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A review of select minerals influencing the haematopoietic process

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Abstract

Micronutrients are indispensable for adequate metabolism, such as biochemical function and cell production. The production of blood cells is named haematopoiesis and this process is highly consuming due to the rapid turnover of the haematopoietic system and consequent demand for nutrients. It is well established that micronutrients are relevant to blood cell production, although some of the mechanisms of how micronutrients modulate haematopoiesis remain unknown. The aim of the present review is to summarise the effect of Fe, Mn, Ca, Mg, Na, K, Co, iodine, P, Se, Cu, Li and Zn on haematopoiesis. This review deals specifically with the physiological requirements of selected micronutrients to haematopoiesis, showing various studies related to the physiological requirements, deficiency or excess of these minerals on haematopoiesis. The literature selected includes studies in animal models and human subjects. In circumstances where these minerals have not been studied for a given condition, no information was used. All the selected minerals have an important role in haematopoiesis by influencing the quality and quantity of blood cell production. In addition, it is highly recommended that the established nutrition recommendations for these minerals be followed, because cases of excess or deficient mineral intake can affect the haematopoiesis process.

Key words: Minerals: Trace elements: Haematopoiesis: Blood cells

Introduction

Haematopoiesis is the process of blood cell production. Blood is a tissue with a high renewal rate due to the physiologically short life span of cells in the circulation. The production of these cells is dependent on a highly specialised bone marrow microenvironment, which regulates the quiescence, differentiation and self-renewal of haematopoietic stem cells (HSC)[1–3]. HSC have the ability to proliferate and differentiate to produce progenitor lineage cells and consequently mature to form the following cells: leucocytes (which include neutrophils, eosinophils, basophils, lymphocytes and monocytes), erythrocytes and platelets[2]. This process has a rapid turnover rate and is highly consuming due to the high demand for nutrients needed for constant blood cell production. Specific nutrients are required in each production phase, from the maintenance of HSC self-renewal until the release of mature cells of each lineage into the bloodstream[1–3].

It is well established that macronutrients such as protein, carbohydrates and lipids are required for successful haematopoiesis as blood cells begin forming in the embryo and continue until the end of life. Nutrient requirements are maintained throughout life due to continual blood cell formation and replacement[3–5]. Micronutrients are also relevant to blood cell production: each mineral will be required in distinct production stages of each blood cell lineage. Micronutrients fulfill roles in the differentiation and proliferation processes intrinsic to the complex haematopoietic process, although some of the mechanisms of how micronutrients modulate haematopoiesis are still poorly known.

Furthermore, intake recommendations[6] as well as clinical manifestations, especially with respect to haematopoiesis, in cases of mineral deficiency are usually known. However, in situations where there is increased mineral intake or bioavailability, the effects on haematopoiesis are poorly understood.

The aim of the present review is to highlight the role of the minerals Fe, Ca, Mn, Na, K, Co, iodine, P, Se, Cu, Li and Zn in haematopoiesis, based on data available in the literature and focusing on the effects of these minerals in modulating the haematopoietic process, either positively or negatively. Understanding how micronutrients influence the haematopoietic process is relevant to highlighting the importance of each nutrient in the complex physiology of blood cell production, providing insights regarding the roles of minerals in physiological process such as cell proliferation or in pathologies such as anaemia and leukaemia. The main findings of the present review are compiled in Table 1.

Iron

The first recordings in the literature concerning the presence of Fe in the blood are dated more than one century ago and report

Abbreviations: CFU, colony-forming units; CSF, colony-stimulating factor; EPO, erythropoietin; HIF, hypoxia-inducible transcription factor; HSC, haematopoietic stem cells; IP_3, inositol 1,4,5-trisphosphate; MnSOD, Mn-dependent superoxide dismutase; PLC, phospholipase C. T_3, triiodothyronine; T_4, tetraiodothyronine; TfR1, transferrin receptor 1; TR, thyroid hormone receptor.

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Table 1. Main findings of the effects of minerals on haematopoiesis

Reference	Main findings	Cell or tissue	Species
Fe			
Doty *et al.* (2015)[25]	Haeme excess causes erythroid marrow failure	Erythroblasts	Mouse
Alcantara *et al.* (2001)[26]	Fe deprivation induces apoptosis-related genes inhibition	HL-60 promonocytes	Human cell line
Callens *et al.* (2010)[27]	Fe availability modulates myeloid cell differentiation in normal and pathological conditions	Fresh AML blasts and HL-60 cells, $CD34^+$ cord blood progenitors	Human and mouse
Xie *et al.* (2016)[28]	Fe homeostasis contributes to adjustment of osteoclast development	Bone marrow, osteoclast lineage cells	Mouse
Djeha *et al.* (1993)[29]	Transferrin synthesised by macrophages supports lymphocyte proliferation, eliminating effect of hypoferraemia on the immune system	Lymph node cells, peritoneal cells	Mouse
Kinik *et al.* (1999)[30]	Fe-deficiency anaemia affects CD71 expression in peripheral blood lymphocytes	Blood	Human
Golding & Young (1995)[32]	Intra- and extracellular Fe differentially supports the proliferation of lymphocytes	T lymphocytes	Human
Ali *et al.* (2012)[36]	Fe overload is a complication associated with haematopoietic stem cell transplant and bloodstream infection	Liver	Human
Trottier *et al.* (2013)[37]	Survival or complications in allogeneic transplant are not associated with liver Fe overload	Serum, liver	Human
Lu *et al.* (2013)[38]	Fe overload induces ROS-related signalling protein mediating haematopoietic cell damage	Bone marrow mononuclear cells, umbilical cord-derived mesenchymal stem cells	Human
Efebera *et al.* (2009)[39]	Ferritin level pre-haematopoietic stem cell transplant has an impact on post-haematopietic stem cell transplant	Blood	Human
Tataranni *et al.* (2015)[44]	Deferasirox chelates Fe and induces ROS signalling activation, influencing self-renewal/differentiation of haematopoietic stem cells	Peripheral blood mononuclear cells	Human
Zhang *et al.* (2015)[45]	Fe overload impairs bone marrow microenvironment, including the quantity and quality of bone marrow mesenchymal stem cells	Bone marrow-derived mesenchymal stem cells	Mouse
Mn			
Kizaki *et al.* (1993)[53]	TNF up-regulates the levels of superoxide in haematopoietic cells, leading to cell injury in the absence of Mn-dependent antioxidant enzyme pathways	Cell lines KG-1, HL-60, ML-3, THP-1, HEL	Human
Lebovitz *et al.* (1996)[54]	SOD deficiency leads to haematopoiesis malfunction	Embryos, bone marrow	Mouse
Friedman *et al.* (2001)[55]	Loss of SOD2 in erythroid progenitor cells enhances oxidative damage, damaging membrane, and reducing survival of erythrocytes	Embryos, blood	Mouse
Case *et al.* (2013)[56]	Loss of SOD2 disrupts normal Fe homeostasis	Blood, spleen	Mouse
Ca			
Leon *et al.* (2011)[62]	Ca modulates MEK/ERK pathways, influencing proliferation and differentiation of haematopoietic precursors	Bone marrow	Human and mouse
Adams *et al.* (2006)[63]	Ca-sensing receptor is related to haematopoietic stem cell retention in close physical proximity to the endosteal surface	Haematopoietic stem cells	Mouse
Wölwer *et al.* (2016)[66]	Erythroblasts require Ca uptake to enucleate	Spleen	Mouse
Mg			
Elin *et al.* (1980)[78]	Mg deficiency leads to erythrocyte biochemical and morphological abnormalities	Erythrocytes	Rat
Fedorocko *et al.* (2000)[79]	K and Mg increased spleen erythropoiesis in elderly	Spleen, blood	Mouse
K			
Sing *et al.* (2016)[81]	Impaired ion homeostasis due to altered membrane transporters including functional and compositional changes may be one of the reasons responsible behind rat erythrocyte ageing	Cell membrane	Rat
Brugnara & Tosteson (1987)[84]	K transport plays a role in determining the erythrocyte water and cation content	Erythrocytes	Human
Shirihai *et al.* (1998)[93]	Variable expression of two essential inward rectifying K channels early in the course of haematopoietic progenitor cell differentiation may play a potentially important role in K homeostasis in these cells	Haematopoietic progenitor cells	Human

