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Review

A storm in the niche: Iron, oxidative stress and haemopoiesis

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ABSTRACT

Iron, although essential, is harmful in high amounts. Oxidative stress as a result of excess reactive oxygen species (ROS) and a prooxidative/antioxidative imbalance between ROS production and elimination, play a key role in cellular damage. There is evidence to support the role of ROS in the pathogenesis of a range of diseases including the myelodysplastic syndromes (MDS) and leukaemia. Oxidative stress seems to affect the self-renewal, proliferation and differentiation of haematopoietic stem cells and impair cell growth. Three aspects of these defective haemopoietic mechanisms may be associated with the activities of ROS: clonal evolution, haematological improvement and recovery of haemopoiesis after haematopoietic stem cell transplantation (HSCT). This review aims to provide haematologists with an overview of results from in vitro and murine models and preliminary clinical evidence on the diagnostic, prognostic and therapeutic implications of the complex interactions between the haemopoietic niche, iron, oxidative stress and inadequate haemopoiesis.

1. Introduction

Iron is fundamental for many cellular functions such as the cell cycle of growth and replication, metabolism and DNA synthesis/repair and iron-requiring proteins such as Fe-sulphur cluster proteins that are abundant in mitochondria [1]. However, the ability to gain and lose electrons gives iron the possibility of participating in potentially harmful free radical-generating reactions, producing the hydroxyl radical (OH) – a reactive oxygen species (ROS) based on the Fenton reaction [2]. The hydroxyl radical, the most reactive chemical species in biological systems, when present in excess, can not only damage lipids, proteins, and mitochondria but also cause oxidative DNA damage including DNA base modifications and DNA strand breaks [3,4], all of which can be mutagenic [5]. ROS levels are regulated by pro-oxidant and anti-oxidant systems and a correct balance between these two mechanisms is essential for cellular life.

The modern history of redox biology began with the discovery by McCord and Fridovich in 1969 of superoxide dismutase – an enzyme that promotes ROS production [6]. Later in 1985 the term oxidative stress was coined by Sies and Cadenas [7]. Greater knowledge of the effects of ROS activities has shed light on the role of iron and oxidative stress in cellular lifecycle and has revealed 'the dark side of iron' – an essential but potentially toxic element.

There is now a substantial body of literature supporting the role of ROS in the pathogenesis of many diseases and in particular those related to cell proliferation and differentiation such as the myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) [8,9]. Iron overload, caused by ineffective erythropoiesis, increased gastrointestinal iron intake and transfusion dependency allow us to consider the MDS as the ideal disease model to try to understand the complex relationship between the haemopoietic niche, iron, oxidative stress and inadequate haemopoiesis. This review aims to provide haematologists with an overview of results from in vitro and murine models and preliminary clinical evidence on the diagnostic, prognostic and therapeutic implications of the complex interactions between the haemopoietic niche, iron, oxidative stress and inadequate haemopoiesis.

2. Cellular activities of ROS

Iron from gastrointestinal intake and blood transfusions is typically bound to transferrin when it circulates in the plasma. This complex is internalized by different tissue cells through the transferrin receptor and the iron-transferrin complex is then split and the free iron form, called labile cellular iron (LCI), is used by the cell for vital functions such as mitochondrial energy production. Excess iron is generally accumulated as ferritin and hemosiderin [10]. Under normal physiological conditions mitochondrial respiration is the main source of ROS within the cell during adenosine triphosphate (ATP) production. Other major sources of ROS in vivo are the enzymatic activity as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [9] or activated phagocytic cells [11]. If the level of LCI increases it is responsible

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for potentially dangerous free radical-generating reactions, with the production of the hydroxyl radical and ultimately leading to cellular death and consequent tissue damage [12].

Essentially, when the transferrin saturation excess is more than 60–70%, non-transferrin bound iron (NTBI) and its subcomponent labile plasma iron (LPI) appear in the serum [13]. LPI ability to enter the cells through alternative channels (other than transferrin receptor canals), results in an increase in LCI levels. When ROS production exceeds the antioxidant enzyme systems, an excessive accumulation of ROS occurs, leading to intracellular oxidative stress [14]. This biochemical model seems to be at the basis of liver, heart, endocrine gland tissue damage. However, it has only recently been considered that bone marrow, and consequently haemopoiesis, could be another important target for iron-mediated damage [15]. There are in vitro data showing that in haematopoietic stem cells in the MDS and AML and other tumours the constitutional ROS balance is often defective [16,17]. An interesting in vitro study, showed that various molecules involved in cell metabolism (such as kinases, phosphatases or transcription factors) are considered crucial regulators of ROS levels and at the same time redox sensor molecules [14]. In other words an oxidative abnormality, in one or more of the different signals in which these molecules are involved (mostly present in tumours), may alter the key metabolic pathways related to stem cell fate, changing processes that regulate cell cycle progression, apoptosis, quiescence or differentiation [14]. The basic idea is that cellular toxicity does not result directly from storage iron, but from the disruption of the dynamic balance that exists between storage iron pool and functional iron pool [18].

