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# A Review of the Action of Magnesium on Several Processes Involved in the Modulation of Hematopoiesis

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**Abstract:** Magnesium ($Mg^{2+}$) is an essential mineral for the functioning and maintenance of the body. Disturbances in $Mg^{2+}$ intracellular homeostasis result in cell-membrane modification, an increase in oxidative stress, alteration in the proliferation mechanism, differentiation, and apoptosis. $Mg^{2+}$ deficiency often results in inflammation, with activation of inflammatory pathways and increased production of proinflammatory cytokines by immune cells. Immune cells and others that make up the blood system are from hematopoietic tissue in the bone marrow. The hematopoietic tissue is a tissue with high indices of renovation, and $Mg^{2+}$ has a pivotal role in the cell replication process, as well as DNA and RNA synthesis. However, the impact of the intra- and extracellular disturbance of $Mg^{2+}$ homeostasis on the hematopoietic tissue is little explored. This review deals specifically with the physiological requirements of $Mg^{2+}$ on hematopoiesis, showing various studies related to the physiological requirements and the effects of deficiency or excess of this mineral on the hematopoiesis regulation, as well as on the specific process of erythropoiesis, granulopoiesis, lymphopoiesis, and thrombopoiesis. The literature selected includes studies in vitro, in animal models, and in humans, giving details about the impact that alterations of $Mg^{2+}$ homeostasis can have on hematopoietic cells and hematopoietic tissue.

**Keywords:** magnesium; hematopoietic tissue; hematopoietic cells; bone marrow; immune cells

## 1. Introduction

In recent years, researches have shown that alterations in $Mg^{2+}$ homeostasis, a result of the inadequacy of consumption or the moderate or severe deficiency of this mineral, in animal or in vitro and human models, can result in inflammation. $Mg^{2+}$ deficiency frequently results in nuclear factor kappa B (NF-kB) pathway activation in immune cells with increased production of proinflammatory cytokines and acute-phase proteins such as interleukin (IL)-6, tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP), and it is related to the development of chronic diseases [1]. The number of experimental studies that demonstrated how $Mg^{2+}$ deficiency alters the functioning of cells from hematopoietic origin are uncountable. These alterations include increased numbers of leukocytes in the peripheral blood, activation of cells such as neutrophils and macrophages, decreased antibody production, and the arrest of the cell cycle, thereby altering cell-cycle regulation and the activity of cyclins and cyclin-dependent kinases (CDKs) [2–6]. In lymphocytes, data indicate a role for magnesium in cell proliferation, also modulating the development of B cells and immunoglobulin production, as

well as affecting functions of T cells [2,7,8]. In this context, much remains to be explored about the importance of intracellular $Mg^{2+}$ homeostasis in cells of hematopoietic origin.

In addition to leukocytes, we and others have shown that $Mg^{2+}$ is important for mechanisms of proliferation, differentiation, and immunomodulation of MSCs (mesenchymal stem cells), and these cells are relevant to both the immune system and the hematopoietic tissue due to its immunomodulatory properties and differentiation capacity in osteoblasts, adipocytes, and chondrocytes [9–11]. In vitro studies have shown that reduced $Mg^{2+}$ concentration in the culture cell medium is able to decrease the expression of genes such as *ALP* (alkaline phosphatase), *COL1* (Collagenase I) and *RUNX*2 (RUNX family transcription factor 2), during the differentiation of bone-marrow-derived MSCs into osteoblasts [12]. Osteoblasts are very important for hematopoietic tissue [13,14]. However, the impact of changes in $Mg^{2+}$ homeostasis in osteoblasts on bone marrow and, consequently, on hematopoietic tissue is unknown.

Studies showing the effect of disturbances in $Mg^{2+}$ homeostasis on the mechanisms of differentiation, proliferation, and maturation of hematopoietic cells in the bone marrow are rare, and there are few references in recent decades about this topic, whereby the majority of the results were obtained only in experimental models [15]. These studies demonstrated the impact of $Mg^{2+}$ deficiency on peripheral blood cells [4,5] or on the lymphocyte maturation process, as well as on thrombopoiesis, with a focus on the transient receptor potential cation channel subfamily M member 7 (TRPM7) channel [16,17]. Several studies raised the importance of intracellular $Mg^{2+}$ homeostasis via the TRPM7 channel, which in addition to being permeable to $Mg^{2+}$, is also permeable to $Ca^{2+}$ and $Zn^{2+}$, relevant for processes such as growth, survival, differentiation, and cell migration [18–23]. However, the importance of TRPM7 in $Mg^{2+}$ homeostasis has been questioned, especially in T cells, where TRPM7 deletion did not affect acute uptake or maintenance of total cellular $Mg^{2+}$; this is because, in immune cells, $Mg^{2+}$ may be taken up by magnesium transporter 1 (MagT1) [7]. Nevertheless, these processes are not entirely clear and remain need to be investigated.

Although the impact of alterations in $Mg^{2+}$ homeostasis needs to be clarified, especially $Mg^{2+}$ deficiency in bone marrow and hematopoiesis, many clues indicate that changes in $Mg^{2+}$ concentrations may have profound impacts on hematopoietic tissue. In the last few decades, several studies pointed indirectly to this when they related the importance of $Mg^{2+}$ for cell-cycle progress, cell differentiation, apoptosis, the balance between osteoblast and adipocytes, etc. [3,24–30]. In light of the above, our objective in this review is to discuss how changes in $Mg^{2+}$ homeostasis could influence bone marrow and, consequently, the hematopoiesis process, and what mechanisms may be involved. Understanding how this micronutrient can influence the hematopoietic process is relevant to highlight the importance of this mineral in the complex physiology of blood cell production, providing insight into the roles of this mineral in the physiological process or even in some hematopoietic pathologies. Given the scarcity of data related to the impact of changes on $Mg^{2+}$ homeostasis in hematopoietic tissue, we focused on publications that evaluated the importance of $Mg^{2+}$ for various types of cells of hematopoietic origin and stromal cells, with the latter being fundamental for the maintenance of hematopoietic tissue. The main findings of this review are compiled in Table 1.

It is important to note that the literature has many mechanistic studies performed in vitro using hematopoietic or lineage cells cultivated in combination with a supraphysiological concentration of $Mg^{2+}$ or even using reduced or absent $Mg^{2+}$ concentrations, which is often incompatible with real life. Therefore, understanding how changes in $Mg^{2+}$ homeostasis can influence hematopoietic cells in vivo is a challenge. Since, the serum $Mg^{2+}$ does not reflect its intracellular content, serum $Mg^{2+}$ levels below the reference range (commonly used to diagnose deficiency) reflect only severe deficiency of this mineral, whereas the effects of moderate deficiency may be discrete and clinically underestimated.

**Table 1.** Main findings of relationships between $Mg^{2+}$ and hematopoietic tissue.

| Reference | Main Findings | Source |
|---|---|---|
| | **Mesenchymal Stem Cells and Osteoblasts** | |
| [31] | Increase in $Mg^{2+}$ enhanced expression of *RUNX2*, *OSTERIX*, and *OSTEOCALCIN* genes, increased the levels cyclin D1 and PCNA proteins, and induced the activation of Notch signaling. | BMSCs |
| [32] | Higher $Mg^{2+}$ concentration led to upregulation of RUNX2, BMP2, ALP, OPN, and ColI and increased PI3K/Akt signaling pathway. | Osteoblasts from animal model |
| [33] | Higher $Mg^{2+}$ levels triggered PI3K phosphorylation via TRPM7 and led to migration of osteoblasts. | hFOB1.19 (human osteoblast cells) |
| [34] | Increase in $Mg^{2+}$ led to changes in the expression of TRPM7 and in homeostasis of other important metal ions for bone tissue, inhibiting ALP activity in osteoblasts. | SaOS-2 cells and human osteoblasts |
| [35] | Decreased osteoblast number. | Bone marrow from mice |
| | **Endothelial Cells** | |
| [36] | Lower $Mg^{2+}$ levels impaired proliferation and migration, and increased IL-6, NOS activity, and VCAM expression. | 1G11 cells |
| [37] | $Mg^{2+}$ deficiency triggered higher NF-kB activation, and increased IL-8, RANTES, and GM-CSF. | HUVEC cells |
| [38] | Lower $Mg^{2+}$ concentration decreased proliferation taxa and downregulation of TRPM7. | HMEC cells |
| [39] | $Mg^{2+}$ deficiency increased ROS, PGE2, TNFα, and IL-1β levels, triggered changes in mRNA of *ICAM-1* and *VCAM-1*, decreased viability and cell proliferation, triggered changes in the endothelial permeability, and influenced integrity of the endothelial barrier through the S1P1–Rac1 pathway. | ECs from animal model |
| [40] | $Mg^{2+}$ supplementation improved endothelial function. | Clinical trial |
| [41] | Daily $Mg^{2+}$ supplement of 350 mg for 24 weeks led to no improvement in soluble vascular cell adhesion molecule (sVCAM)-1, soluble intercellular adhesion molecule (sICAM)-1, and soluble endothelial selectin (sE-selectin), along with no change in FMD markers of endothelial function or inflammatory parameters. | Clinical trial |
| | **Macrophages** | |
| [42] | $Mg^{2+}$ deficiency increased *TNF-α* and *IL-1* mRNA levels with the involvement of $Ca^{2+}$ signaling pathways. | Rat alveolar macrophages |
| [43] | Low $Mg^{2+}$ concentration increased NF-κB activity and changed HMGB1 expression. | RAW264.7 cells |
| [44] | Increased $Mg^{2+}$ concentration inhibited the nuclear translocation and phosphorylation of NF-κB and led to a rise in basal IkBα levels. | Human PBMCs |
| | **Erythropoiesis** | |
| [45] | $Mg^{2+}$ deficiency decreased plasma level, and led to faster aging of RBCs, as well as reticulocytosis. | Animal model |
| [46] | $Mg^{2+}$ deficiency increased Fe absorption and concentration, but reduced the number of RBCs. | Animal model |
| [47] | Inverse association between $Mg^{2+}$ intake and anemia. | Cross-sectional study |
| [48] | Association between increased serum $Mg^{2+}$ and decreased risk of anemia in women, dependent on ferritin levels. | Cross-sectional study |
| [49] | Decreased levels of serum ferritin and $Mg^{2+}$ were associated with anemia in pregnant women. | Cross-sectional study |
| [50] | $Mg^{2+}$ supplementation raised the hemoglobin levels and counts of erythrocytes. | Clinical trial |

**Table 1.** *Cont.*

| Reference | Main Findings | Source |
|---|---|---|
| | **Granulopoiesis** | |
| [51] | Boost in circulating eosinophils during $Mg^{2+}$ deficiency. | Experimental model |
| [52] | $Mg^{2+}$ deficiency impaired mast-cell functions. | Experimental model |
| [53] | $Mg^{2+}$ deficiency increased the mast cells in the bone marrow. | Experimental model |
| [54] | Increase in the number and activity of PMNs during $Mg^{2+}$ deficiency. | Experimental model |
| [26] | Lower $Mg^{2+}$ levels triggered granulocytic differentiation and changes in proteins related to cell-cycle control. | HL-60 cells |
| [15] | $Mg^{2+}$ deficiency resulted in hypercellular bone marrow, as well as a greater number of granulocytic cell; one animal also developed leukemia with granulocytic infiltrate in several organs. | Experimental model |
| | **Thrombopoiesis** | |
| [55] | Higher serum $Mg^{2+}$ levels were associated with increased platelet numbers and lower risk of development of thrombocytopenia. | Cross-sectional study |
| [56] | $Mg^{2+}$ deficiency impaired the number and shape of megakaryocytes from bone marrow. | Experimental model |
| [16] | Changes in the TRPM7 channel and $Mg^{2+}$ homeostasis in megakaryocytes triggered macrothrombocytopenia, altering the activity of the NMMIIA and the cytoskeleton, affecting the maturation of platelets in the bone marrow. | Experimental model |

Abbreviations: RUNX2 (RUNX Family Transcription Factor 2); PCNA (Proliferating Cell Nuclear Antigen); BMP2 (Bone Morphogenetic Protein 2); OPN (Osteoprotegerin); ALP (Alkaline Phosphatase), COL1 (Collagenase I); PI3K ( Phosphoinositide 3-Kinase); Akt (Protein Kinase B); TRPM7 (Transient Receptor Potential Cation Channel Subfamily M Member 7); IL-6 (Interleukin-6); NOS (Nitric Oxide Synthase); VCAM (Vascular Cell Adhesion Molecule); NF-kB (Nuclear Factor Kappa B); RANTES (Regulated upon activation, normal T cell expressed and secrete); GM-CSF (Granulocyte Macrophage Colony-Stimulating Factor); ROS (Reactive Oxygen Species), PGE2 ( Prostaglandin E2); TNFα (Tumor Necrosis Factor Alpha); ICAM (Intercellular Adhesion Molecule); HGMB1(High-Mobility Group Box 1); IkBα (Inhibitor of NF-κB); S1P1 (Sphingosine-1-Phosphate Receptor 1 ); Rac1 (Ras-related C3 Botulinum Toxin Substrate 1); RBCs (Red Blood Cells); PMNs (Polymorphonuclear Cells); NMMIIA (Nonmuscular Myosin Protein IIA).

