefore the site of hematopoietic stem cell division and differentiation; hematopoietic progenitor cells are found at its level, in different stages of maturation (Arai and Suda, 2007). From this niche, hematopoietic cells pass into the peripheral blood, crossing the endothelial wall of the sinusoids, which is composed of fenestrated endothelial cells (Arai and Suda, 2007; Kaplan et al., 2007; Kiel and Morrison, 2008; Weiss and Wardrop, 2010). As in the case of the osteoblastic niche, reticular cells are likewise present in the vascular niche, with an important role in the secretion of factor CXC12, involved in the process of cell migration (Kiel and Morrison, 2008).

It should be taken into consideration that niches are involved in regulating the homeostasis of hematopoietic stem cells and these in turn can also influence the cellular elements of their niche (Weiss and Wardrop, 2010). Due to this, it is necessary to maintain the balance within these niches, because any imbalance can cause the cells to be blocked at its level or their chaotic release in circulation (Kaplan et al., 2007).

REGULATION OF HEMATOPOIESIS

Hematopoietic stem cells proliferation and differentiation are the main processes in order to maintain the blood cells population and these two depend on certain specific hematopoietic growth factors (HGF), which are represented by:

- Transcription factors, usually proteins which are needed to activate or inhibit the transcription of a gene. These factors are essential for the commitment of stem cells to a specific line (Iwasaki et al., 2006).
- Physical cell-cell interactions involving adhesion proteins, such as N-cadherins and osteopontin (Kaplan et al., 2007; Weiss and Wardrop, 2010).
- Cytokines produced, among others, by bone marrow stromal cells and mature blood cells (Weiss and Wardrop, 2010)

Cytokines are soluble glycoproteins, represented by interleukins and growth factors. Mechanism of action consists of binding to specific receptors present on the surface of hematopoietic cells. They can be divided into two groups: lineage nonspecific factors that act on multipotent early progenitors and lineage specific factors that act on cells already engaged in a particular line (Ogawa, 1994; Metcalf, 1998; Robb, 2007). Interleukin-3 (IL-3), interleukin-6 (IL-6), interleukin-11 (IL-11), stem cell factor (SCF) and granulocyte-macrophage-colony stimulating factor (GM-CSF) are some of the non-specific lineage factors (Metcalf, 1998) and erythropoietin (Epo), thrombopoietin (Tpo) and granulocyte-colony stimulating factor (G-CSF) are considered lineage specific factors (Figure 1).