3. The haematological niche in normal conditions

Haematopoietic stem and progenitors cell reside within the so called 'haemopoietic niche', defined as cellular and molecular microenvironments that collaborate through cell mechanisms to maintain and regulate stem cell functions, ensuring stem cell growth, proliferation and differentiation. The haematological niche is ideally divided in an osteoblastic marrow compartment and a vascular marrow compartment. Haematopoietic stem cell growth is a two-phase process – a quiescent phase (when the cell cycle is in G0 phase) and an activated phase (when the cell cycle is in G1-G2-S-M phase). At this particular point of the cell cycle, the haematopoietic stem cell can choose to return to the quiescent phase or proceed from the activated phase to proliferation and differentiation (self-renewal). Haematopoietic stem cells are found mainly adjacent to sinusoids when in the activated phase and near the osteoblastic cells compartment when in the quiescent phase [9].

Endothelial cells, mesenchymal stromal cells, macrophages and perivascular stromal cells promote haematopoietic stem cell self-renewal by producing stem cell factor (SCF), CXCL12 and other regulating factors. It is likely that other cells also contribute to this niche, probably including cells near bone surfaces in trabecular rich areas. All the support elements (endothelial cells, mesenchymal stromal cells, macrophages, osteoclast/osteoblast) are essential to haematopoietic stem cell growth. The cross-talking between these elements guarantees a correct haematopoietic stem cell growth [19].

Recent studies suggest that ROS plays a role in haematopoietic stem cell state and function and it has been well described how ROS levels are essential to maintain the self-renewal of stem cells [11]. Haematopoietic stem cells in the quiescent phase need low ROS levels and low NOX enzyme expression, but when enter the activated phase, it is necessary they to proceed from the periosteal hypoxic area to the sinusoid area following an oxygen gradient. This increase in ROS (associated with the oxygen gradient) is essential for the activated phase and elevated ROS levels appear to drive haematopoietic stem cells out of quiescence and reduce self-renewal capacity. The stem cell distances itself from the osteoblastic interface of the niche where the microenvironment encourages quiescence and goes close to the vascular side of the niche, through oxygen gradient, where the microenvironment favours proliferation and differentiation. This migration of haematopoietic stem cells seems to be governed by ROS levels and the interaction of chemokines [9]. It is important to underline that ROS play a decisive physiological role in haematopoietic stem cell self-renewal, migration, maturation and differentiation.

4. The haematological niche in oxidative stress conditions

Ludin and colleagues [11] showed in vitro how oxidative stress influences the fate of haematopoietic stem cells by compromising migration, development, self-renewal and cell cycle status. The hypoxic conditions [20] and several environmental factors (HIF1, COX2, PGE2, CCXCR4, CXCL12) [21] participate to maintain low ROS levels. However extremely low ROS levels in haemopoietic stem cells can cause defects in their differentiation ability leading to impaired repopulation capacity [22]. On the other hand increases in ROS levels, drives stem cell differentiation to short term repopulating cells and further on to myeloid differentiation [23,24]. Exceedingly high ROS levels, as may occur during important oxidative stress conditions such as chronic inflammation or iron overload, can promote stem cell exhaustion and subsequent apoptosis [25]. The overall message of these studies is that haematopoietic stem cells quiescent and active state is a balance between ROS levels – 'too much' or 'too little' ROS seems be a determining factor in the fate of many pathways critical to cell survival and proliferation [9]. In essence ROS balance may determinate stem cell destiny (Fig. 1).

Similar effects have been described with osteogenic progenitors and differentiation of mesenchymal stem and progenitor cells [26,27]. Bulycheva and colleagues described the direct connection between haematopoietic stem and progenitor cells (HSPCs) and osteoblast/osteoclast activity in the haematopoietic niche, introducing the concept of osteo-haematology. They described how a disturbed microenvironment (including osteogenic elements) might affect haematopoietic stem cell growth modifying the cross talking between the haematopoietic niche components [28]. In a myelodysplastic mouse model, they reported decreased osteoblasts and osteoclasts number and decreased bone formation rate. In particular, they identified iron overload as responsible for osteoblast inhibition and increases in osteoclasts. They concluded that oxidative stress is involved in the pathogenesis of bone loss during iron excess and that oxidative stress may affect the relationship between haematopoietic cells and the microenvironment in MDS [28].

Taken together these results suggest it is reasonable to consider that iron overload and the consequent increases in ROS levels could impair haematopoietic stem cell self-renewal, proliferation and differentiation by distressing oxygen gradient and impairing the microenvironment cell growth, including osteogenesis.

5. Possible clinical implications of ROS activity in the haemopoietic system

Three important aspects of haematopoiesis may be associated with altered levels of ROS: clonal evolution, haematological improvement and haematopoietic cell transplantation engraftment (Fig. 2). We summarize and link the in vitro and in vivo evidence supporting the role of ROS in these three different circumstances.

5.1. Clonal evolution

5.1.1. In vitro results

Inadequate ROS homeostasis, resulting in oxidative stress and genetic instability in haematopoietic stem cells and myeloid progenitors, has been linked with myeloid malignancy [29–32]. The notion that ROS may drive stem cell dysfunction with age draws precedence from the free radical theory of ageing, first described by Harman in 1972 [33]. Cellular ageing is associated with reduced organ function, increased oxidative stress, genomic mutations and increased incidence of certain