## 2. The Role of $Mg^{2+}$ in Hematopoiesis

### *2.1. The Hematopoietic Microenvironment*

Since the 1920s, a series of studies made it possible to understand the role of hematopoietic stem cells (HSCs) and hematopoiesis [57–59]. Together, several studies showed that hematopoiesis is a complex, dynamic, and continuous process, in which HSCs proliferate, differentiate, and aggregate in the myeloid or lymphoid lineages, giving rise to the different types of cells that make up the blood system [60–63]. These processes occur in the bone marrow of mammalian adults under normal conditions and are highly regulated such that the hematopoietic system supplies thousands of mature blood cells to the body daily. The hematopoietic cells perform many essential functions for the survival of the organism, such as oxygen supply, regulation of blood homeostasis, and control of adaptive and innate immunity [64,65]. In this way, the continuous production of many blood cell types requires a highly regulated yet highly responsive system. In 1978, one of the first reports was published that proposed a concept called "niche" in the bone marrow microenvironment, which is a complex multicellular network that provides molecular cues and physical interactions that are essential for the proliferation, self-renewal, differentiation, and migration of HSCs and progenitor cells [66].

The cellular constituents of the bone marrow microenvironment largely derive from a common progenitor of mesenchymal origin called mesenchymal stem cells (MSCs); these cells are rare hematopoiesis-supporting stromal cells that have self-renewal potential and the capacity to differentiate into bone, fat, and cartilage. Furthermore, it is postulated that MSCs are essential in the formation and

control of hematopoietic niches, which include the osteoblastic, vascular, and perivascular niches [67]. These niches can modulate different aspects of the hematopoiesis process, having the important role of cell–cell interaction and contact for the medullary microenvironment, as well as the production of soluble factors (cytokines and growth factors) and formation of an extracellular matrix that forms the supporting parenchyma [66,68]. All these elements act in different ways for the homeostasis of HSCs, as well as for the differentiation process of HSCs and progenitor hematopoietic cells and the mobilization of mature cells into peripheral blood [69–71]. However, the initiating factors that determine the differentiation process of HSCs are not entirely clear, and it is unknown how changes in $Mg^{2+}$ homeostasis can influence the bone marrow microenvironment. However, on the basis of studies that demonstrated the influence of this mineral on the cells that make up the medullary microenvironment, which are cells that support and maintain hematopoiesis, it is possible to infer that $Mg^{2+}$ is very important for the homeostasis of this tissue, since it is an essential mineral for several cellular functions.

#### 2.1.1. The Influence of $Mg^{2+}$ in Mesenchymal Stem Cells, Osteoblasts, and Adipocytes

Among the cells that make up the stroma, bone marrow mesenchymal stem cells (BMSCs) play a central role in the bone marrow microenvironment due to their ability to differentiate into strains that are very important for the maintenance of hematopoietic tissue, such as osteoblasts and adipocytes. A balance in the differentiation between osteoblasts and adipocytes is extremely significant because adipocytes are a negative regulator of hematopoiesis and osteoblasts are promoters [14,72,73]. Alterations in $Mg^{2+}$ homeostasis are implicated in changes in the differentiation process of MSCs; whereas their increase promotes osteoblastogenesis, $Mg^{2+}$ deficiency appears to be detrimental to bone health [74,75]. In BMSCs from experimental models, an increase in $Mg^{2+}$ concentration elevated the expression of *RUNX2, OSTERIX*, and *OSTEOCALCIN* genes, increased the levels of cyclin D1 and proliferating cell nuclear antigen (PCNA) proteins, and induced the activation of Notch signaling [31]. Studies with osteoblasts from animal models verified that 6 mM and 10 mM $Mg^{2+}$ upregulated *RUNX2, BMP2, ALP, OPN*, and *COL1* expression and increased the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway [32]. In addition to *RUNX2* and *ALP*, researchers showed in hFOB1.19 human osteoblast cells that increased of $Mg^{2+}$ ions might also enhance osteoblastogenesis across the TRPM7/PI3K signaling pathway, as PI3K phosphorylation occurs via TRPM7 and leads to the migration of osteoblasts, whereas knockdown of *TRPM7* gene decreased alkaline phosphatase (ALP) activity [33].

Human mesenchymal stem cell (hMSC) studies demonstrated that TRPM7 and MagT1 may be important for osteoblastogenesis due to the increase in their expression during differentiation into osteoblasts. Moreover, downregulation of TRPM7 and MagT1 leads to autophagy, which could lead to accelerating osteoblastic differentiation, leading the authors to describe TRPM7 and MagT1 as possible osteoblastogenesis regulators [76,77]. However, others also showed that higher $Mg^{2+}$ may have adverse effects on bone metabolism, maybe in part due to changes in the expression of TRPM7 and in the homeostasis of other important metal ions for bone tissue, in addition to inhibiting ALP activity in osteoblasts [34].

In experimental models, dietary $Mg^{2+}$ deficiency leads to decreased bone mineral content in the trabecular compartment, decreased osteoblast and increased osteoclast numbers, reduced alkaline phosphatase (ALP) and osteocalcin, and elevated TNF-α, substance P, and IL-1 observed in the bone marrow microenvironment following immunohistochemical analysis in the bone [35,78]. In addition, observed changes were seen in the receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) rates in the tibia of animals with $Mg^{2+}$ deficiency, suggesting greater stimulus for bone resorption [79].

In view of these studies from human and experimental models, $Mg^{2+}$ deficiency can affect bone health and is related to low BMD and bone mass, where the latter are conditions that can trigger an increase of adipogenesis, leading to an imbalance of osteoblasts/adipocytes in bone marrow [80–83]. In this way, $Mg^{2+}$ deficiency could indirectly affect the osteoblast/adipocyte taxa. An in vitro study with

cell line C3H10T1/2 verified that the increase in $H_2O_2$, a reactive oxygen species (ROS), resulted in higher adipogenesis, decreased sirtuin-1 (SIRT1) protein expression, increased expression levels of Kruppel-like factor 5 (KLF5) and peroxisome proliferator-activated receptor (PPAR) γ2, and decreased RUNX2 levels, resulting in enhancing adipogenesis to the detriment to osteogenesis [84]. $Mg^{2+}$ deficiency is also a condition that leads to oxidative stress, increasing $H_2O_2$ and lipid peroxidation [85–87]; therefore, $Mg^{2+}$ deficiency could affect the osteoblast/adipocyte balance not only by increasing adipogenesis due to alterations in bone homeostasis, but also by raising oxidative stress, elevating inducible nitric oxide synthase (iNOS) and $H_2O_2$ [84,88,89]. Our group and others also observed previously that nutritional aspects are extremely relevant for the osteoblast/adipocyte balance [90,91]. It is worth mentioning that, although some studies showed that bone marrow adipocytes may have a relevant role in hematopoiesis [91,92], an increase in these cells in bone marrow is seen as a negative hematopoiesis regulator [72] and is related to several diseases [81,93,94].

#### 2.1.2. $Mg^{2+}$ and Endothelial Cells

The microarchitecture of the medullary microenvironment is composed of different types of vessels (arterial and sinusoidal vessels, arterioles, and capillaries), resulting in an upper vascularized network composed of endothelial cells (ECs), which are indispensable for modulating HSCs [95,96]. ECs in the bone marrow microenvironment are a crucial component for niche vascular homeostasis, especially for their role in sustaining HSCs [97]. Stem-cell factor (SCF) is important for the maintenance of HSCs, and it was reported that SCF inhibition from ECs using Tie2-cre leads to exhausting HSCs in bone marrow, reinforcing the significance of ECs for the support of HSCs [98]. Moreover, ECs also support self-renewal and expansion of HSCs with the involvement of Notch signaling [99,100].

The sinusoidal and arterial niches seem to influence the balance between proliferation and quiescence of HSCs. Many studies found that the permeability properties of vessels play a central role in this balance. Arterial vessels with less permeability are capable of maintaining HSCs in a resting state. On the other hand, higher-permeability sinusoids promote HSCs and progenitor cells and, therefore, alterations in these microenvironments may be related to hematological abnormalities [96,101,102]. It is unknown how $Mg^{2+}$ influences endothelial cells from bone marrow. However, $Mg^{2+}$ deficiency is a condition that triggers endothelial dysfunction [103]. In vitro, murine microvascular endothelial 1G11 cells cultured with lower $Mg^{2+}$ resulted in less proliferation, altered migration, and increased IL-6, NOS activity, and vascular cell adhesion molecule (VCAM) expression [36], whereas increased levels of plasminogen activator inhibitor (PAI-1) and IL-1 were also observed during $Mg^{2+}$ deficiency [104].

Other studies, using different sources of endothelial cells, also showed interesting results. In human umbilical vein endothelial cells (HUVECs), $Mg^{2+}$ deficiency triggered higher NF-kB activation, along with increases in IL-8, regulated upon activation, normal T cell expressed and secreted (RANTES), and granulocyte macrophage colony-stimulating factor (GM-CSF) [37]. The TRPM7 channel is permeable to $Mg^{2+}$ and relevant for intracellular homeostasis of this mineral, and it appears to play an important role in endothelial function [105]. Human microvascular endothelial cells (HMECs) cultured with a lower concentration of $Mg^{2+}$ resulted in impaired proliferation, increasing the number of cells in the gap ($G_0$–$G_1$) phase of the cell cycle and downregulation of TRPM7, whereas silencing of TRPM7 showed similar results in this model [38]. In an experimental model, TRPM7 and MagT1 were seen as relevant for $Mg^{2+}$ homeostasis in endothelial cells [39]. In this same study, the deficiency of $Mg^{2+}$ increased the levels of reactive oxygen species (ROS), prostaglandin E2 (PGE2), TNF-α, and IL-1β, and altered the messenger RNA (mRNA) expression of *ICAM-1* and *VCAM-1*. In addition, less viability and cell proliferation were observed during $Mg^{2+}$ deficiency, along with changes in endothelial permeability, and a possible role in regulating the integrity of the endothelial barrier through the sphingosine-1-phosphate receptor 1 (S1P1)–Ras-related C3 botulinum toxin substrate 1 (Rac1) pathway. On the other hand, the authors found that treatment with $Mg^{2+}$ was able to reestablish endothelial homeostasis [39] (Figure 1).

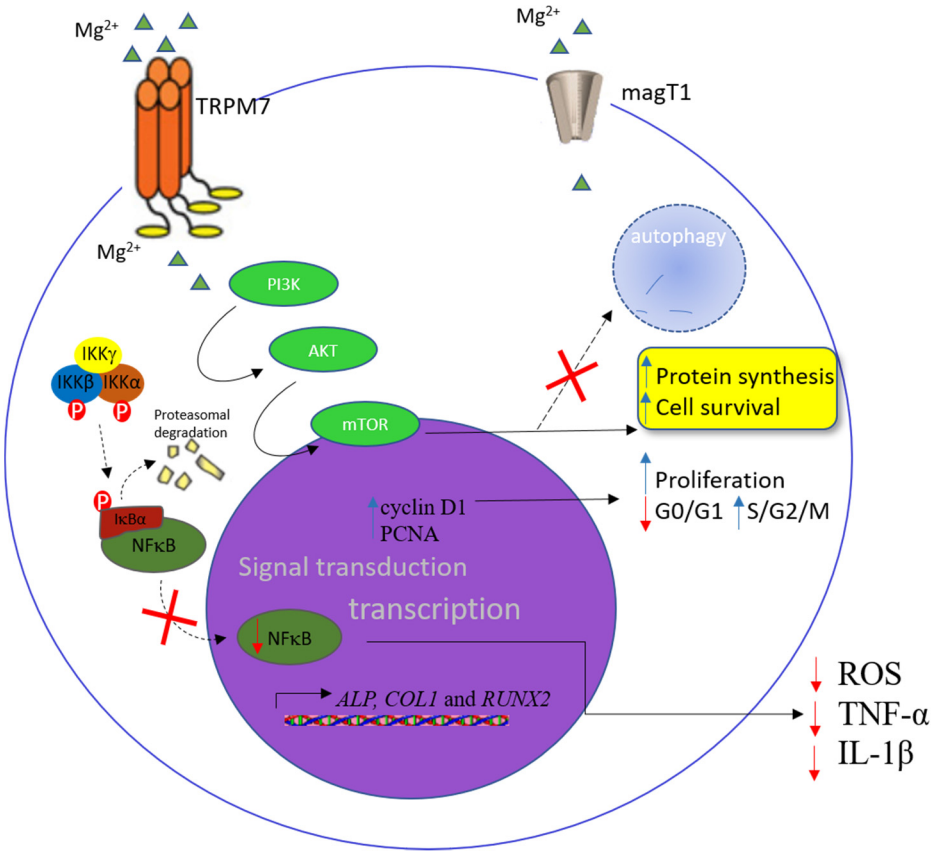


**Figure 1.** On the hematopoietic cell surface, transient receptor potential cation channel subfamily M member 7 (TRPM7) and magnesium transporter 1(MagT1) facilitate magnesium influx into the cell. In the cytoplasm, the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is magnesium-sensitive, and the activation of this signaling cascade induces cell growth, proliferation, and the inhibition of autophagy. Additionally, increased $Mg^{2+}$ concentration is able to decrease proinflammatory cytokine production, by inhibiting the nuclear translocation and phosphorylation of nuclear factor kappa B (NF-κB) and rise in basal inhibitor of NF-κB (IkBα) levels, downregulating tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β release, and reducing ROS production. Solid black arrows indicate the pathway activated, while dot black arrows indicate the pathways inhibited. Red arrows pointing down indicates reduction, while blue arrows pointing up indicates increase.