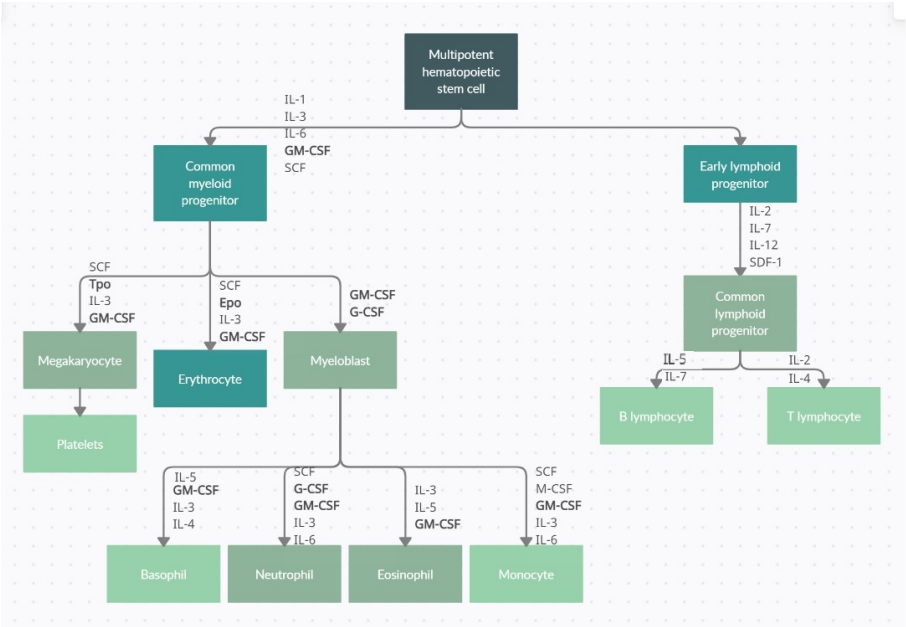

Figure 1. Factors wich regulate hematopoiesis (Adapted from: Matsuda et al., 2000; Mehta et al., 2015). IL-: interleukin-; GM-CSF: granulocyte-macrophage-colony stimulating factor, G-CSF: granulocyte-colony stimulating factor; Epo: erythropoietin; Tpo: thrombopoietin; SCF: stem cell factor; SDF-1: stromal-cell derived factor-1.

Erythropoietin is a hormone which is secreted mainly by the kidneys, in smaller amounts by the liver and brain, and in special situations, by bone tissue, being the most important humoral factor with implications in regulating the process of erythropoiesis (Weiss and Wardrop, 2010; Wenger and Kurtz, 2011). This glycoprotein is essential for the production process of red blood cells, and its level in the body is closely related to the tissue and blood oxygenation (Eggold and Rankin, 2019), its plasma concentration being inversely proportional to the oxygen content of the blood (Wenger and Kurtz, 2011). The secretion of this hormone is determined by the transcription rate of Epo gene, which in turn is dependent on the amount of oxygen in the body (Wenger and Kurtz, 2011). Tissue hypoxia is the main factor that determines the secretion of erythropoietin, the cells able to synthesize this hormone being sensible to changes in the oxygen capacity, tension and affinity of the blood (Figure 2) (Jelkmann, 1992).

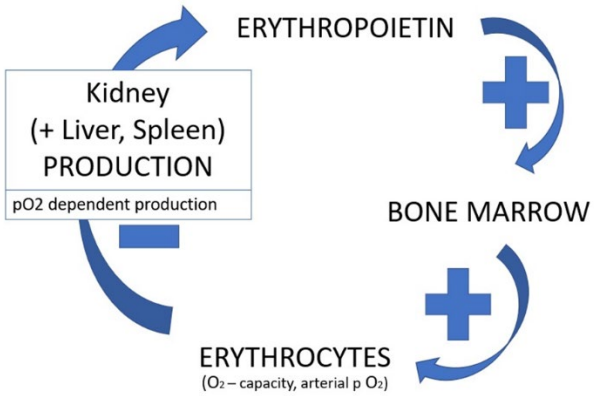

Figure 2. Regulation of erythropoietin secretion (Adapted from: Wolber and Jelkmann, 2002)

Erythropoietin stimulates the process of hematopoiesis by attaching to specific receptors (Epo-R) at the level of erythroid precursors in the hematogenous marrow, causing cell proliferation and differentiation (Eggold and Rankin, 2019). Epo-R is represented by a membrane protein consisting of seven binding sites, each representing the specific control point for different stages of the erythropoiesis process, some of them being activated in the regulation of the process only under stress conditions (Weiss and Wardrop, 2010).

The synthesis of hemoglobin is the main action on which erythropoietin exerts its influence since the beginning of the process of cell differentiation; from an early stage, erythrocyte precursors respond to Epo by increasing their hemoglobin production (Wenger and Kurtz, 2011).

In vitro, erythropoietin influences the size of CFU-E (Colony Forming Unit-Erythroid). First, Epo increases the survival rate of the cells, by preventing apoptosis, and will influence the mitotic division (Wenger and Kurtz, 2011). The hormone also determines the synthesis of certain elements necessary in the process of cell differentiation and maturation, such as globin chains, hemoglobin and certain receptors and membrane proteins (Wenger and Kurtz, 2011). Erythropoietin, in addition to influencing the process of erythropoiesis, can also stimulate the formation of blood platelets and megakaryocytes - Epo binding sites have been discovered on their surface (Weiss and Wardrop, 2010; Wenger and Kurtz, 2011).