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Table 1 *Continued*

Reference	Main findings	Cell or tissue	Species
Kettenmann *et al.* (1990)[95]	Cultured microglial cells have a distinct pattern of membrane channels different from peritoneal macrophages	Microglial cells	Human
Wieland *et al.* (1987)[96]	Increase of voltage-activated current in differentiation toward the macrophage	Leukaemia (HL-60) cells	Human
Gallicchio & Murphy Jr (1979)[89]	K increased the number of erythroid progenitor cells	Bone marrow	Murine
Banati *et al.* (1991)[94]	In the bone marrow distinct pools of precursor cells exist, possibly reflecting an early differential lineage determination for body and brain macrophages	Macrophages	Mouse
Lu *et al.* (1993)[98]	The K^+ channels are activated upon the stimulation of proliferation in lymphoid cells exposed to mitogens	ML-1 cells	Human
McCann *et al.* (1987)[97]	Differences in ion channel properties suggest fundamentally different behaviours between these two cell types at the level of the cell membrane	Macrophages and U-937 cells	Human
Furukawa *et al.* (1981)[86]	The enhanced rate of K^+ accumulation in the reticulocyte can be quantitatively attributed to an increased number of pump units	Reticulocyte	Mouse
Canessa *et al.* (1987)[85]	The large volume-stimulated K : Cl efflux in AA (normal Hb) young cells raises the possibility that these fluxes may be involved in the maturation of erythropoietic precursors	Erythrocytes	Human
Shirihai *et al.* (1996)[92]	An essential role for Kir suggested in the process of cytokine-induced primitive progenitor cell growth and differentiation	Haematopoietic progenitor cells	Human
Co			
Andrès *et al.* (2006)[105]	Correction of the haematological abnormalities was achieved in at least two-thirds of the patients, equally well in patients treated with either intramuscular or oral crystalline cyanocobalamin	Peripheral blood	Human
Duckham & Lee (1976)[113]	Therapy with enteric coated cobalt chloride has a definite place in the treatment of the refractory anaemia of chronic renal failure	Peripheral blood	Human
Thorling & Erslev (1972)[109]	Increase in the 24 h Fe utilisation of hyper-transfused rats	Peripheral blood	Mouse
Berk *et al.* (1949)[111]	Co can cause increase of erythropoiesis	Peripheral blood	Human
Iodine			
Flores-Morales *et al.* (2002)[119]	Direct and indirect gene regulation by TR in liver is complex and involves both ligand-dependent and -independent actions by the major TR isoforms	Liver	Mouse
Hara *et al.* (2000)[120]	Cooperative action of T_3 with an RXR-specific ligand is different from that with an RAR ligand in cellular apoptotic regulation	Promyeloleukaemic HL-60 cells	Human
Lin *et al.* (1999)[121]	T_4-directed STAT1α Ser-727 phosphorylation is MAPK mediated and results in potentiated STAT1α activation and enhanced interferon-γ activity	HeLa and CV-1 cells	Human
Golde *et al.* (1977)[127]	Thyroid hormones have a direct effect on erythroid precursor proliferative capacity	Bone marrow	Human and murine
Gruber *et al.* (1999)[128]	Single cells exhibit wide variations in intensity of specific signals for all the receptors investigated	Bone marrow	Mouse
Milne *et al.* (1999)[129]	Three predominant TR isoforms are highly expressed in bone and osteoblasts from femurs and vertebrae	Bone marrow	Mouse
Grymuła *et al.* (2007)[130]	A direct influence of T_3 on haematopoiesis indicated	Cord blood	Human
Kawa *et al.* (2010)[131]	TR expression in human haematopoietic cells depends on thyroid hormone status, both hypo- and hyperthyroidism significantly influence clonogenicity and induce apoptosis in $CD34^+$-enriched haematopoietic progenitor cells	Haematopoietic progenitor cells	Human
Bauer *et al.* (1998)[132]	The crucial role of the mutations activating v-erbA as an oncogene is to 'freeze' c-ErbA/TRα in its non-liganded, repressive conformation and to facilitate its overexpression	Culture media depleted from thyroid hormone (T_3) and retinoids	Human
P			
Raanani *et al.* (2001)[134]	Hypophosphataemia occurs in the post-transplant period, due to an increased consumption by the dividing leucocytes	Blood	Human
Uçkan *et al.* (2003)[135]	Paediatric allogeneic bone marrow transplant leads to hypophosphataemia	Blood	Human
Kovesdy *et al.* (2011)[138]	Higher serum P is associated with anaemia in kidney transplant recipients	Serum	Human