In humans, the influence of $Mg^{2+}$ in endothelial function is controversial. On the one hand, $Mg^{2+}$ supplementation appears to be beneficial for endothelial function. A randomized, double-blind clinical trial with hypertensive women showed that $Mg^{2+}$ supplementation improved endothelial function [40]. A meta-analysis evaluated the effects of $Mg^{2+}$ supplementation on endothelial function and found that treatment with $Mg^{2+}$ improves the flow-mediated dilation (FMD) parameter [106]. On the other hand, a study examined the effects of $Mg^{2+}$ supplementation on the endothelial function of overweight and obese individuals, middle-aged adults, and the elderly, subjected to a daily magnesium supplement of 350 mg for 24 weeks. There was no observed improvement in soluble vascular cell adhesion molecule (sVCAM)-1, soluble intercellular adhesion molecule (sICAM)-1, and soluble endothelial selectin (sE-selectin), along with no change in FMD markers of endothelial function or inflammatory parameters [41].

Taken together, data from the literature show that $Mg^{2+}$ influences endothelial function, partly due to the increase in ROS, activation of the NF-kB pathway, and alteration of the expression of ICAM-1 and VCAM-1 during $Mg^{2+}$ deficiency. However, while data from in vitro studies show an improvement

in endothelial function with higher $Mg^{2+}$ concentration, in humans, the data are conflicting. It is highly relevant to expand research focused directly on the relationship between changes in $Mg^{2+}$ homeostasis and its impact on endothelial cells that are part of the bone marrow microenvironment, to try to understand how these changes could affect HSC homeostasis and hematopoietic progenitors.

#### 2.1.3. Influence of $Mg^{2+}$ in Macrophages

Bone marrow-resident macrophages are essential for homeostasis of the medullary microenvironment due to its capacity to act in the maintenance of HSC niches and to regulate hematopoiesis [107,108]. Macrophages appear to regulate the retention of HSCs in the bone marrow, altering the expression of genes such as *CXCL12*, *ANGPT1*, *KITL*, and *VCAM1* in $Nestin^{+}$ niche cells from bone marrow, and they are fundamental for normal erythropoiesis [109,110]. Recently, a subset of $VCAM\text{-}1^{+}$ macrophages named "usher cells" were demonstrated to be involved in the homing and retention of HSCs and hematopoietic progenitors in a zebrafish model, reinforcing the pivotal role of these cells in the control of bone marrow niches [111]. Furthermore, macrophages are essential for immune regulation, mainly due to their enormous capacity to produce various cytokines, which control both immune response and hematopoiesis [112]. Cytokines are too important for hematopoiesis [113], and the intra- and extracellular concentration of $Mg^{2+}$ can affect their production by leading to the activation of several immune cells including macrophages, but the mechanisms are not entirely clear and the data are conflicting [114]. However, several studies agree that the main initiating factors that contribute to the activation of immune cells and consequently increased inflammatory cytokines during $Mg^{2+}$ deficiency are the increase in intracellular substance P and $Ca^{2+}$ (since $Mg^{2+}$ is a natural blocker of the latter), the rise in oxidative stress, and greater activation of the NF-kB pathway [115–117].

Additional studies using different sources of macrophages also show an interesting influence of $Mg^{2+}$ levels. In rat alveolar macrophages, $Mg^{2+}$ deficiency in vitro led to an increase of *TNF-α* and *IL-1* mRNA levels with the involvement of $Ca^{2+}$ signaling pathways [42]. In this same study, when these cells were cultured in a control medium or lower $Mg^{2+}$ concentration and stimulated with lipopolysaccharide (LPS), there was a rise in the lower $Mg^{2+}$ condition for both cytokines compared to controls. Yet, $Mg^{2+}$ deficiency is able to increase NO production via iNOS [118]. In order to investigate how different types of liver cells respond to $Mg^{2+}$ deficiency in vitro, RAW264.7 cells grown in $Mg^{2+}$-deficient medium showed increased expression of the *Nqo1* and *Prdx1* genes related to protection against oxidative stress, and this increase could be secondary to the rise in oxidative stress that occurs during $Mg^{2+}$ deficiency [119]. In addition, low $Mg^{2+}$ concentration showed an increase in NF-κB activity in RAW264.7 cells, in addition to alterations in the production and expression of high-mobility group box 1 (HMGB1), a molecule with inflammatory properties [43]. On the other hand, studies showed that increased $Mg^{2+}$ concentration is able to decrease the proinflammatory cytokine production in mononuclear cells from human and animal sources, by inhibiting the nuclear translocation and phosphorylation of NFκB and the rise in basal IkBα levels [44,120]. Moreover, the effects of preventing inflammation by increased $Mg^{2+}$ concentration in macrophages also include modulation of PI3K/Akt pathway activity, downregulation of TNF-α and IL-1β, enhanced M2 macrophage phenotype, and BMP2 and VEGF expression, with the latter seen in cell subject biomaterials coated with $Mg^{2+}$ [121–123] (Figure 1).

$Mg^{2+}$ deficiency results in low-grade chronic inflammation, activating macrophages in tissues and immune cells in peripheral blood, and elevating the concentration of cytokines, such as IL-1, IL-6, and TNF-α [6]. IL-1 and TNF-α are known to induce myelopoiesis, whereas the latter is involved in mechanisms of cell activation and survival in the bone marrow, and both can influence hematopoiesis according to the intensity and duration of their production [124]. Furthermore, it was shown that IL-1 induces PU.1 activation in HSCs with NF-κB pathway involvement, and that chronic exposure to this cytokine triggers changes in HSC homeostasis, principally in the autorenovation mechanisms [125]. In addition, a rise in TNF-α and IL-6 is related to hematopoietic diseases, such as myelodysplasic syndrome and disruption of erythropoiesis [110]; therefore, $Mg^{2+}$ deficiency could negatively affect

hematopoiesis. However, it is important to mention that most studies that evaluated the influence of $Mg^{2+}$ in macrophages were performed in vitro, with lineage cells, while many of them were cultured with supraphysiological or the lowest concentrations of $Mg^{2+}$. Thus, it is difficult to conclude how changes in vivo in $Mg^{2+}$ homeostasis may influence human macrophages in the bone marrow, and comprehensive studies on the topic are required.

### 2.2. $Mg^{2+}$ and Erythropoiesis

Erythropoiesis occurs from pluripotent stem cells in the bone marrow, with the erythroid progenitor being BFU-E (erythroid explosion-forming unit), which results in colony-forming units (CFU-E), mature erythroid precursors, reticulocytes, and red blood cells [126]. Erythroid differentiation and maturation occur in erythroblastic islands, and these complex events of proliferation, differentiation, and maturation depend on several factors, such as GATA-binding protein 1 and 2 (GATA 1 and 2), SCF, IGF (insulin-like growth factor), BPA (erythroid burst-promoting activity), IL-3, and EPO (erythropoietin) [127–130], in addition to nutritional aspects, like iron, folate, and B12 vitamin [131]. Yet, the influence of $Mg^{2+}$ on the erythropoiesis process in the bone marrow is not clear. It is known that there is a relationship between $Mg^{2+}$ and anemia; nevertheless, most studies focused on the importance of this mineral in peripheral blood erythrocytes.

Studies carried out since the 1930s have shown a relationship between $Mg^{2+}$ status and erythrocytes in experimental models. First, it was identified that the $Mg^{2+}$ content in erythrocytes was higher in cases of anemia [132]. Subsequently, a series of studies showed that $Mg^{2+}$ deficiency triggered fetal growth restriction and microcytic anemia, fragmentation of red blood cells, and impaired osmotic fragility in offspring from deficient mothers and in adult rats, while the latter also displayed reticulocytosis, which was attributed to changes in the energy metabolism and membrane of erythrocytes [133–135]. Moreover, red blood cells (RBC) from animals with $Mg^{2+}$ deficiency seem to age faster, whereas reticulocytosis indicates that the bone marrow might maintain erythropoiesis during low plasma $Mg^{2+}$ concentration [45]. However, a study showed that $Mg^{2+}$ deficiency increased Fe absorption and concentration in many tissues, but reduced the number of RBCs, possibly due to ineffective erythropoiesis [46]. Macrocytic anemia and decreased exercise capacity were also observed in rats after dietary $Mg^{2+}$ deficiency, in addition to varying the content of $K^+$ and $Na^+$, raising the activity of cotransport of K–CI, which is related to volume and density in RBC, and decreasing of glutathione in erythrocytes [136–139].

In humans, the influence of $Mg^{2+}$ status on erythrocytes was also investigated. In preeclampsia, erythrocyte deformability and, consequently, microcirculation are reduced, and $Mg^{2+}$ therapy was able to increase the deformability of these cells [140,141]. A cross-sectional study with adults evaluated the association between consumption of $Mg^{2+}$ and Fe with anemia, and found an inverse association between $Mg^{2+}$ intake and anemia [47]. Researchers analyzed data from the 2009 China Health and Nutrition Survey and verified an association between increased serum $Mg^{2+}$ and decreased risk of anemia in women and men from nine provinces of China. However, this association was significantly greater in women and dependent on ferritin levels [48]. In addition, the dietary pattern (traditional vs. modern pattern) was analyzed in elderly subjects, and a positive association was found between the traditional dietary pattern and anemia with the influence of serum $Mg^{2+}$ [142]. A cross-sectional study with 180 pregnant women (up to 14 weeks of gestation) from Khartoum in Sudan, showed that 65.0% and 57.2% had anemia and $Mg^{2+}$ deficiency, respectively, and that low levels of serum ferritin and $Mg^{2+}$ were associated with anemia [49]. On the other hand, $Mg^{2+}$ supplementation seems to increase the hemoglobin levels and counts of erythrocytes [50].

EPO is a glycoprotein produced mainly by the kidneys and is influenced by hypoxia, with a pivotal role in the mechanisms of survival, proliferation, and differentiation of erythrocytes in the bone marrow [143]. Anemia is a frequent finding in individuals undergoing hemodialysis, mainly due to the decrease in EPO concentrations, but also due to the impaired response to EPO, and an increase in serum $Mg^{2+}$ seems to decrease the risk of a lesser response to EPO [144]. In vitro, lower

$Mg^{2+}$ concentrations inhibited the activity of HIF-1α (hypoxia- inducible factor) mediated by ROS through the activation of NF-κB involving T-type calcium channels, with HIFs being an important factor in the promotion of EPO levels [145,146].

Although several studies showed an association between the concentration of $Mg^{2+}$ and the development of anemia and its influence on the erythrocytes in peripheral blood, there is no direct evidence to support how the intra- and extracellular concentration of $Mg^{2+}$ may affect erythropoiesis in the bone marrow. However, we suppose that $Mg^{2+}$ deficiency may partially affect erythropoiesis by altering the NF-κB pathway in macrophages and iron homeostasis, indirectly triggering changes in the membrane and accelerating the aging and destruction of RBCs. Nevertheless, research showing how $Mg^{2+}$ concentration could directly affect erythropoiesis in the bone marrow and how and which pathways are related is important and remains open to investigation. As human studies show a relationship between hypomagnesemia and anemia, it is important to encourage more studies on the topic, given that the correction of hypomagnesemia in addition to Fe could perhaps be considered for the treatment of these hematological alterations.

### 2.3. $Mg^{2+}$ and Granulopoiesis

Among the cells of granulocytic lineage, $Mg^{2+}$ deficiency affects neutrophils most severely, but eosinophils and mast cells can also be affected. Hypomagnesemia triggers a boost of eosinophils in the peripheral blood, increasing the number of mast cells in several tissues and in the bone marrow, impairing their function [51–53,147].

Neutrophilia is a common finding during hypomagnesemia in experimental models [4,54,148]. In general, the main justification for this is due to the increased inflammation observed during the deficiency of this mineral. Nevertheless, the mechanisms behind these observations are unclear, and an issue remains if this neutrophilia is a consequence of the inflammatory stimulus resulting from $Mg^{2+}$ deficiency or if molecular changes occur in the development, differentiation, and maturation of this lineage in the bone marrow even before the development of inflammatory phenotype. Perhaps, it is a combination of these two possibilities. However, there is little direct evidence to support which molecular alterations could be involved in the development of neutrophils in the bone marrow during hypomagnesemia.