Certain bioactive molecules such as IL-3 and SCF can enhance erythropoietin activity on the processes of cell proliferation and differentiation of erythrocyte progenitors (Weiss and Wardrop, 2010). However, tumor necrosis factor (TNF) and interleukin-1 (IL-1) have inhibitory effects on both the development of erythroid precursors and Epo secretion (Weiss and Wardrop, 2010).

It can be concluded that in physiological situations the cytokine called erythropoietin has the role of controlling the survival of erythrocyte progenitors in their process of differentiation (von Lindern et al., 2004). Under stress conditions such as tissue hypoxia or anemia, Epo together with stem cell factor and other bioactive molecules have the role of determining the proliferation and differentiation of erythroid progenitors (von Lindern et al., 2004).

Thrombopoietin (Tpo) or c-Mpl ligand is a hormone secreted mainly by the liver and to a lesser extent by the kidneys, spleen, lungs, bone marrow and brain (Kato et al., 1998; Wolber and Jelkmann, 2002), being the main molecule responsible for the humoral stimulation of megakaryopoiesis and the production of blood platelets (Wolber and Jelkmann, 2002; Weiss and Wardrop, 2010). This glycoprotein influences the whole process of thrombocytopoiesis, from the development of hematopoietic stem cells, the proliferation of megakaryocyte progenitors, to the maturation of platelet-producing cells (Kaushansky, 2005).

The most important function of Tpo is to inhibit the apoptosis process of target cells (Wolber and Jelkmann, 2002), to promote the proliferation, differentiation and maturation of megakaryocyte precursors (Wolber and Jelkmann, 2002; Kaushansky, 2005). However, the process of megakaryocyte's fragmentation into blood platelets

is not under the direct influence of this hormone (Kato et al., 1998). Though, this glycoprotein has influences on mature platelets, causing some changes necessary for platelets aggregation and promoting their adhesion to fibrinogen and fibronectin (Kaushansky, 2005). Tpo receptors are called c-Mpl receptors because they were first identified as being produced by certain proto-oncogenes associated with myeloproliferative leukemia, called c-mpl (Wolber and Jelkmann, 2002). They are located mainly in hematopoietic cells belonging to the megakaryocyte line, from HSCs to platelets (Wolber and Jelkmann, 2002) and in vascular endothelial cells (Weiss and Wardrop, 2010). Even though endothelial cell receptors outnumber hematopoietic cells, they have no role in regulating thrombopoietin levels in the body (Kaushansky, 2005; Weiss and Wardrop, 2010). Each platelet has about 30 to 60 Tpo binding sites (Wolber and Jelkmann, 2002), receptors that after activation by Tpo molecules cause the transmission of a series of biochemical signals at the cellular level with multiple effects on HSCs, megakaryocytes and platelets (Kaushansky, 2005). The amount of hormone found in the blood is inversely proportional to the number of circulating platelets, their number being the factor which controls thrombopoietin secretion; thus, it can be said that thrombopoietin secretion is under the influence of a self-control loop (**Figure 3**.) (Kaushansky, 2005).
It has been shown that thrombopoietin is one of the molecules involved in the survival and development of hematopoietic stem cells but it is not involved in the process of their differentiation, except on the megakaryocyte line (Kaushansky, 2005). However, in synergistic relationships with molecules such as SCF, Il-3, Il-11 or Epo, Tpo supports the survival and proliferation of hematopoietic progenitors (Kaushansky, 2005). In humans, thrombopoietin also has effects on the erythrocyte line, and in the intrauterine life of mice, on erythroid and erythromegakaryotic progenitors (Kato et al., 1998).