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Table 1 *Continued*

Reference	Main findings	Cell or tissue	Species
Se			
Kaushal *et al.* (2011)[144]	Se nutrition regulates erythrocyte homeostasis and influences differentiation of erythroid progenitors		
Costa *et al.* (2014)[145]	Erythrocyte Se concentration is a predictor of hospital mortality in patients with septic shock	Blood	
Gandhi *et al.* (2014)[146]	Se-dependent modulation influences apoptosis of cancer stem-like cells	Spleen, blood and BRC-ABL + cell line	
Li			
Gallicchio & Chen (1980)[160]	Li may modulate granulopoiesis by increasing the CFU stem cell compartment, thereby increasing the committed progenitor stem cell (CFUc) population	Pluripotential stem cells	Mouse
Gallicchio *et al.* (1995)[161]	Li restricts the development of haematopoietic suppression that develops in this retroviral animal model of immunodeficiency	Peripheral blood progenitors	Mouse
Gallicchio & Murphy Jr (1983)[90]	*In vitro* erythropoiesis reduced in the presence of Li^+	Bone marrow	Murine
Walasek *et al.* (2012)[162]	Combination of valproic acid and Li potently delays differentiation at the biological and molecular levels of expression of stem cell-related genes and repressed genes involved in differentiation	Haematopoietic/progenitor stem cells	Mouse

ROS, reactive oxygen species; SOD, superoxide dismutase; MEK, MAPK/ERK kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; TR, thyroid hormone receptor; T_3, triiodothyronine; RXR, retinoid X receptor; RAR, retinoic acid receptor; T_4, tetraiodothyronine; STAT, signal transducer and activator of transcription; CFU, colony-forming unit.

the existence of Fe in the liver[7]. From the mid-1920s, scientists were engaged in developing a method of measuring the Fe content of different tissues: blood[8], plasma[9] and organs[7]; in addition, the determination of the Fe content of food was also in progress[10,11]. These decades of studies gave rise to the standards of reference values for Fe and many other inorganic compounds, as well as cellular blood parameters, which are used nowadays in clinical laboratories worldwide[12,13]. On this basis, the deficiency parameter of Fe characterised by the reduction of total corporeal Fe and the exhaustion of tissue-level stores can be addressed[14]. Fe deficiency leads to the best-known common micronutrient-derived blood disorder: Fe-deficiency anaemia, which affects nearly two billion individuals, of whom children as well as pregnant women and women of child-bearing age are the most affected populations[13,15].

Fe is provided by food, and its absorption occurs in the superior jejunum and duodenum via the enterocytes, which can retain Fe bound to ferritin protein in the cytoplasm or deliver it to the plasma for distribution to different tissues in the body in a process mediated by the ferroportin transporter[16]. Macrophages also act as a reservoir of Fe but do so differently from the duodenal mucosal cells: they store Fe from phagocytised senescent erythrocytes[17,18]. The placenta is also an important organ for Fe storage during fetal life, when Fe is retained by transferrin receptor 1 (TfR1) present on the apical membrane of syncytiotrophoblasts (and in many other cell types), internalised, and then dissociated and released into the cytoplasm, becoming available for transfer to the fetal circulation[19]. Lastly, the hepatocytes represent the major storage site for Fe, displaying high uptake rates for the non-transferrin-bound Fe present when the Fe exceeds the Fe total binding capacity of transferrin[20,21] (Fig. 1).

Erythropoietic tissue is the major user of Fe, as Fe is essential for haeme as well as Hb synthesis by the reticulocytes (maturing

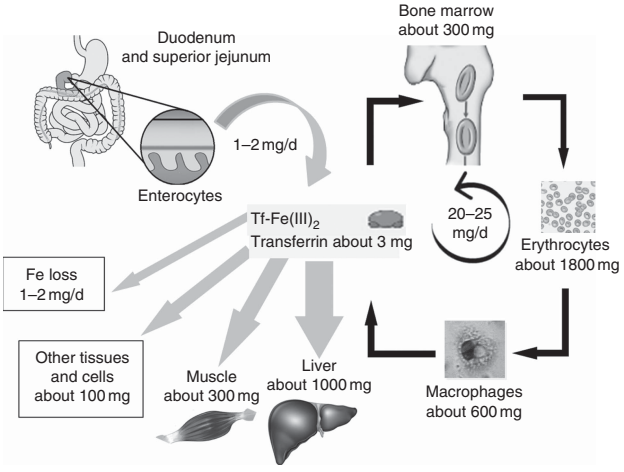

Fig. 1. Iron absorption and metabolism. Most of the iron content is incorporated in erythrocyte Hb, and the hepatocytes represent the main site for iron storage.

erythroblasts); the haeme Fe content of erythrocytes is approximately 1 mg Fe per ml of erythrocytes[1]. The reticulocyte Hb content provides an indirect measure of the functional Fe available for new erythrocyte production, and its measurement in peripheral blood is useful for the diagnosis of Fe deficiency in both adults and children[22]. An imbalance between Hb synthesis and erythroid proliferation results in the production of hypochromic microcytic cells[23]. On the other hand, a lack of the haeme exporter feline leukaemia virus, subgroup C, receptor 1 (FLVCR1) leads to severe macrocytic anaemia[24], which is mechanistically determined by the up-regulation of the TfR1[25].