Neutrophils are leukocytes that act in the first cell line of defense of organisms against various types of infectious agents, through the mechanism of phagocytosis and production of cytotoxic molecules, and it is not by chance that most bone marrow leukocytes are granulocytic precursors [149]. It is not yet clear, but $Mg^{2+}$ deficiency seems to alter the differentiation and maturation mechanisms of myeloid cells, favoring the granulocytic lineage during the deficiency of this mineral. Alterations in cell-cycle control, intracellular $Mg^{2+}$ levels, and $Mg^{2+}$ compartmentalization may be the main mechanisms behind the neutrophilia observed during hypomagnesemia in vitro [26]. In vivo, an experimental study analyzed the repercussions of long-term consumption of an $Mg^{2+}$-deficient diet on the bone marrow of rats. The authors found that more than half of the bone marrow samples were hypercellular, with a greater number of granulocytic cells, and one animal developed leukemia with granulocytic infiltrate in several organs. Furthermore, cells from granulocytic infiltrate inoculated in newborn animals resulted in leukemia in half of the animals after 3 months of inoculation [15].

The emergence and the steady state of granulopoiesis in the bone marrow are highly regulated, mainly by G-CSF, GM-CSF, CCAAT-enhancer-binding proteins (C/EBPα and C/EBPβ), IL-6, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways [150–152]. We conjecture that $Mg^{2+}$ status may alter these signaling pathways, given that changes in granulopoiesis, mainly neutrophilia, occur during hypomagnesemia. Nevertheless, there is no direct evidence of the relationship between $Mg^{2+}$ and these molecular pathways to support this claim, and the repercussions of hypomagnesemia in these signaling pathways and in the granulopoiesis process remain to be elucidated. Additionally, lower $Mg^{2+}$ levels affect the cell-cycle control and aging cell process, beyond upregulation of inflammatory markers, and these changes may affect not only granulopoiesis but

also hematopoiesis in general. Yet, it is unknown if $Mg^{2+}$ may affect the C–X–C motif chemokine 12 (CXCL12)/CXCR4 axis that controls the traffic of neutrophils in the bone marrow or whether hypomagnesemia could lead to alterations in dendritic cells [153]. Dendritic cells seem to control the traffic of neutrophils from bone marrow, and their decrease triggers a boost of neutrophils in the peripheral blood, even in the lack of infection [154].

### 2.4. Influence of $Mg^{2+}$ in Lymphopoiesis

Studies showed that extra- and intracellular $Mg^{2+}$ concentrations are important for the activation and proliferation of lymphocytes, and that $Mg^{2+}$ deficiency may affect the function of these cells in peripheral blood, decreasing immunoglobulin production and the number of cells that produce antibodies [2,155,156]. However, the influence of $Mg^{2+}$ homeostasis on the lymphopoiesis process and the progenitor's lymphoid in bone marrow is less elucidated. Experimental studies showed that severe $Mg^{2+}$ deficiency leads to bone marrow changes that appear to occur at the same time as thymic changes, resulting in hyperplastic bone marrow, lymphoproliferative disorder, and leukemia [157,158]. In addition, dietary $Mg^{2+}$ deficiency resulted in thymic changes, impairing its function, triggering increased necrosis, apoptosis, and phagocytosis, and favoring a tumor microenvironment in rats [86,159,160]. In humans, it was observed that patients with acute lymphocytic leukemia (ALL) have reduced levels of $Mg^{2+}$ in serum and hair; these changes appear to occur in part due to bone alterations resulting from the treatment of the disease [161–164]. However, the consequences of hypomagnesemia for the health of individuals with hematological diseases and its influence on the development of these diseases are not clear.

The role of TRPM7 and MagT1 in the function and development of lymphocytes is most frequently investigated [165]. Nevertheless, the relationship among intracellular $Mg^{2+}$, TRPM7, and MagT1 homeostasis in the development and function of lymphocytes remains to be established and is not fully understood. In vitro, DT40 cells that lack the *TRPM7* gene showed arrest of the cell cycle in the $G_0$–$G_1$ phase and led to changes in the PI3K /Akt/mammalian target of rapamycin (mTOR)/S6K pathway, but the increased $Mg^{2+}$ concentration in these cells improved the proliferation levels [166] (Figure 1). A study showed that the absence of the TRPM7 channel in B cells from mice abolished mature B cells in the spleen, lymph nodes, and peripheral blood, and it led to an arrest in the development of pre-pro-B cells and pro-B cells. In addition, it impaired serum levels of immunoglobulins (IgM, IgG, and IgA) and triggered a boost of myeloid cells, especially neutrophils, in the spleen and peripheral blood. In the same study, increased $Mg^{2+}$ concentration in vitro was able to partially improve the development of B cells [167]. However, the same was not noted in T cells, where the deletion of the *TRPM7* gene did not trigger changes in $Mg^{2+}$ homeostasis, while impairing thymopoiesis [7].

One of the most relevant studies about the relationship between lymphocytes and $Mg^{2+}$ was described in the XMEN syndrome (X-linked immunodeficiency $Mg^{2+}$ defect, Epstein–Barr virus infection, and neoplasia), which was first described as Magt1 loss affecting intracellular $Mg^{2+}$ homeostasis and leading to defective T-cell immune responses and uncontrolled EBV infection with increased susceptibility to $EBV^+$ lymphoma [168]. This syndrome is a rare primary immunodeficiency caused by hemizygous loss-of-function mutations in the X-linked MagT1 gene in males [169]. Magt1 was initially recognized as an $Mg^{2+}$ transporter, and early studies placed it as a plasma membrane protein; however, more recent data also postulated that Magt1 is localized in the endoplasmic reticulum and is a subunit of the oligosaccharyltransferase (OST) complex and more specifically of the STT3B complex [170]. In this way, the XMEN syndrome and its relationship with $Mg^{2+}$ has now been revised. As the molecular relationship to OST subunits and complexities of $Mg^{2+}$ suggested that pivotal manifestations of XMEN syndrome may rotate around defective glycosylation, in addition to or instead of alterations in $Mg^{2+}$ transport [171]. However, a study from the same group also showed that glycosylation is sensitive to $Mg^{2+}$ levels and that reduced $Mg^{2+}$ impairs immune cell function via the loss of specific glycoproteins [172].

Nevertheless, $Mg^{2+}$ homeostasis is too important for restoring the functions of T cells of individuals that suffer from genetic deficiencies in MagT1 and mutations in the kinase domain of interleukin-2-inducible kinase (ITK). These mutations display impaired function in T cells, such as changes in activation after T-cell receptor (TCR) stimulation, cytotoxicity, and degranulation, resulting in a great predisposition to infections by EBV that is associated with a high risk of development of lymphoma; hence, $Mg^{2+}$ supplementation is important for improving the function of T cells in these conditions [8,173].

### 2.5. Influence of $Mg^{2+}$ in Thrombopoiesis

Regarding thrombopoiesis, the influence of $Mg^{2+}$ in megakaryocytes is not clear. $Mg^{2+}$ is important for platelet homeostasis. Studies showed that lower $Mg^{2+}$ concentrations are involved with platelet-dependent thrombosis and hyperreactivity, whereas increased $Mg^{2+}$ concentration seems to inhibit platelet aggregation, partially altering intracellular $Ca^{2+}$ levels and decreasing the production of molecules involved in this process, such as eicosanoids [174–176]. Research found that changes in the intracellular $Mg^{2+}$ concentration in platelets from individuals with obesity and diabetes could be related to the development of future disorders in the coagulation process [177]. A cross-sectional study with Chinese women and men observed that a rise in serum $Mg^{2+}$ level was associated with increased platelet numbers and a lower risk of development of thrombocytopenia [55]. Nevertheless, few studies investigated the role of intra- and extracellular $Mg^{2+}$ concentrations in megakaryocytes in the bone marrow. $Mg^{2+}$ deficiency may promote defects in platelet biogenesis due to changes in the cytoskeleton, promoting changes in platelet function [178]. In an experimental model, dietary $Mg^{2+}$ deficiency impaired megakaryocytes from bone marrow, resulting in a decrease in the number and larger shape than the cells of the control animals [56]. A study showed that disorders in the TRPM7 channel and $Mg^{2+}$ homeostasis in megakaryocytes trigger macrothrombocytopenia by altering the activity of the nonmuscular myosin protein IIA (NMMIIA) and the cytoskeleton, affecting the maturation of platelets in the bone marrow [16].

## 3. Conclusions and Perspectives

$Mg^{2+}$ is the fourth most abundant mineral in the body showing a significant positive correlation with the protein synthesis rate, suggesting a key role of this mineral in the regulation of protein synthesis and in the cell proliferation rate in normal tissue cell populations, especially those with a high turnover such as the hematopoietic system. Due to the importance of this mineral in hematopoiesis, an imbalance can disrupt the hematopoiesis process, as well as the effective activities of mature blood cells. In conclusion, it is crucial to understand the impact of $Mg^{2+}$ on the correct hematopoietic functions, to understanding the mechanisms, and to understand when or how some therapeutic intervention is necessary. However, despite the existence of several studies showing the extensive role of $Mg^{2+}$, more studies are necessary to address the exact impact of this mineral on the hematopoietic system.

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## Abbreviations

| | |
|---|---|
| 1G11 | Murine pulmonary vascular endothelial cell |
| Akt | Protein kinase B |
| ALL | Acute lymphocytic leukemia |
| ALP | Alkaline phosphatase |
| BFU-E | Burst forming unit, erythroid |
| BMD | Bone mineral density |
| BMP2 | Bone morphogenetic protein 2 |
| C/EBPα | CCAAT-enhancer-binding protein α |
| C/EBPβ | CCAAT-enhancer-binding protein β |
| C3H10T1/2 | Murine C3H embryo sarcoma |
| $Ca^{2+}$ | Calcium |
| c-fos | Member of Fos family of transcription factors |
| CFU-E | Colony-forming unit, erythroid |
| COL10A1 | Collagen type X alpha 1 chain |
| CXCL12 | C–X–C motif chemokine 12 |
| Angpt1 | Angiopoietin 1 |
| CXCL12 | C–X–C motif chemokine 12 |
| CXCR4 | C–X–C chemokine receptor type 4 |
| G-CSF | Granulocyte colony-stimulating factor |
| DC-STAMP | Dendritic cell-specific transmembrane protein |
| DNA | Deoxyribonucleic acid |
| DT40 cell | Chicken B cell line |
| EBV | Epstein–Barr virus |
| ECM | Extracellular matrix |
| EPO | Erythropoietin |
| Fe | Iron |
| FMD | Flow-mediated dilation |
| GATA | GATA-binding protein 1 |
| G-CSF | Granulocyte colony-stimulating factor |
| GM-CSF | Granulocyte macrophage colony-stimulating factor |
| H2O2 | Hydrogen peroxide |
| hFOB1.19 | Human bone osteoblast; SV40 large T antigen transfected |
| HIF1-α | Hypoxia-inducible factor 1α |
| HMGB1 | High-mobility group box 1 |
| hMSCs | Human mesenchymal stem cells |
| HSC | Hematopoietic stem cell |
| HUVEC | Human umbilical vein endothelial cell |
| IgA | Immunoglobulin A |
| IGF2 | Insulin-like growth factor 2 |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| IL-1 | Interleukin-1 |
| IL-6 | Interleukin-6 |
| IL-8 | Interleukin-8 |
| iNOS | Inducible nitric oxide synthase |
| ITK | Interleukin-2-inducible kinase |
| JAK/STAT | Janus kinase/signal transducer |
| K | Potassium |
| KLF5 | Kruppel-like factor 5 |
| MagT1 | Magnesium transporter 1 |
| $Mg^{2+}$ | Magnesium |
| mTOR | Mammalian target of rapamycin |

| | |
|---|---|
| Na | Sodium |
| NF-kB | Nuclear factor kappa B |
| NKG2D | Natural killer group 2 member D |
| NMMIIA | Nonmuscular myosin protein IIA |
| OPG | Osteoprotegerin |
| OST | Oligosaccharyltransferase |
| PCNA | Proliferating cell nuclear antigen |
| CRP | C-reactive protein |
| PGC-1 α | Peroxisome proliferator-activated receptor gamma coactivator 1-alpha |
| PGE2 | Prostaglandin E2 |
| PI3-kinase | Phosphoinositide 3-kinase |
| PPARγ2 | Peroxisome proliferator-activated receptor γ2 |
| PTH | Parathyroid hormone |
| PU.1 | Transcription factor PU.1 |
| Rac1 | Ras-related C3 botulinum toxin substrate 1 |
| RANKL | Receptor activator of nuclear factor kappa B ligand |
| RANTES | Regulated upon activation, normal T cell expressed and secreted |
| RBC | Red blood cells |
| RNA | Ribonucleic acid |
| ROS | Reactive oxygen species |
| RUNX2 | RUNX family transcription factor 2 |
| S1P1 | Sphingosine-1-phosphate receptor 1 |
| S6K | Ribosomal S6 kinase |
| SaOS-2 | Human osteosarcoma cell line |
| SCF | Stem-cell factor |
| sE-selectin | Soluble endothelial selectin |
| sICAM-1 | Soluble intercellular adhesion molecule 1 |
| SIRT1 | Sirtuin-1 |
| STAT | Signal transducer and activator of transcription |
| STT3B | Oligosaccharyltransferase complex catalytic subunit B |
| sVCAM-1 | Soluble vascular cell adhesion molecule 1 |
| TCR | T-cell receptor |
| TNF-α | Tumor necrosis factor α |
| TRPM7 | Transient receptor potential cation channel subfamily M member 7 |
| VCAM1 | Vascular cell adhesion molecule 1 |
| VEGF | Vascular endothelial growth factor |