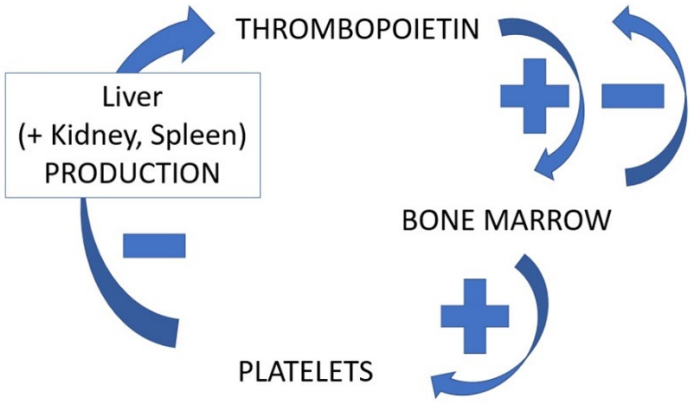

Figure 3. Regulation of thrombopoietin secretion (Adapted from: Wolber and Jelkmann, 2002)

Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage-colony stimulating factor (GM-CSF) have as main functions the proliferation and terminal differentiation of granulocyte, especially neutrophils (Weiss and Wardrop, 2010; Mehta et al., 2015). These two glycoproteins are produced and secreted by macrophages, T lymphocytes, endothelial cells and fibroblasts, following their activation by certain cytokines such as Il-1, Il-6 and TNF or as a result of antigenic stimulation (Mehta et al., 2015). G-CSF determines only the production of granulocytes, being the fundamental bioactive molecule that controls granulopoiesis, while GM-CSF also influences the formation process of macrophages (Mehta et al., 2015).

Macrophage-colony stimulating factor (M-CSF) and interleukin-1 (Il-1) are implicated in the synthesis of monocytes and macrophages (Sanderson, 1992; Ogawa, 1994; Weiss and Wardrop, 2010; Mehta et al., 2015).
Interleukin-5 (Il-5) is necessary for the synthesis of eosinophils and basophils (Sanderson, 1992; Ogawa, 1994).

For the lymphoid line, interleukins 5 and 7 participate in the differentiation of B lymphocytes, while interleukins 2 and 4 stimulate the differentiation of T lymphocytes (Matsuda et al., 2000).
These factors can be produced locally, in the bone marrow, or they can be transported to this, through the blood, being produced elsewhere (Harvey, 2001; Harvey, 2012). All hematopoietic cells have multiple receptors on their surface for several factors that either increase and/or inhibit hematopoiesis (Harvey, 2012). The number of each type of receptors depends on the stage of development and differentiation of the cell and their activation by the attachment of the characteristic factor causing a cascade of enzymatic reactions (Harvey, 2012). These reactions maintain the homeostasis of the differentiation and maturation processes and determine the production of other surface receptors and other specific hematopoietic growth factors (Harvey, 2012). These specific factors either act directly in the processes of cell proliferation and differentiation, or have stimulating actions on cellular receptors that can bind other factors directly involved in these processes (Harvey, 2012). In addition, some molecules have

the ability to stimulate other cell types than specific ones, which in turn will determine the synthesis of stimulation factors necessary for specific proliferation and differentiation processes (Harvey, 2012).

However, a basic feature of these factors is that none of them has 100% specificity for a single cell line and they are influencing together the cell's lines. For example, molecules such as G-CSF, Epo or Tpo have dominant actions on cell lines such as granulocyte, erythrocyte or platelet, but they can also influence the processes that take place in the development of other cell lines (Metcalf, 1998). In addition, these factors may exert certain actions on other non-hematopoietic cells, but the physiological mechanisms are not fully defined (Metcalf, 1998).

CONCLUSIONS

The study of hematopoiesis, including HSC and control mechanisms of this process are important in both physiological and pathological situations. In physiological conditions through hematopoiesis all the blood cells are renewed and regenerated, in order to maintain homeostasis. Moreover, understanding hematopoiesis may help intercept various pathophysiological pathways of inflammatory, degenerative or malignant processes.

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Conflicts of Interest

The authors declare that they do not have any conflict of interest.

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