Fe is also important for the proliferation and differentiation of haematopoietic cells. Upon Fe deprivation, HL-60 (human

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leukaemia cell line) promonocytes bypass differentiation into macrophages/monocytes and increase apoptosis by a process involving greater than 50 % inhibition of the cyclins A, D3 and E1, cdk2, c-myc, Rb, p21 (WAF1/Cip1), bad, egr-1, FasL and iNOS genes[26]. In AML3 promyelocytic leukaemia cells, Fe-chelating therapy induces differentiation in a manner involving modulation of reactive oxygen species and the mitogen-activated protein kinase (MAPK) pathway activation; a similar effect was obtained in an AML patient refractory to chemotherapy, by using Fe-chelating agents and vitamin D_3, resulting in blast differentiation and reversal of pancytopenia[27]. Osteoclast development and Fe homeostasis are also correlated and Fe can act in the proliferation of osteoclast progenitor cells. This involves increasing the levels of transcripts encoding TfR1 and divalent metal transporter 1 and decreasing the levels of transcripts encoding ferroportin[28].

A correlation between Fe and lymphocyte proliferation is widely reported in the literature[29–31]. Intra- and extra-cellular Fe differentially support the proliferation of lymphocytes, dependent on TfR1 mRNA expression rather than on extracellular Fe availability[32]. In addition to TfR1, ferritin is an important component of immune cell function, being involved in binding to T cells, suppression of the delayed-type hypersensitivity to induce allergy, suppression of the production of antibodies by B cells, reduction of the phagocytosis of granulocytes, and regulation of granulomonocytopoiesis. Cytokines (especially TNF-α and IL-1α) induce ferritin gene expression, which in turns requires Fe[33], evidencing the relationship of Fe deficiency with the triggering of several defects in both the humoral and cellular immune response[34]. However, the pro-proliferative effects of Fe on lymphocytes may be analysed and explored distinctly according to the status of the immune system (for example, homeostasis *v.* disease/inflammation), taking into consideration, beyond other factors, the poor ability of lymphocytes to sequester excess Fe in ferritin in Fe-overloaded patients[35].

Much has been described in terms of Fe overload in patients who have received bone marrow transplantation[36–40]. Fe overload results from multiple erythrocyte transfusions due to the lack of an efficient Fe export system[41]. Fe overload may contribute to post-transplant liver toxicity, veno-occlusive disease, infection susceptibility, and graft *v.* host disease and negatively affect cell survival. In this sense, Fe chelators may represent an alternative option for patients with an inadequate haematological recovery[42]. It has been shown that Fe overload affects HSC, decreasing both the erythroid and granulocytic colony-forming units (CFU) and the femoral absolute number of HSC LSK^+ cells, in addition to a diminished long-term and multilineage engraftment capability after transplantation in a process involving the enhancement of oxidative stress, mainly in the HSC LSK^+ cells, erythroid cells and granulocytic cells[43]. Corroborating this finding, several reports are available in the literature evidencing the detrimental effects of oxidative stress on HSC and the components involved in haematopoiesis[38,44,45].

Nitrosative stress is also implicated in this effect. Absence of the antioxidant enzyme haeme oxygenase-1 (HO-1), which catalyses stereospecific degradation of haeme to biliverdin, with release of ferrous Fe and carbon monoxide, disrupts HSC maintenance, reducing its reconstitution capacity[46]. However, although oxidative stress triggered by Fe overload results in damage to the normal haematopoietic cells/environment, it can have positive effects on tumoral HSC and progenitor cells of the same origin; this may not be restricted to HSC, as modulation of the haematopoietic system at the level of Fe metabolism also occurs in mature cell populations. The challenge is to achieve an ideal outcome by using Fe chelators or otherwise inducing Fe overload, improving the haematopoietic system and/or haematological disorders without disturbing the homeostasis of the whole organism[38,44–46].

Manganese

Mn is a mineral with both nutritional relevance and potential toxicity; this ambiguous feature has prompted studies for decades attempting to understand the effects of Mn deficiency and Mn toxicity[47]. Mn functions as a cofactor of multiple enzymes, playing a role in many physiological processes[48]. Mn is a required cofactor for arginase, superoxide dismutase (Mn-dependent superoxide dismutase (MnSOD; also called SOD2) is critical to preventing cellular oxidative stress), as well as pyruvate carboxylase[49,50]. Although its toxicity in many different tissues and organs has been described[51], there is no evidence in the literature concerning damage to the haematopoietic system from direct sources, for example, occupational overexposure, dietary supplementation, or intracorporeal administration. However, an indirect effect of Mn through MnSOD has been reported, as the MnSOD enzyme is dependent on Mn availability[52].

In myeloid leukaemic cells from the HL-60 and K562 lineages, MnSOD provides a protective effect against the cytotoxicity driven by TNF stimuli[53]. MnSOD (SOD2) knockout mice show hypocellular bone marrow associate with a severe anaemia[54]. Loss of SOD2 in erythroid progenitor cells leads to increased oxidative damage, change in the membrane deformation capacity and induction of reticulocytosis[55]. The same study showed that SOD2 reduction affects the bone marrow stem cells' ability to reconstitute haematopoiesis in an irradiated recipient mouse and the long-term cell survival of the animal. More recently, Case *et al.*[56] showed that the loss of SOD2 in HSC causes defects in erythrocyte maturation leading to a compensatory extramedullary haematopoiesis involving disrupted Fe homeostasis and increased mitochondrial oxidative stress, which in turns lead to global epigenetic dysregulation, suggesting a link between mitochondrial redox and epigenetic control of nuclear gene regulation.

Calcium

Since 1883 when studies in London with frogs demonstrated that cardiac contraction was dependent on Ca[57], many later works have shown the importance of this ion for/in cellular functions. It is fully established that Ca controls various cellular functions, due to the great versatility of responses to this ion. Several proteins are modulated directly or indirectly by the action of Ca, such as kinases, phosphatases and transcription factors[58]. Ca acts as a second messenger because of its high

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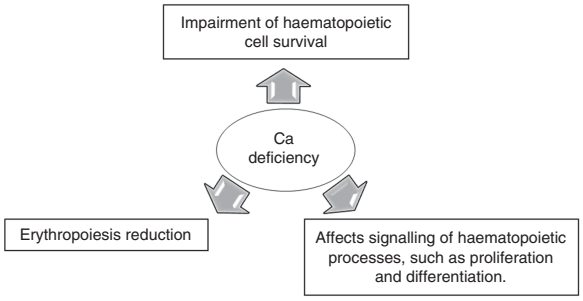

Fig. 2. Main effects of calcium deficiency on the haematopoietic system.

concentration in the extracellular medium and organelles and low concentration in the intracellular environment. Responses may be short-lived like cytokine secretion and muscle motility or contraction but may also be long-lasting like gene transcription, division and cell death[59]. The signs of intracellular Ca are always oscillating. Cells utilise various mechanisms to control cytoplasmic Ca levels[60].