## References


1. Nielsen, F.H. Dietary Magnesium and Chronic Disease. *Adv. Chronic Kidney Dis.* **2018**, *25*, 230–235. [CrossRef]
2. Elin, R.J. The Effect of Magnesium Deficiency in Mice on Serum Immunoglobulin Concentrations and Antibody Plaque-Forming Cells. *Exp. Boil. Med.* **1975**, *148*, 620–624. [CrossRef] [PubMed]
3. Wolf, F.I. Magnesium in cell proliferation and differentiation. *Front. Biosci.* **1999**, *4*, D607–D617. [CrossRef] [PubMed]
4. Malpuech-Brugère, C.; Nowacki, W.; Daveau, M.; Gueux, E.; Linard, C.; Rock, E.; Lebreton, J.-P.; Mazur, A.; Rayssiguier, Y. Inflammatory response following acute magnesium deficiency in the rat. *Biochim. Biophys. Acta (BBA)-Mol. Basis Dis.* **2000**, *1501*, 91–98. [CrossRef]
5. Van Orden, R.; Eggett, D.L.; Franz, K.B. Influence of graded magnesium deficiencies on white blood cell counts and lymphocyte subpopulations in rats. *Magnes. Res.* **2006**, *19*, 93–101. [PubMed]
6. Nielsen, F.H. Magnesium deficiency and increased inflammation: Current perspectives. *J. Inflamm. Res.* **2018**, *11*, 25–34. [CrossRef]
7. Jin, J.; Desai, B.N.; Navarro, B.; Donovan, A.; Andrews, N.C.; Clapham, D.E. Deletion of Trpm7 Disrupts Embryonic Development and Thymopoiesis Without Altering Mg2+ Homeostasis. *Science* **2008**, *322*, 756–760. [CrossRef]

8. Howe, M.K.; Dowdell, K.; Roy, A.; Niemela, J.E.; Wilson, W.; McElwee, J.J.; Hughes, J.D.; Cohen, J.I. Magnesium Restores Activity to Peripheral Blood Cells in a Patient With Functionally Impaired Interleukin-2-Inducible T Cell Kinase. *Front. Immunol.* **2019**, *10*, 2000. [CrossRef]
9. Yoshizawa, S.; Chaya, A.; Verdelis, K.; Bilodeau, E.A.; Sfeir, C. An in vivo model to assess magnesium alloys and their biological effect on human bone marrow stromal cells. *Acta Biomater.* **2015**, *28*, 234–239. [CrossRef]
10. Luthringer-Feyerabend, B.J.; Willumeit-Römer, R. Effects of magnesium degradation products on mesenchymal stem cell fate and osteoblastogenesis. *Gene* **2016**, *575*, 9–20. [CrossRef]
11. Lima, F.D.S.; Romero, A.B.D.R.; Hastreiter, A.; Nogueira-Pedro, A.; Makiyama, E.; Colli, C.; Fock, R.A. An insight into the role of magnesium in the immunomodulatory properties of mesenchymal stem cells. *J. Nutr. Biochem.* **2018**, *55*, 200–208. [CrossRef] [PubMed]
12. Zheng, J.; Mao, X.; Ling, J.; Chen, C.; Zhang, W. Role of Magnesium Transporter Subtype 1 (MagT1) in the Osteogenic Differentiation of Rat Bone Marrow Stem Cells. *Boil. Trace Element Res.* **2015**, *171*, 131–137. [CrossRef] [PubMed]
13. Taichman, R.S.; Emerson, S.G. Human osteoblasts support hematopoiesis through the production of granulocyte colony-stimulating factor. *J. Exp. Med.* **1994**, *179*, 1677–1682. [CrossRef] [PubMed]
14. Taichman, R.S.; Reilly, M.; Emerson, S. Human osteoblasts support human hematopoietic progenitor cells in vitro bone marrow cultures. *Blood* **1996**, *87*, 518–524. [CrossRef] [PubMed]
15. McCreary, P.A.; Battifora, H.A.; Hahneman, B.M.; Laing, G.H.; Hass, G.M.; Singh, K. Leukocytosis, Bone Marrow Hyperplasia and Leukemia in Chronic Magnesium Deficiency in the Rat. *Blood* **1967**, *29*, 683–690. [CrossRef]
16. Stritt, S.; Nurden, P.; Favier, R.; Favier, M.; Ferioli, S.; Gotru, S.K.; Van Eeuwijk, J.M.M.; Schulze, H.; Nurden, A.T.; Lambert, M.P.; et al. Defects in TRPM7 channel function deregulate thrombopoiesis through altered cellular Mg2+ homeostasis and cytoskeletal architecture. *Nat. Commun.* **2016**, *7*, 11097. [CrossRef]
17. Krishnamoorthy, M.; Wasim, L.; Buhari, F.H.M.; Zhao, T.; Mahtani, T.; Ho, J.; Kang, S.; Deason-Towne, F.; Perraud, A.-L.; Schmitz, C.; et al. The channel-kinase TRPM7 regulates antigen gathering and internalization in B cells. *Sci. Signal.* **2018**, *11*, eaah6692. [CrossRef]
18. Yee, N.S.; Kazi, A.A.; Yee, R.K. Cellular and Developmental Biology of TRPM7 Channel-Kinase: Implicated Roles in Cancer. *Cells* **2014**, *3*, 751–777. [CrossRef]
19. Zierler, S.; Sumoza-Toledo, A.; Suzuki, S.; Dúill, F. Ó; Ryazanova, L.V.; Penner, R.; Ryazanov, A.G.; Fleig, A. TRPM7 kinase activity regulates murine mast cell degranulation. *J. Physiol.* **2016**, *594*, 2957–2970. [CrossRef]
20. Nadolni, W.; Zierler, S. The Channel-Kinase TRPM7 as Novel Regulator of Immune System Homeostasis. *Cells* **2018**, *7*, 109. [CrossRef]
21. Sun, Y.; Sukumaran, P.; Singh, B.B. Magnesium-Induced Cell Survival Is Dependent on TRPM7 Expression and Function. *Mol. Neurobiol.* **2019**, *57*, 528–538. [CrossRef] [PubMed]
22. Cao, R.; Meng, Z.; Liu, T.; Wang, G.; Qian, G.; Cao, T.; Guan, X.; Dan, H.; Xiao, Y.; Wang, X. Decreased TRPM7 inhibits activities and induces apoptosis of bladder cancer cells via ERK1/2 pathway. *Oncotarget* **2016**, *7*, 72941–72960. [CrossRef] [PubMed]
23. Zou, Z.G.; Rios, F.J.; Montezano, A.C.; Touyz, R.M. TRPM7, Magnesium, and Signaling. *Int. J. Mol. Sci.* **2019**, *20*, 1877. [CrossRef]
24. Ikari, A.; Sawada, H.; Sanada, A.; Tonegawa, C.; Yamazaki, Y.; Sugatani, J. Magnesium deficiency suppresses cell cycle progression mediated by increase in transcriptional activity of p21Cip1 and p27Kip1 in renal epithelial NRK-52E cells. *J. Cell. Biochem.* **2011**, *112*, 3563–3572. [CrossRef] [PubMed]
25. Hartwig, A. Role of magnesium in genomic stability. *Mutat. Res. Mol. Mech. Mutagen.* **2001**, *475*, 113–121. [CrossRef]
26. Covacci, V.; Bruzzese, N.; Sgambato, A.; Di Francesco, A.; Russo, M.A.; Wolf, F.I.; Cittadini, A. Magnesium restriction induces granulocytic differentiation and expression of p27Kip1 in human leukemic HL-60 cells. *J. Cell. Biochem.* **1998**, *70*, 313–322. [CrossRef]
27. Wu, L.; Witte, F.M.; Schilling, A.F.; Willumeit-Römer, R.; Luthringer-Feyerabend, B.J. Effects of extracellular magnesium extract on the proliferation and differentiation of human osteoblasts and osteoclasts in coculture. *Acta Biomater.* **2015**, *27*, 294–304. [CrossRef]
28. Mammoli, F.; Castiglioni, S.; Parenti, S.; Cappadone, C.; Farruggia, G.; Iotti, S.; Davalli, P.; Maier, J.A.; Grande, A.; Frassineti, C. Magnesium Is a Key Regulator of the Balance between Osteoclast and Osteoblast Differentiation in the Presence of Vitamin D3. *Int. J. Mol. Sci.* **2019**, *20*, 385. [CrossRef]

29. Martin, H.; Richert, L.; Berthelot, A. Magnesium deficiency induces apoptosis in primary cultures of rat hepatocytes. *J. Nutr.* **2003**, *133*, 2505–2511. [CrossRef]
30. Ohyama, T. New Aspects of Magnesium Function: A Key Regulator in Nucleosome Self-Assembly, Chromatin Folding and Phase Separation. *Int. J. Mol. Sci.* **2019**, *20*, 4232. [CrossRef]
31. Díaz-Tocados, J.M.; Herencia, C.; Martínez-Moreno, J.M.; De Oca, A.M.; Rodríguez-Ortiz, M.E.; Vergara, N.; Blanco, A.; Steppan, S.; Almadén, Y.; Rodríguez, M.; et al. Magnesium Chloride promotes Osteogenesis through Notch signaling activation and expansion of Mesenchymal Stem Cells. *Sci. Rep.* **2017**, *7*, 7839. [CrossRef] [PubMed]
32. Wang, J.; Ma, X.-Y.; Feng, Y.-F.; Ma, Z.-S.; Ma, T.-C.; Zhang, Y.; Li, X.; Wang, L.; Lei, W. Magnesium Ions Promote the Biological Behaviour of Rat Calvarial Osteoblasts by Activating the PI3K/Akt Signalling Pathway. *Boil. Trace Element Res.* **2017**, *179*, 284–293. [CrossRef] [PubMed]
33. Zhang, X.; Zu, H.; Zhao, D.W.; Yang, K.; Tian, S.; Yu, X.; Lu, F.; Liu, B.; Yu, X.; Wang, B.; et al. Ion channel functional protein kinase TRPM7 regulates Mg ions to promote the osteoinduction of human osteoblast via PI3K pathway: In vitro simulation of the bone-repairing effect of Mg-based alloy implant. *Acta Biomater.* **2017**, *63*, 369–382. [CrossRef] [PubMed]
34. Leidi, M.; Dellera, F.; Mariotti, M.; Maier, J.A. High magnesium inhibits human osteoblast differentiation in vitro. *Magnes Res* **2011**, *24*, 1–6. [CrossRef] [PubMed]
35. Rude, R.K.; Gruber, H.; Wei, L.; Frausto, A.; Mills, B. Magnesium Deficiency: Effect on Bone and Mineral Metabolism in the Mouse. *Calcif. Tissue Int.* **2003**, *72*, 32–41. [CrossRef]
36. Bernardini, D.; Nasulewic, A.; Mazur, A.; Maier, J.A.M. Magnesium and microvascular endothelial cells: A role in inflammation and angiogenesis. *Front. Biosci.* **2005**, *10*, 1177–1182. [CrossRef]
37. Ferrè, S.; Baldoli, E.; Leidi, M.; Maier, J.A. Magnesium deficiency promotes a pro-atherogenic phenotype in cultured human endothelial cells via activation of NFkB. *Biochim. Et Biophys. Acta (BBA)-Mol. Basis Dis.* **2010**, *1802*, 952–958. [CrossRef]
38. Baldoli, E.; Maier, J.A. Silencing TRPM7 mimics the effects of magnesium deficiency in human microvascular endothelial cells. *Angiogenesis* **2011**, *15*, 47–57. [CrossRef]
39. Zhu, D.; You, J.; Zhao, N.; Xu, H. Magnesium Regulates Endothelial Barrier Functions through TRPM7, MagT1, and S1P1. *Adv. Sci.* **2019**, *6*, 1901166. [CrossRef]
40. Cunha, A.R.; D'El-Rei, J.; Medeiros, F.; Umbelino, B.; Oigman, W.; Touyz, R.M.; Neves, M.F. Oral magnesium supplementation improves endothelial function and attenuates subclinical atherosclerosis in thiazide-treated hypertensive women. *J. Hypertens.* **2017**, *35*, 89–97. [CrossRef]
41. Joris, P.; Plat, J.; Bakker, S.J.L.; Mensink, R.P. Effects of long-term magnesium supplementation on endothelial function and cardiometabolic risk markers: A randomized controlled trial in overweight/obese adults. *Sci. Rep.* **2017**, *7*, 106. [CrossRef] [PubMed]
42. Shogi, T.; Oono, H.; Nakagawa, M.; Miyamoto, A.; Ishiguro, S.; Nishio, A. Effects of a low extracellular magnesium concentration and endotoxin on IL-1beta and TNF-alpha release from, and mRNA levels in, isolated rat alveolar macrophages. *Magnes. Res.* **2002**, *15*, 147–152. [PubMed]
43. Liu, Z.; Chang, Y.; Zhang, J.; Huang, X.; Jiang, J.; Li, S.; Wang, Z. Magnesium deficiency promotes secretion of high-mobility group box 1 protein from lipopolysaccharide-activated macrophages in vitro. *J. Surg. Res.* **2013**, *180*, 310–316. [CrossRef] [PubMed]
44. Sugimoto, J.; Romani, A.M.; Valentin-Torres, A.M.; Luciano, A.A.; Ramirez Kitchen, C.M.; Funderburg, N.; Mesiano, S.; Bernstein, H.B. Magnesium decreases inflammatory cytokine production: A novel innate immunomodulatory mechanism. *J. Immunol.* **2012**, *188*, 6338–6346. [CrossRef]
45. Elin, R.J.; Utter, A.; Tan, H.K.; Corash, L. Effect of magnesium deficiency on erythrocyte aging in rats. *Am. J. Pathol.* **1980**, *100*, 765–778.
46. Sanchez-Morito, N.; Planells, E.; Aranda, P.; Llopis, J. Influence of magnesium deficiency on the bioavailability and tissue distribution of iron in the rat. *J. Nutr. Biochem.* **2000**, *11*, 103–108. [CrossRef]
47. Shi, Z.; Hu, X.; He, K.; Yuan, B.; Garg, M. Joint association of magnesium and iron intake with anemia among Chinese adults. *Nutrition* **2008**, *24*, 977–984. [CrossRef]
48. Zhan, Y.; Chen, R.; Zheng, W.; Guo, C.; Lu, L.; Ji, X.; Chi, Z.; Yu, J. Association between serum magnesium and anemia: China health and nutrition survey. *Biol. Trace Element Res.* **2014**, *159*, 39–45. [CrossRef]