Ca is a signalling ion that regulates various systems, such as haematopoiesis. Even though the participation of Ca in haematopoiesis is still not fully understood, it is known that intracellular Ca acts on the signalling of several processes, such as proliferation, differentiation and cell death[61] (Fig. 2). Cytokine receptors, such as stem cell factor (SCF), erythropoietin (EPO), IL-3, granulocyte macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) can also be activated by Ca signalling. The binding of GM-CSF and IL-3 to their receptors promotes the dimerisation of these cytokine receptors and elicits the Janus kinase/signal transducer and activator of transcription (JAK/STAT) as well as RAS/RAF/ERK pathways[61].

Intracellular Ca can also be released by the activation of phospholipase C (PLC) γ2 through cytokines or PLCβ by ATP and analogues, producing inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). These second messengers (IP_3 and DAG) act synergistically to cause the phosphorylation of proteins necessary for the processes of proliferation and differentiation of haematopoietic cells. In addition, DAG appears to act by increasing the affinity of protein kinase C for Ca and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), proteins involved with the proliferation and differentiation of primitive haematopoietic cells[62]. The Ca-sensing receptor (CaSR) is critical for retaining HSC near the endosteal region, possibly mediating the association of HSC with collagen type I. It was also observed that HSC detect relatively high levels of Ca (up to 40 mmol/l) through CaSR[63]. Upon detecting changes in Ca concentrations, cells promote the release of Ca from the stocks in the endoplasmic reticulum and mitochondria through specific channels to the cytosol or extracellular medium, in order to maintain cellular homeostasis[64].

Studies in zebrafish have shown that cytokinesis requires intracellular Ca signalling and signal transduction via the calmodulin pathway (CaM)[65]. In addition, erythropoiesis requires Ca signalling for nuclear extrusion. The uptake of extracellular Ca is fundamental for the enucleation in the orthochromatic erythroblasts[66]. The maturation of erythrocytes is highly impaired with intracellular Ca deficiency. This evidence leads us to believe that a lack of Ca can lead to nutrient-deficiency anaemia[66]. Although calcimimetic drugs imitate the action of Ca on the tissues by allosteric activation of the Ca receptor, no direct or indirect beneficial effects of these drugs on anaemia due to chronic disease have been observed[67].

Barbosa *et al.*[68] also demonstrated the role of the Ca signalling pathway without myeloid involvement, relating an action of protein kinase C and PLCγ2 with M-CSF and G-CSF-mediated differentiation activated by cytokines. In addition, PLCβ2 is activated by ATP. Both PLCγ and PLCβ induce release of intracellular Ca via IP_3 formation. Increased intracellular Ca induced by G-protein (P2Y)-coupled receptors and ATP-activated ion channels (P2X) is also related to myeloid differentiation[69]. ATP induces differentiation of HSC in the myeloid lineage, and this effect is modulated by cytokines such as SCF, IL-3 and GM-CSF[70].

Understanding the role of Ca in haematopoiesis is fundamental to perceiving the mechanisms of cell proliferation and differentiation as well as changes resulting from deficiencies in this process. Mechanisms of the haematopoietic system are complex, and Ca-dependent mechanisms are still under investigation.

Magnesium

Since 1975, Mg has been considered a key factor in the so-called 'coordinated growth and metabolism response', i.e. the up-regulation of energy metabolism and the synthesis of proteins and DNA that precedes cell division[71]. The large amount of Mg in the intracellular medium reflects its involvement with phospholipids, proteins, nucleic acids and a wide range of biological functions and enzymic reactions[72,73]. Mg is important for cell cycle regulation, particularly at the beginning of DNA synthesis and mitosis, in both micro-organisms and mammals. In addition, it has been reported that cell transformation can cause selective loss of this regulatory function for Mg, implying that Mg is important in oncogenesis[74]. Mg concentration has a significant positive correlation with the protein synthesis rate, suggesting a key role of Mg in the regulation of protein synthesis and in the cell proliferation rate in normal tissue cell populations[75].

Studies with interferon-α and ATP stimuli demonstrate a correlation with Ca metabolism, promoting signalling that activates phospholipase A (PLA) by inducing arachidonic acid release from the cell membrane. The prostaglandins produced by arachidonic acid through cyclo-oxygenase stimulate adenyl cyclase, which synthesises cAMP. Intracellular Mg may influence adenyl cyclase, down-regulating the same efflux of Mg. Modulation of cellular Mg homeostasis parallels the molecular control of cell proliferation, differentiation and death[76].

The physiological process of haematopoiesis has a characteristic high turnover, so it is expected that the demand for Mg is high. Mg deficiency may promote defects in platelet biogenesis due to changes in the cytoskeleton, promoting changes in platelet function. In addition, changes in the transient receptor potential melastatin 7 ion channels (TRPM7) may cause macrothrombocytopenia in human subjects and in

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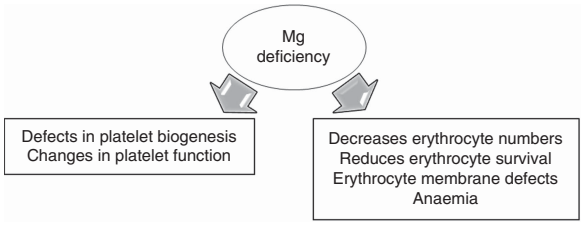

Fig. 3. Main effects of magnesium deficiency on the haematopoietic system.

mice[77]. Rats fed with a diet deficient in Mg show decreased erythrocyte numbers in addition to reduced erythrocyte survival and erythrocyte membrane defects and become anaemic[78] (Fig. 3). Mg and K administration promotes accelerated restoration of spleen erythropoiesis in irradiated rats[79]. However, the pathological processes that cause these changes are unknown. Few studies have correlated Mg with haematopoiesis. Research showing this relationship should be encouraged to better understand the mechanisms involved in the regulation of important cellular functions, such as cell proliferation and differentiation.

Sodium and potassium

Homeostatic regulation is critical for all cellular functions, primarily for cell viability. The electrochemical Na and K gradient is crucial for ionic homeostasis and is regulated by the transmembrane protein Na^+K^+-ATPase[80,81]. Erythrocyte maturation is linked to changes in cell volume, regulated by pump Na^+K^+-ATPase and K^+Cl^- co-transport. The enhanced activity of the Na/K pump is observed in reticulocytes and decreases during cell maturation[82,83]. Reticulocytes are characterised by higher cellular volume due to enhanced K turnover, which is increased approximately 3-fold compared with that of mature cells[84–86]. During maturation and ageing, the loss of cellular K^+ by K^+Cl^- cotransport decreases reticulocyte and erythrocyte volume[87]. One of the reasons for increased Na/K pump activity might be a functional demand to keep pace with augmented Na leak[88].

K is important for erythroid colony formation and maintenance of self-renewal of erythroid stem cells and their differentiation *in vitro*[89,90]. In Friend erythroleukaemia cells, a widely used model of murine erythropoiesis, exposure to high K and low Na levels is capable of completing erythroid differentiation, suggesting that cell maturation involves a selective change in K permeability[91]. K inward rectifier channels are essential for the development of $CD34^+/CD38^-$ primitive haematopoietic cells[92,93]. Because these channels are not detected in most mature haematopoietic cells, their transient expression in primitive cells suggests that their role is in the early stages of HSC differentiation[94,95]. The differentiation of some leukaemic myeloid lineage cells is also correlated with K channels. Promyelocytic HL-60 cells present a slow-inactivated K channel[96], and promonocytic U-937 cells exhibit abnormal conductance in K channels[97]. On the other hand, in myeloid ML-1 cells, K current is suppressed during cell differentiation[98]. Few studies have correlated Na and K with haematopoietic differentiation. Understanding the signals involved in this regulation can lead us to elucidate molecular mechanisms and develop novel strategies to control haematological disorders.

Cobalt

Co is a metal with chemical properties similar to Fe and Ni[99]. Metal ions perform a wide role in natural proteins, including nucleophilic catalysis, electron transfer as well as the stabilisation of protein structure[99,100]. Co is a fundamental component in the tetrapyrrole ring of hydroxocobalamin (vitamin B_{12}), which is an essential coenzyme of cell mitosis, acting on the synthesis of methionine and metabolism of folates and purines[101–104]. Under conditions of hydroxocobalamin deficiency, haematopoiesis is widely affected and erythropoiesis turns ineffective because erythrocytic progenitors cannot mature adequately. This has implications for the development of megaloblastic anaemia and hypofunction of erythrocytic cells[105,106]. However, Co does not only participate in haematopoiesis via hydroxocobalamin but also acts in inorganic forms (Co^{2+}), usually $CoCl_2$ or $CoSO_4$. In 1929, Waltner & Waltner[107] showed that Co stimulates erythropoiesis and induces polycythaemia in animal models. Weissbecker[108] related increases in reticulocytes, erythrocytes, and Hb, as well as bone marrow erythroid hyperplasia, in oral administration of Co salts. In addition, Co induces EPO and blocks iodine uptake by the thyroid[102].

Co is considered one of the most reliable and potent stimulators of erythrocyte production[109]. Co enhances erythropoiesis by indirect activation of EPO gene expression. Co binds to hypoxia-inducible transcription factors (HIF), and this association inhibits the proteasomal degradation of HIF by von Hippel–Lindau (pVHL) proteins. The accumulation of HIF promotes the dimerisation of HIF-2α and HIF-1β subunits in the nucleus and powerfully activates EPO expression[110].

Co has been used extensively since the late 1970s in the treatment of several types of anaemia in children and adults, as well as in anaemia of chronic renal disease[111,112]. However, soluble Co salts are toxic to the human body, and because of the side effects associated with chronic Co use, Co is rarely used nowadays, since the administration of Co is shown to induce DNA damage and promote the development of carcinomas[113–115].

Iodine

Iodine is a vital micronutrient required at all stages of life, promoting general growth and development within the body as well as aiding in metabolism. In addition, iodine is an essential constituent of the thyroid thyroxine hormones (tetraiodothyronine (T_4) and triiodothyronine (T_3))[116]. Iodine acts indirectly on haematopoiesis, through thyroid hormones and prohormones, which are the only known iodine-containing compounds with biological activity. The thyroid gland produces T_4 and T_3, which are largely known to control metabolism, with emphasis on renal and cardiac function. Furthermore, thyroid hormones handle carbohydrate and fat metabolism, protein synthesis and fetal neurodevelopment[117,118].

At the cellular level, thyroid hormones undergo several metabolic reactions by different cytosolic enzymes and play a role in a variety of cellular pathways and functions, comprising insulin

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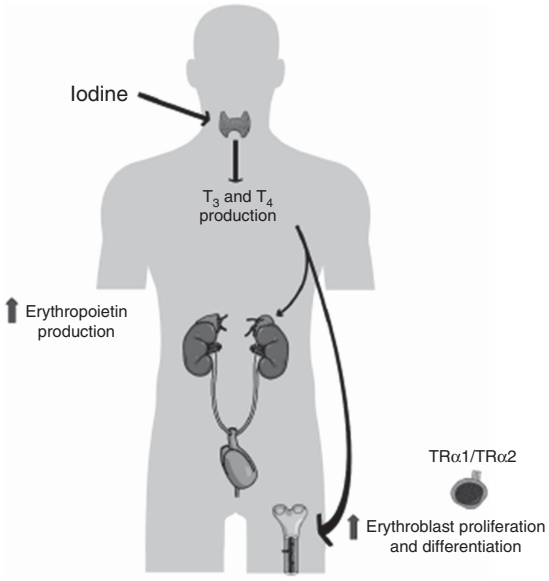

Fig. 4. Iodine is an essential constituent of the thyroid thyroxine hormones. Thyroid hormones classically stimulate erythropoiesis by increasing the oxygen demand on the kidneys and stimulating erythropoietin production. T_3, triiodothyronine; T_4, tetraiodothyronine; TR, thyroid hormone receptor.

signalling, apoptosis, the cell cycle and proliferation[119–122]. Kocher[123] first described the haematological findings of thyroid abnormalities, which showed that hyperthyroidism patients presented leucopenia, relative lymphocytosis and neutropenia. Since then, several studies have correlated thyroid diseases and haematopoiesis, but this relationship is complex and some studies are inconclusive or present important limitations.