49. Eltayeb, R.; Rayis, D.A.; Sharif, M.E.; Ahmed, A.B.A.; Elhardello, O.; Adam, I. The prevalence of serum magnesium and iron deficiency anaemia among Sudanese women in early pregnancy: A cross-sectional study. *Trans. R. Soc. Trop. Med. Hyg.* **2019**, *113*, 31–35. [CrossRef]
50. Cinar, V.; Nizamlioglu, M.; Mogulkoc, R.; Baltaci, A.K. Effects of magnesium supplementation on blood parameters of athletes at rest and after exercise. *Biol. Trace Elem. Res.* **2007**, *115*, 205–212. [CrossRef]
51. Hungerford, G.F. Role of histamine in producing the eosinophilia of magnesium deficiency. *Proc. Soc. Exp. Biol. Med.* **1964**, *115*, 182–185. [CrossRef] [PubMed]
52. Kraeuter, S.L.; Schwartz, R. Blood and mast cell histamine levels in magnesium-deficient rats. *J. Nutr.* **1980**, *110*, 851–858. [CrossRef] [PubMed]
53. Bélanger, L.F. Variations in the mast cell population of skin and bone marrow in magnesium-deprived rats. The influence of sex hormones. *J. Nutr.* **1977**, *107*, 2164–2170. [CrossRef] [PubMed]
54. Bussière, F.I.; Gueux, E.; Rock, E.; Girardeau, J.-P.; Tridon, A.; Mazur, A.; Rayssiguier, Y. Increased phagocytosis and production of reactive oxygen species by neutrophils during magnesium deficiency in rats and inhibition by high magnesium concentration. *Br. J. Nutr.* **2002**, *87*, 107–113. [CrossRef]
55. Lu, L.; Zhan, Y.; Yu, J.; Sui, L. Prevalence of Thrombocytopenia and Its Association with Serum Magnesium. *Biol. Trace Elem. Res.* **2016**, *169*, 46–51. [CrossRef]
56. Rishi, M.; Ahmad, A.; Makheja, A.; Karcher, D.; Bloom, S. Effects of reduced dietary magnesium on platelet production and function in hamsters. *Lab. Investig.* **1990**, *63*, 717–721.
57. Maximow, A.A. Relation of Blood cells to connective tissues and endothelium. *Physiol. Rev.* **1924**, *4*, 533–563. [CrossRef]
58. Owen, R.D.; Miller, N.E.; Bailey, C.J.; Stevenson, J.A.F. Immunogenetic consequences of vascular anastomoses between bovine twins. *Science* **1945**, *102*, 400–401. [CrossRef]
59. McCulloch, J.E.T.A. A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells. *Radiat. Res.* **1961**, *14*, 213.
60. Papayannopoulou, T.; Scadden, D.T. Stem-cell ecology and stem cells in motion. *Blood* **2008**, *111*, 3923–3930. [CrossRef]
61. Weissman, I.L.; Shizuru, J.A. The origins of the identification and isolation of hematopoietic stem cells, and their capability to induce donor-specific transplantation tolerance and treat autoimmune diseases. *Blood* **2008**, *112*, 3543–3553. [CrossRef] [PubMed]
62. Zhang, C.C.; Lodish, H.F. Cytokines regulating hematopoietic stem cell function. *Curr. Opin. Hematol.* **2008**, *15*, 307–311. [CrossRef] [PubMed]
63. Zhang, Y.; Gao, S.; Xia, J.; Liu, F. Hematopoietic Hierarchy – An Updated Roadmap. *Trends Cell Boil.* **2018**, *28*, 976–986. [CrossRef] [PubMed]
64. Orkin, S.H.; Zon, L.I. Hematopoiesis: An Evolving Paradigm for Stem Cell Biology. *Cell* **2008**, *132*, 631–644. [CrossRef] [PubMed]
65. Rieger, M.A.; Schroeder, T. Hematopoiesis. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*, a008250. [CrossRef]
66. Schofield, R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood Cells* **1978**, *4*, 7–25.
67. Agas, D.; Marchetti, L.; Douni, E.; Sabbieti, M.G. The unbearable lightness of bone marrow homeostasis. *Cytokine Growth Factor Rev.* **2015**, *26*, 347–359. [CrossRef]
68. Scadden, D.T. Nice neighborhood: Emerging concepts of the stem cell niche. *Cell* **2014**, *157*, 41–50. [CrossRef]
69. Kopp, H.-G.; Avecilla, S.T.; Hooper, A.T.; Rafii, S. The Bone Marrow Vascular Niche: Home of HSC Differentiation and Mobilization. *Physiology* **2005**, *20*, 349–356. [CrossRef]
70. Morrison, S.J.; Scadden, D.T. The bone marrow niche for haematopoietic stem cells. *Nature* **2014**, *505*, 327–334. [CrossRef]
71. Kumar, R.; Godavarthy, P.S.; Krause, D.S. The bone marrow microenvironment in health and disease at a glance. *J. Cell Sci.* **2018**, *131*, jcs201707. [CrossRef] [PubMed]
72. Naveiras, O.; Nardi, V.; Wenzel, P.L.; Hauschka, P.V.; Fahey, F.; Daley, G.Q. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. *Nature* **2009**, *460*, 259–263. [CrossRef] [PubMed]
73. Sugimura, R.; Li, L. Shifting in Balance between Osteogenesis and Adipogenesis Substantially Influences Hematopoiesis. *J. Mol. Cell Boil.* **2009**, *2*, 61–62. [CrossRef] [PubMed]

74. Rude, R.K.; Gruber, H.E. Magnesium deficiency and osteoporosis: Animal and human observations. *J. Nutr. Biochem.* **2004**, *15*, 710–716. [CrossRef]
75. Castiglioni, S.; Cazzaniga, A.; Albisetti, W.; Maier, J.A.M. Magnesium and Osteoporosis: Current State of Knowledge and Future Research Directions. *Nutrients* **2013**, *5*, 3022–3033. [CrossRef]
76. Castiglioni, S.; Romeo, V.; Locatelli, L.; Cazzaniga, A.; Maier, J.A. TRPM7 and MagT1 in the osteogenic differentiation of human mesenchymal stem cells in vitro. *Sci. Rep.* **2018**, *8*, 16195. [CrossRef]
77. Castiglioni, S.; Romeo, V.; Locatelli, L.; Zocchi, M.; Zecchini, S.; Maier, J.A. The simultaneous downregulation of TRPM7 and MagT1 in human mesenchymal stem cells in vitro: Effects on growth and osteogenic differentiation. *Biochem. Biophys. Res. Commun.* **2019**, *513*, 159–165. [CrossRef]
78. Gruber, H.; Rude, R.K.; Wei, L.; Frausto, A.; Mills, B.G.; Norton, H.J. Magnesium deficiency: Effect on bone mineral density in the mouse appendicular skeleton. *BMC Musculoskelet. Disord.* **2003**, *4*, 7. [CrossRef]
79. Rude, R.K.; Gruber, H.E.; Wei, L.; Frausto, A. Immunolocalization of RANKL is Increased and OPG Decreased during Dietary Magnesium Deficiency in the Rat. *Nutr. Metab.* **2005**, *2*, 24. [CrossRef]
80. Verma, S.; Rajaratnam, J.H.; Denton, J.; A Hoyland, J.; Byers, R. Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis. *J. Clin. Pathol.* **2002**, *55*, 693–698. [CrossRef]
81. Justesen, J.; Stenderup, K.; Ebbesen, E.; Mosekilde, L.; Steiniche, T.; Kassem, M. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. *Biogerontology* **2001**, *2*, 165–171. [CrossRef] [PubMed]
82. Beekman, K.M.; Veldhuis-Vlug, A.G.; Heijer, M.D.; Maas, M.; Oleksik, A.; Tanck, M.W.; Ott, S.M.; Hof, R.J.V. 'T; Lips, P.; Bisschop, P.H.; et al. The effect of raloxifene on bone marrow adipose tissue and bone turnover in postmenopausal women with osteoporosis. *Bone* **2019**, *118*, 62–68. [CrossRef] [PubMed]
83. Schwartz, A.V.; Sigurdsson, S.; Hue, T.F.; Lang, T.F.; Harris, T.B.; Rosen, C.J.; Vittinghoff, E.; Siggeirsdottir, K.; Sigurdsson, G.; Oskarsdottir, D.; et al. Vertebral Bone Marrow Fat Associated With Lower Trabecular BMD and Prevalent Vertebral Fracture in Older Adults. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 2294–2300. [CrossRef] [PubMed]
84. Lin, C.; Li, N.; Cheng, H.; Yen, M.-L. Oxidative stress induces imbalance of adipogenic/osteoblastic lineage commitment in mesenchymal stem cells through decreasing SIRT1 functions. *J. Cell. Mol. Med.* **2017**, *22*, 786–796. [CrossRef] [PubMed]
85. Petrault, I.; Zimowska, W.; Mathieu, J.; Bayle, D.; Rock, E.; Favier, A.; Rayssiguier, Y.; Mazur, A. Changes in gene expression in rat thymocytes identified by cDNA array support the occurrence of oxidative stress in early magnesium deficiency. *Biochim. Biophys. Acta* **2002**, *1586*, 92–98. [CrossRef]
86. Malpuech-Brugère, C.; Nowacki, W.; Gueux, E.; Kuryszko, J.; Rock, E.; Rayssiguier, Y.; Mazur, A. Accelerated thymus involution in magnesium-deficient rats is related to enhanced apoptosis and sensitivity to oxidative stress. *Br. J. Nutr.* **1999**, *81*, 405–411. [CrossRef]
87. Yang, Y.; Wu, Z.; Chen, Y.; Qiao, J.; Gao, M.; Yuan, J.; Nie, W.; Guo, Y. Magnesium Deficiency Enhances Hydrogen Peroxide Production and Oxidative Damage in Chick Embryo Hepatocyte In Vitro. *BioMetals* **2006**, *19*, 71–81. [CrossRef]
88. Leidi, M.; Dellera, F.; Mariotti, M.; Banfi, G.; Crapanzano, C.; Albisetti, W.; Maier, J.A. Nitric oxide mediates low magnesium inhibition of osteoblast-like cell proliferation. *J. Nutr. Biochem.* **2012**, *23*, 1224–1229. [CrossRef]
89. Rock, E.; Astier, C.; Lab, C.; Malpuech, C.; Nowacki, W.; Gueux, E.; Mazur, A.; Rayssiguier, Y. Magnesium deficiency in rats induces a rise in plasma nitric oxide. *Magnes. Res.* **1995**, *8*, 237–242.
90. Cunha, M.C.R.; Lima, F.D.S.; Vinolo, M.A.R.; Hastreiter, A.; Curi, R.; Borelli, P.; Fock, R.A. Protein Malnutrition Induces Bone Marrow Mesenchymal Stem Cells Commitment to Adipogenic Differentiation Leading to Hematopoietic Failure. *PLoS ONE* **2013**, *8*, e58872. [CrossRef]
91. Wilson, A.; Fu, H.; Schiffrin, M.; Winkler, C.; Koufany, M.; Jouzeau, J.-Y.; Bonnet, N.; Gilardi, F.; Renevey, F.; Luther, S.A.; et al. Lack of Adipocytes Alters Hematopoiesis in Lipodystrophic Mice. *Front. Immunol.* **2018**, *9*, 2573. [CrossRef] [PubMed]
92. Zhou, B.O.; Yu, H.; Yue, R.; Zhao, Z.; Rios, J.J.; Naveiras, O.; Morrison, S.J. Bone marrow adipocytes promote the regeneration of stem cells and haematopoiesis by secreting SCF. *Nature* **2017**, *19*, 891–903. [CrossRef]