Thyroid hormones classically stimulate erythropoiesis by increasing the oxygen demand on the kidneys and stimulating EPO production[124] (Fig. 4). That is why normocytic normochromic anaemia is associated with hypothyroidism, and hyperthyroidism frequently coincides with erythrocytosis and erythroid hyperplasia on bone marrow[125,126]. It was unclear if thyroid hormones acted exclusively by way of EPO or could also act on haematopoietic progenitor cells until Golde *et al.*[127] demonstrated that T_3 and T_4 directly stimulate mice erythroid colony formation *in vitro*. Thereafter, the expression and activity of thyroid hormone receptors (TR) were reported in mature bone marrow cells in both rats and mice[128,129].

In humans, TRα1 and TRα2 are important for fate determination in haematopoietic progenitors. TRα1 and TRα2 receptors are expressed on $CD34^+$ haematopoietic cells and regulate apoptosis and cell growth[130,131]. In erythroblasts, the activation of these receptors induces proliferation and accelerates cell differentiation[132] (Fig. 4). The mechanisms by which thyroid hormones regulate haematopoiesis *in vivo* are not fully understood. Novel insights into the interactions between T_3 and T_4 and the classical haematopoietic inductors are required, so we can develop ways of intervening in both haematological and thyroid disorders.

Phosphorus

P plays a major role in physiological functions, including energy production, cellular replication and bone mineral metabolism[133]. It is well established that rapid cell synthesis and turnover may be associated with high phosphate consumption. Low levels of phosphate leading to hypophosphataemia are associated after bone marrow transplantation[134,135]. Although different research groups affirm the correlation between hypophosphataemia in bone marrow or stem cell transplantation, there are few data available in the literature offering a concise explanation of how the decreased level of phosphates can affect haematopoiesis.

Raanani *et al.*[134] emphasised that the release of cytokines, such as IL-6 and IL-8, is commonly associated with the development of hypophosphataemia observed in HSC transplant. The explanation for the hypophosphataemia observed was that it was due to phosphate consumption by proliferating cells after bone marrow HSC transplantation in human subjects[134–137]. Increased P levels can be harmful to the haematopoietic process. Recent studies state that higher P serum levels increase the likelihood of anaemia. EPO deficiency, inflammation and oxidative stress have been implicated as potential factors associating hyperphosphataemia and anaemia. The possible mechanisms linking hyperphosphataemia and anaemia were described in 2011 by Kovesdy *et al.*[138], who suggested that high serum P may lead to a higher production of polyamines, which can function as uraemic toxins inhibiting erythropoiesis[138,139].

Another possible mechanism is that high serum P leads to vascular calcification within renal arteries, which may eventually result in EPO deficiency and anaemia[133,140]. All these results highlight that increased levels of P can modulate haematopoietic functions. However, there is a lack of data in the literature clearly explaining how hyperphosphataemia affects the production of erythrocytes. Low dietary intake, decreased absorption or increased urinary phosphate excretion and shifts of phosphate from the extracellular into the intracellular fluid are conditions known to induce moderate hypophosphataemia[134].

Selenium

Se is a chemical element and can be determined in blood, plasma or serum, and by assaying the activity of the selenoprotein glutathione peroxidase (GPx) in whole blood or platelets[141,142]. Se is a trace element that exerts crucial effects on erythropoiesis. The cells that exhibit higher Se consumption are those of the haematopoietic system, such as immune cells, erythrocytes and platelets[141] Se is an important component of GPx, which assists in intracellular defence mechanisms against oxidative damage by preventing the production of reactive oxygen species. It is known that Se is not restricted to its antioxidant function but is also involved in multiple other aspects of human metabolism[142,143].

Haematopoiesis is characterised by tight control of cell expansion, with differentiation and maintenance of progenitors. These processes expose the cells to oxidative stress, and this could possibly affect erythropoiesis because Hb is prone to oxidative damage[144]. Se functions as an antioxidant through selenoproteins, preventing erythrocyte lysis. Alterations in the physiological levels of Se are usually linked with numerous pathological conditions, associated with oxidative stress[141,142,144]. Se deficiency is associated with increased denaturation of Hb as well as increased methaemoglobin content, protein carbonyls,

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lipid peroxidation, Heinz bodies and increased erythrocyte osmotic fragility[144].

Forkhead transcription factor (FoxO3a) is one of the most expressed protein in erythroid cells and is essential for the maintenance of the HSC pool. Se status is important in erythrocyte homeostasis by modulating FoxO3a localisation, which is pivotal for mitigating oxidative stress in erythroid cells[144]. Erythrocyte Se concentration is correlated with hospital mortality in septic shock patients. In addition, erythrocyte Se concentrations can be a predictor of mortality in patients with septic shock[143,145].

Gandhi *et al.*[146] demonstrated that Se-dependent modulation of arachidonic acid metabolism can trigger apoptosis of primary leukaemic cells. The pro-apoptotic effects of Se were, in part, related to exacerbated oxidative stress in leukaemia stem cells that involved NADPH oxidases, particularly Nox1. In contrast, Se treatment did not affect normal HSC, suggesting that leukaemic cells are uniquely sensitive to changes in intracellular reactive oxygen species[146].

Although environmental toxicity of Se in humans is rare, clinical signs such as hypochromic anaemia, leukopoenia, damaged nails, and others have been found in long-term workers who manufacture Se rectifiers[141,142,147]. Many researchers have shown that Se supplementation provides positive effects on the general cellular condition. Se plays crucial roles in the physiology of blood formation and pathologies such as cancer; however, the mechanism of action has yet to be unveiled[143].