93. Xu, Y.; Takahashi, Y.; Wang, Y.; Hama, A.; Nishio, N.; Muramatsu, H.; Tanaka, M.; Yoshida, N.; Villalobos, I.B.; Yagasaki, H.; et al. Downregulation of GATA-2 and overexpression of adipogenic gene-PPARγ in mesenchymal stem cells from patients with aplastic anemia. *Exp. Hematol.* **2009**, *37*, 1393–1399. [CrossRef] [PubMed]
94. Liu, H.; He, J.; Koh, S.P.; Zhong, Y.; Liu, Z.; Wang, Z.; Zhang, Y.; Li, Z.; Tam, B.T.; Lin, P.; et al. Reprogrammed marrow adipocytes contribute to myeloma-induced bone disease. *Sci. Transl. Med.* **2019**, *11*, eaau9087. [CrossRef] [PubMed]
95. Nombela-Arrieta, C.; Pivarnik, G.; Winkel, B.; Canty, K.J.; Harley, B.; Mahoney, J.E.; Park, S.-Y.; Lu, J.; Protopopov, A.; Silberstein, L.E. Quantitative imaging of haematopoietic stem and progenitor cell localization and hypoxic status in the bone marrow microenvironment. *Nat. Cell Biol.* **2013**, *15*, 533–543. [CrossRef]
96. Filipowska, J.; Tomaszewski, K.A.; Niedźwiedzki, Ł.; Walocha, J.A.; Niedźwiedzki, T. The role of vasculature in bone development, regeneration and proper systemic functioning. *Angiogenesis* **2017**, *20*, 291–302. [CrossRef]
97. Kiel, M.J.; Yilmaz, Ö.H.; Iwashita, T.; Yilmaz, O.H.; Terhorst, C.; Morrison, S.J. SLAM Family Receptors Distinguish Hematopoietic Stem and Progenitor Cells and Reveal Endothelial Niches for Stem Cells. *Cell* **2005**, *121*, 1109–1121. [CrossRef]
98. Ding, L.; Saunders, T.L.; Enikolopov, G.; Morrison, S.J. Endothelial and perivascular cells maintain haematopoietic stem cells. *Nature* **2012**, *481*, 457–462. [CrossRef]
99. Butler, J.M.; Nolan, D.J.; Vertes, E.L.; Varnum-Finney, B.; Kobayashi, H.; Hooper, A.T.; Seandel, M.; Shido, K.; White, I.A.; Kobayashi, M.; et al. Endothelial Cells Are Essential for the Self-Renewal and Repopulation of Notch-Dependent Hematopoietic Stem Cells. *Cell Stem Cell* **2010**, *6*, 251–264. [CrossRef]
100. Poulos, M.G.; Guo, P.; Kofler, N.M.; Pinho, S.; Gutkin, M.C.; Tikhonova, A.; Aifantis, I.; Frenette, P.S.; Kitajewski, J.; Rafii, S.; et al. Endothelial Jagged-1 Is Necessary for Homeostatic and Regenerative Hematopoiesis. *Cell Rep.* **2013**, *4*, 1022–1034. [CrossRef]
101. Shahrabi, S.; Rezaeeyan, H.; Ahmadzadeh, A.; Shahjahani, M.; Saki, N. Bone marrow blood vessels: Normal and neoplastic niche. *Oncol. Rev.* **2016**, *10*, 306. [CrossRef] [PubMed]
102. Itkin, T.; Gur-Cohen, S.; Spencer, J.A.; Schajnovitz, A.; Ramasamy, S.; Kusumbe, A.P.; Ledergor, G.; Jung, Y.; Milo, I.; Poulos, M.G.; et al. Distinct bone marrow blood vessels differentially regulate haematopoiesis. *Nature* **2016**, *532*, 323–328. [CrossRef]
103. Maier, J.A. Endothelial cells and magnesium: Implications in atherosclerosis. *Clin. Sci.* **2011**, *122*, 397–407. [CrossRef] [PubMed]
104. Maier, J.A.; Malpuech-Brugère, C.; Zimowska, W.; Rayssiguier, Y.; Mazur, A. Low magnesium promotes endothelial cell dysfunction: Implications for atherosclerosis, inflammation and thrombosis. *Biochim. Biophys. Acta* **2004**, *1689*, 13–21. [CrossRef] [PubMed]
105. Baldoli, E.; Castiglioni, S.; Maier, J.A. Regulation and Function of TRPM7 in Human Endothelial Cells: TRPM7 as a Potential Novel Regulator of Endothelial Function. *PLoS ONE* **2013**, *8*, e59891. [CrossRef]
106. Mofrad, M.D.; Djafarian, K.; Mozaffari, H.; Shab-Bidar, S. Effect of magnesium supplementation on endothelial function: A systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis* **2018**, *273*, 98–105. [CrossRef]
107. Winkler, I.G.; Sims, N.A.; Pettit, A.R.; Barbier, V.; Nowlan, B.; Helwani, F.; Poulton, I.J.; van Rooijen, N.; Alexander, K.A.; Raggatt, L.J.; et al. Bone marrow macrophages maintain hematopoietic stem cell (HSC) niches and their depletion mobilizes HSCs. *Blood* **2010**, *116*, 4815–4828. [CrossRef]
108. McCabe, A.; MacNamara, K.C. Macrophages: Key regulators of steady-state and demand-adapted hematopoiesis. *Exp. Hematol.* **2016**, *44*, 213–222. [CrossRef]
109. Chow, A.; Lucas, D.; Hidalgo, A.; Méndez-Ferrer, S.; Hashimoto, D.; Scheiermann, C.; Battista, M.; Leboeuf, M.; Prophete, C.; van Rooijen, N.; et al. Bone marrow CD169+ macrophages promote the retention of hematopoietic stem and progenitor cells in the mesenchymal stem cell niche. *J. Exp. Med.* **2011**, *208*, 261–271. [CrossRef]
110. Chasis, J.A.; Mohandas, N. Erythroblastic islands: Niches for erythropoiesis. *Blood* **2008**, *112*, 470–478. [CrossRef]
111. Li, D.; Xue, W.; Li, M.; Dong, M.; Wang, J.; Wang, X.; Li, X.; Chen, K.; Zhang, W.; Wu, S.; et al. VCAM-1+ macrophages guide the homing of HSPCs to a vascular niche. *Nature* **2018**, *564*, 119–124. [CrossRef] [PubMed]

112. Cavaillon, J.M. Cytokines and macrophages. *Biomed. Pharmacother.* **1994**, *48*, 445–453. [CrossRef]
113. Metcalf, D. Hematopoietic cytokines. *Blood* **2008**, *111*, 485–491. [CrossRef] [PubMed]
114. Libako, P.; Nowacki, W.; Castiglioni, S.; Mazur, A.; Maier, J.A. Extracellular magnesium and calcium blockers modulate macrophage activity. *Magnes. Res.* **2016**, *29*, 11–21. [CrossRef]
115. Tam, M.; Gomez, S.; González-Gross, M.; Marcos, A. Possible roles of magnesium on the immune system. *Eur. J. Clin. Nutr.* **2003**, *57*, 1193–1197. [CrossRef]
116. Weglicki, W.B.; Phillips, T.M. Pathobiology of magnesium deficiency: A cytokine/neurogenic inflammation hypothesis. *Am. J. Physiol. Integr. Comp. Physiol.* **1992**, *263*, R734–R737. [CrossRef]
117. Mazur, A.; Maier, J.A.; Rock, E.; Gueux, E.; Nowacki, W.; Rayssiguier, Y. Magnesium and the inflammatory response: Potential physiopathological implications. *Arch. Biochem. Biophys.* **2007**, *458*, 48–56. [CrossRef]
118. Yokoyama, T.; Oono, H.; Miyamoto, A.; Ishiguro, S.; Nishio, A. Magnesium-deficient medium enhances NO production in alveolar macrophages isolated from rats. *Life Sci.* **2003**, *72*, 1247–1257. [CrossRef]
119. Shigematsu, M.; Tomonaga, S.; Shimokawa, F.; Murakami, M.; Imamura, T.; Matsui, T.; Funaba, M. Regulatory responses of hepatocytes, macrophages and vascular endothelial cells to magnesium deficiency. *J. Nutr. Biochem.* **2018**, *56*, 35–47. [CrossRef]
120. Hu, T.; Xu, H.; Wang, C.; Qin, H.; An, Z. Magnesium enhances the chondrogenic differentiation of mesenchymal stem cells by inhibiting activated macrophage-induced inflammation. *Sci. Rep.* **2018**, *8*, 3406. [CrossRef]
121. Su, N.-Y.; Peng, T.-C.; Tsai, P.-S.; Huang, C.-J. Phosphoinositide 3-kinase/Akt pathway is involved in mediating the anti-inflammation effects of magnesium sulfate. *J. Surg. Res.* **2013**, *185*, 726–732. [CrossRef] [PubMed]
122. Sun, L.; Li, X.; Xu, M.; Yang, F.; Wang, W.; Niu, X. In vitro immunomodulation of magnesium on monocytic cell toward anti-inflammatory macrophages. *Regen. Biomater.* **2020**, *7*, 391–401. [CrossRef] [PubMed]
123. Li, B.; Cao, H.; Zhao, Y.; Cheng, M.; Qin, H.; Cheng, T.; Hu, Y.; Zhang, X.; Liu, X. In vitro and in vivo responses of macrophages to magnesium-doped titanium. *Sci. Rep.* **2017**, *7*, 42707. [CrossRef] [PubMed]
124. Yamashita, M.; Passegué, E. TNF-α Coordinates Hematopoietic Stem Cell Survival and Myeloid Regeneration. *Cell Stem Cell* **2019**, *25*, 357–372. [CrossRef] [PubMed]
125. Pietras, E.M.; Mirantes-Barbeito, C.; Fong, S.L.; Loeffler, D.; Kovtonyuk, L.V.; Zhang, S.; Lakshminarasimhan, R.; Chin, C.P.; Techner, J.-M.; Will, B.; et al. Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal. *Nature* **2016**, *18*, 607–618. [CrossRef]
126. Barminko, J.; Reinholt, B.; Baron, M.H. Development and differentiation of the erythroid lineage in mammals. *Dev. Comp. Immunol.* **2016**, *58*, 18–29. [CrossRef]
127. Comazzetto, S.; Murphy, M.M.; Berto, S.; Jeffery, E.; Zhao, Z.; Morrison, S.J. Restricted Hematopoietic Progenitors and Erythropoiesis Require SCF from Leptin Receptor+ Niche Cells in the Bone Marrow. *Cell Stem Cell* **2019**, *24*, 477–486. [CrossRef]
128. Mello, F.V.; Land, M.G.P.; Costa, E.S.; Teodósio, C.; Sanchez, M.-L.; Bárcena, P.; Peres, R.T.; Pedreira, C.E.; Alves, L.R.; Orfao, A. Maturation-associated gene expression profiles during normal human bone marrow erythropoiesis. *Cell Death Discov.* **2019**, *5*, 69. [CrossRef]
129. Eggold, J.T.; Rankin, E.B. Erythropoiesis, EPO, macrophages, and bone. *Bone* **2019**, *119*, 36–41. [CrossRef]
130. Giger, K.M.; Kalfa, T.A. Phylogenetic and Ontogenetic View of Erythroblastic Islands. *Biomed. Res. Int.* **2015**, *2015*, 873628. [CrossRef]
131. Koury, M.J.; Ponka, P. New insights into erythropoiesis: The roles of folate, vitamin B12, and iron. *Annu Rev. Nutr.* **2004**, *24*, 105–131. [CrossRef] [PubMed]
132. Bang, O.; Orskov, S.L. The magnesium content of the erythrocytes in pernicious and some other anemias. *J. Clin. Investig.* **1939**, *18*, 497–500. [CrossRef]
133. Cohlan, S.Q.; Jansen, V.; Dancis, J.; Piomelli, S. Microcytic anemia with erythroblastosis in offspring of magnesium-deprived rats. *Blood* **1970**, *36*, 500–506. [CrossRef] [PubMed]
134. Piomelli, S.; Jansen, V.; Dancis, J. The hemolytic anemia of magnesium deficiency in adult rats. *Blood.* **1973**, *41*, 451–459. [CrossRef] [PubMed]
135. Cosens, G.; Diamond, I.; Theriault, L.L.; Hurley, L.S. Magnesium deficiency anemia in the rat fetus. *Pediatr. Res.* **1977**, *11*, 758–764. [CrossRef] [PubMed]
136. Keen, C.L.; Lowney, P.; Gershwin, M.E.; Hurley, L.S.; Stern, J.S. Dietary magnesium intake influences exercise capacity and hematologic parameters in rats. *Metabolism* **1987**, *36*, 788–793. [CrossRef]

137. De Franceschi, L.; Beuzard, Y.; Jouault, H.; Brugnara, C. Modulation of erythrocyte potassium chloride cotransport, potassium content, and density by dietary magnesium intake in transgenic SAD mouse. *Blood* **1996**, *88*, 2738–2744. [CrossRef]
138. Mak, I.T.; Stafford, R.; Weglicki, W.B. Loss of red blood cell glutathione during Mg deficiency: Prevention by vitamin, E.; D-propranolol, and chloroquine. *Am. J. Physiol.* **1994**, *267 Pt 1*, C1366–C1370. [CrossRef]
139. Mak, I.T.; Komarov, A.M.; Wagner, T.L.; Stafford, R.E.; Dickens, B.F.; Weglicki, W.B. Enhanced NO production during Mg deficiency and its role in mediating red blood cell glutathione loss. *Am. J. Physiol.* **1996**, *271 Pt 1*, C385–C390. [CrossRef]
140. Schauf, B.; Mannschreck, B.; Becker, S.; Dietz, K.; Wallwiener, D.; Aydeniz, B. Evaluation of red blood cell deformability and uterine blood flow in pregnant women with preeclampsia or iugr and reduced uterine blood flow following the intravenous application of magnesium. *Hypertens. Pregnancy* **2004**, *23*, 331–343. [CrossRef]
141. Schauf, B.; Becker, S.; Abele, H.; Klever, T.; Wallwiener, D.; Aydeniz, B. Effect of magnesium on red blood cell deformability in pregnancy. *Hypertens. Pregnancy* **2005**, *24*, 17–27. [CrossRef] [PubMed]
142. Xu, X.; Hall, J.; Byles, J.; Shi, Z. Dietary pattern, serum magnesium, ferritin, C-reactive protein and anaemia among older people. *Clin Nutr.* **2017**, *36*, 444–451. [CrossRef] [PubMed]
143. Jelkmann, W. Regulation of erythropoietin production. *J. Physiol.* **2011**, *589 Pt 6*, 1251–1258. [CrossRef]
144. Yu, L.; Song, J.; Lu, X.; Zu, Y.; Li, H.; Wang, S. Association between Serum Magnesium and Erythropoietin Responsiveness in Hemodialysis Patients: A Cross-Sectional Study. *Kidney Blood Press Res.* **2019**, *44*, 354–361. [CrossRef]
145. Torii, S.; Kobayashi, K.; Takahashi, M.; Katahira, K.; Goryo, K.; Matsushita, N.; Yasumoto, K.-I.; Fujii-Kuriyama, Y.; Sogawa, K. Magnesium deficiency causes loss of response to intermittent hypoxia in paraganglion cells. *J. Biol. Chem.* **2009**, *284*, 19077–19089. [CrossRef] [PubMed]
146. Haase, V.H. Regulation of erythropoiesis by hypoxia-inducible factors. *Blood Rev.* **2013**, *27*, 41–53. [CrossRef] [PubMed]
147. Takemoto, S.; Yamamoto, A.; Tomonaga, S.; Funaba, M.; Matsui, T. Magnesium deficiency induces the emergence of mast cells in the liver of rats. *J. Nutr. Sci. Vitaminol.* **2013**, *59*, 560–563. [CrossRef]
148. Kurantsin-Mills, J.; Cassidy, M.M.; Stafford, R.E.; Weglicki, W.B. Marked alterations in circulating inflammatory cells during cardiomyopathy development in a magnesium-deficient rat model. *Br. J. Nutr.* **1997**, *78*, 845–855. [CrossRef]
149. Kennedy, A.D.; DeLeo, F.R. Neutrophil apoptosis and the resolution of infection. *Immunol. Res.* **2009**, *43*, 25–61. [CrossRef]
150. Manz, M.G.; Boettcher, S. Emergency granulopoiesis. *Nat. Rev. Immunol.* **2014**, *14*, 302–314. [CrossRef]
151. Panopoulos, A.D.; Zhang, L.; Snow, J.W.; Jones, D.M.; Smith, A.M.; El Kasmi, K.C.; Liu, F.; Goldsmith, M.A.; Link, D.C.; Murray, P.J.; et al. STAT3 governs distinct pathways in emergency granulopoiesis and mature neutrophils. *Blood* **2006**, *108*, 3682–3690. [CrossRef] [PubMed]
152. Yvan-Charvet, L.; Ng, L.G. Granulopoiesis and Neutrophil Homeostasis: A Metabolic, Daily Balancing Act. *Trends Immunol.* **2019**, *40*, 598–612. [CrossRef] [PubMed]
153. De Filippo, K.; Rankin, S.M. CXCR4, the master regulator of neutrophil trafficking in homeostasis and disease. *Eur. J. Clin. Investig.* **2018**, *48* (Suppl. 2), e12949. [CrossRef] [PubMed]
154. Nauseef, W.M.; Borregaard, N. Neutrophils at work. *Nat. Immunol.* **2014**, *15*, 602–611. [CrossRef]
155. Rijkers, G.T.; Griffioen, A.W. Changes in free cytoplasmic magnesium following activation of human lymphocytes. *Biochem. J.* **1993**, *289*, 373–377. [CrossRef]
156. Brandao, K.; Deason-Towne, F.; Perraud, A.L.; Schmitz, C. The role of Mg2+ in immune cells. *Immunol. Res.* **2013**, *55*, 261–269. [CrossRef]
157. Hass, G.M.; Laing, G.H.; Galt, R.M.; McCreary, P.A. Recent Advances: Immunopathology of Magnesium Deficiency in Rats. Induction of Tumors; Incidence, Transmission and Prevention of Lymphoma-Leukemia. *Magnes. Bull.* **1981**, *3*, 217–228.
158. Jasmin, G. Thymic lymphosarcoma in magnesium-deficient rats. *Biol. Trace Elem. Res.* **1979**, *1*, 217–228. [CrossRef]
159. Averdunk, R.; Bippus, P.H.; Günther, T.; Merker, H.J. Development and properties of malignant lymphoma induced by magnesium deficiency in rats. *J. Cancer Res. Clin. Oncol.* **1982**, *104*, 63–73. [CrossRef]
160. BOIS, P. Tumour of the thymus in magnesium-deficient rats. *Nature* **1964**, *204*, 1316. [CrossRef]

161. Sahin, G.; Ertem, U.; Duru, F.; Birgen, D.; Yüksek, N. High prevelance of chronic magnesium deficiency in T cell lymphoblastic leukemia and chronic zinc deficiency in children with acute lymphoblastic leukemia and malignant lymphoma. *Leuk. Lymphoma* **2000**, *39*, 555–562. [CrossRef] [PubMed]
162. Merza, W.M.; majid, A.Y.; Daoud, M.S.; Jawad, A.M. Serum Magnesium Concentration in Patients with Leukemia and Lymphoma. *Fac. Med. Baghdad.* **2009**, *51*, 101.
163. Guo, C.Y.; Halton, J.M.; Barr, R.D.; Atkinson, S.A. Hypomagnesemia associated with chemotherapy in patients treated for acute lymphoblastic leukemia: Possible mechanisms. *Oncol. Rep.* **2004**, *11*, 185–189. [CrossRef] [PubMed]
164. Afridi, H.I.; Kazi, T.G.; Talpur, F.N. Correlation of Calcium and Magnesium Levels in the Biological Samples of Different Types of Acute Leukemia Children. *Biol. Trace Elem. Res.* **2018**, *186*, 395–406. [CrossRef]
165. Feske, S.; Skolnik, E.Y.; Prakriya, M. Ion channels and transporters in lymphocyte function and immunity. *Nat. Rev. Immunol.* **2012**, *12*, 532–547. [CrossRef]
166. Sahni, J.; Scharenberg, A.M. TRPM7 ion channels are required for sustained phosphoinositide 3-kinase signaling in lymphocytes. *Cell Metab.* **2008**, *8*, 84–93. [CrossRef]
167. Krishnamoorthy, M.; Buhari, F.H.M.; Zhao, T.; Brauer, P.M.; Burrows, K.; Cao, E.Y.; Moxley-Paquette, V.; Mortha, A.; Zúñiga-Pflücker, J.C.; Treanor, B. The ion channel TRPM7 is required for B cell lymphopoiesis. *Sci. Signal.* **2018**, *11*, eaan2693. [CrossRef]
168. Li, F.Y.; Chaigne-Delalande, B.; Su, H.; Uzel, G.; Matthews, H.; Lenardo, M.J. XMEN disease: A new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus. *Blood* **2014**, *123*, 2148–2152. [CrossRef]
169. Ravell, J.C.; Matsuda-Lennikov, M.; Chauvin, S.D.; Zou, J.; Biancalana, M.; Deeb, S.J.; Price, S.; Su, H.C.; Notarangelo, G.; Jiang, P.; et al. Defective glycosylation and multisystem abnormalities characterize the primary immunodeficiency XMEN disease. *J. Clin. Investig.* **2020**, *130*, 507–522. [CrossRef]
170. Blommaert, E.; Péanne, R.; Cherepanova, N.A.; Rymen, D.; Staels, F.; Jaeken, J.; Race, V.; Keldermans, L.; Souche, E.; Corveleyn, A.; et al. Mutations in MAGT1 lead to a glycosylation disorder with a variable phenotype. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 9865–9870. [CrossRef]
171. Ravell, J.C.; Chauvin, S.D.; He, T.; Lenardo, M. An Update on XMEN Disease. *J. Clin. Immunol.* **2020**, *40*, 671–681. [CrossRef] [PubMed]
172. Matsuda-Lennikov, M.; Biancalana, M.; Zou, J.; Ravell, J.C.; Zheng, L.; Kanellopoulou, C.; Jiang, P.; Notarangelo, G.; Jing, H.; Masutani, E.; et al. Magnesium transporter 1 (MAGT1) deficiency causes selective defects in N-linked glycosylation and expression of immune-response genes. *J. Boil. Chem.* **2019**, *294*, 13638–13656. [CrossRef] [PubMed]
173. Chaigne-Delalande, B.; Li, F.-Y.; O'Connor, G.M.; Lukacs, M.J.; Jiang, P.; Zheng, L.; Shatzer, A.; Biancalana, M.; Pittaluga, S.; Matthews, H.F.; et al. Mg2+ Regulates Cytotoxic Functions of NK and CD8 T Cells in Chronic EBV Infection Through NKG2D. *Science* **2013**, *341*, 186–191. [CrossRef] [PubMed]
174. Shechter, M.; Merz, N.B.; Rude, R.K.; Labrador, M.J.P.; Meisel, S.R.; Shah, P.K.; Kaul, S. Low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease. *Am. Heart J.* **2000**, *140*, 212–218. [CrossRef] [PubMed]
175. Ravn, H.B.; Kristensen, S.D.; Vissinger, H.; Husted, S.E. Magnesium inhibits human platelets. *Blood Coagul. Fibrinolysis* **1996**, *7*, 241–244. [CrossRef]
176. Nadler, J.L.; Malayan, S.; Luong, H.; Shaw, S.; Natarajan, R.D.; Rude, R.K. Intracellular free magnesium deficiency plays a key role in increased platelet reactivity in type II diabetes mellitus. *Diabetes Care* **1992**, *15*, 835–841. [CrossRef]
177. Takaya, J.; Yamato, F.; Higashino, H.; Kobayashi, Y. Relationship of intracellular magnesium of cord blood platelets to birth weight. *Metabolism* **2004**, *53*, 1544–1547. [CrossRef]
178. Oliveira, D.C.; Nogueira-Pedro, A.; Santos, E.W.; Hastreiter, A.; Silva, G.B.; Borelli, P.; Fock, R.A. A review of select minerals influencing the haematopoietic process. *Nutr. Res. Rev.* **2018**, *31*, 267–280. [CrossRef]