Copper

Cu is an important mineral in body metabolism, largely because it allows many critical enzymes, such as cytochrome C oxidase, superoxide dismutase, tyrosinase, peptidylglycine α-amidating mono-oxygenase, and lysyl oxidase, to function properly[148,149]. Cu is essential for normal haematopoiesis, and common features of Cu deficiency include anaemia, leucopenia and neutropenia[149] (Fig. 5). The involvement of Cu in haematopoiesis is also inferred from inherited or acquired Cu deficiency due to genetic mutations or malnourishment, respectively, which causes neutropenia, anaemia and thrombocytopenia due to arrested differentiation at the haematopoietic progenitor cell level[150]. However, nutritional Cu deficiency is extremely rare and occurs in newborns, usually premature, undergoing rapid growth on a diet poor in Cu or in patients receiving parenteral nutrition for long periods of time without Cu supplementation. Although it is rare, Cu deficiency causes hypochromic anaemia unresponsive to Fe supplementation[151,152]. Cu is essential for normal haematopoiesis; however, the effects of fine-tuning of intracellular Cu content on the regulation of self-renewal and differentiation of HSC and progenitor cells are unknown[153,154].

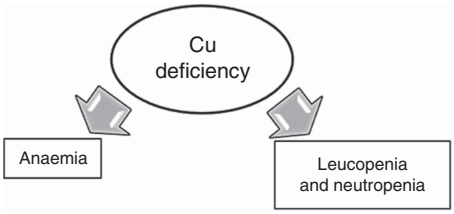

Fig. 5. Main effects of copper deficiency on the haematopoietic system.

Studies with HSC and haematopoietic progenitor cells cultured with the Cu chelator tetraethylenepentamine (TEPA) have suggested that reducing the cellular Cu content with TEPA results in preferential expansion of HSC activity in contrast to arrested differentiation, directly affecting blood cell populations[149]. In addition, several mechanisms have been proposed for the role of Cu in Fe metabolism and erythropoiesis. Cu is required for the formation of erythrocytes, as Cu deficiency results in anaemia, possibly due to chronic ingestion of high amounts of Zn, which impairs Cu absorption[154]. The literature also shows that serum Cu concentrations have an important relationship with blood leucocyte counts and serum Fe parameters. Studies have shown that the addition of Cu increases retinoic acid-induced differentiation of the HL-60 cell line[149,153].

Lithium

Li is a mineral that can modulate the haematopoietic process directly[155]. Studies have shown that ingestion of Li increases the production of neutrophil granulocytes, showing that nanomolar levels of Li can stimulate clonal proliferation of granulocyte precursors[155–158]. The effects of Li on haematopoiesis are not cell-lineage specific. *In vitro* studies have shown that Li enhances colony formation (CFU) of the erythrocyte precursor (CFU-E), the megakaryocyte precursor (CFU-Meg) and the granulocyte macrophage precursor (GM-CFU)[157,158]. Patients treated with Li for manic–depressive illnesses usually develop leucocytosis with increases in peripherical neutrophils and eosinophils and, commonly, monocytes and platelets also tend to be increased; however, lymphocytes and erythrocytes are usually unaffected[159,160].

In addition, a CFU assay performed with bone marrow cells has shown a higher capacity for the formation of CFU[160]. Additionally, mice infected with LP-BM5 murine leukaemia virus (MuLV) and treated with Li showed increased neutrophils and eosinophils in the peripheral blood; moreover, haematopoietic progenitor cells collected from the bone marrow and spleens of these animals showed increased GM-CFU formation[161]. However, high doses of lithium carbonate (greater than 5 mM) can have opposite effects leading to a reduction of the granulocytes in peripheral blood and lower formation of CFU[160,162].

Zinc

Zn is required in the structure and activity of more than 300 enzymes including DNA polymerase, Cu–Zn superoxide dismutase, alkaline phosphatase, alcohol dehydrogenase, carbonic anhydrase and protein chain elongation factor[163]. This mineral is used in nucleic acid and protein synthesis, cell differentiation and replication, non-glucose metabolism and insulin secretion. The Zn requirement of numerous proteins makes it is essential for growth, tissue maintenance and wound healing. Proper Zn intake is critical for the integration of many tissues and systems, such as gastrointestinal, muscular, immune, reproductive and

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behavioural, as well as involved in the wound-healing process[164–166].

Zn can act as a signal to induce erythropoiesis in a dose-dependent manner[167]. In addition, serum Zn levels have a negative effect on anaemia by blocking the utilisation of Fe of anaemic patients[168]. It should be noted that chronic Zn infusion can induce Cu deficiency and sideroblastic anaemia, decreased plasma caeruloplasmin and microcytic anaemia[169].

On the other hand, Zn deficiency occurs in a wide range of pathologies, including haemolytic anaemias such as thalassemias and sickle cell anaemia. Zn deficiency exerts its most profound effects on rapidly proliferating tissues. Severe deficiency is usually accompanied by growth arrest, teratogenicity, hypogonadism and infertility, and commonly but not exclusively with impairment of cellular immunity[169]. Substantial depletion usually occurs in cells of the erythroid and lymphoid lineages, and evaluating the phenotypic distribution of cells of the B-lineage it has been shown that Zn deficiency alters the composition as well as the phenotypic distribution of the remaining cells of the B-lineage. Zn deficiency also reduces immature or IgM-bearing B-cells, whereas the earliest B-cell progenitors are somewhat resistant to the deficiency. In addition, the ratio CD4/CD8 in the thymus is affected[170,171]. However, myelopoiesis is not disrupted in Zn deficiency, as shown by the expansion of all myeloid populations in the bone marrow of Zn-deficient patients[171,172]. Zn deficiency has been reported in patients undergoing intensive therapy with desferrioxamine, an Fe chelator that aims to reduce or stabilise non-body Fe accumulation, and in patients with decreased renal reabsorption of trace minerals.

Conclusion

Minerals are mandatory for the development of effective haematopoiesis, and the absence of these elements can have a deep impact on blood cell formation and/or blood cell functions. In contrast, mineral excess can also be harmful, although the majority of the complete mechanisms that can be disrupted by an excess of minerals are poorly understood. It is crucial to assess whether minerals can interfere to correct haematopoietic functions, providing better therapeutic care in several nutritional and haematopoietic diseases. More research is required to provide data unveiling the roles of minerals in diverse aspects of haematopoiesis.

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The authors have no conflicts of interest to declare.

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