One Tool to Retrieve Them All

Fully automated and uniquely versatile cell imaging and retrieval system to simplify your antibody, rare-cell and stem-cell research.

With CellCelector Flex, you have everything you need for imaging, screening, retrieving and verifying target cells in one place.

It’s an all-in-one solution that reduces steps, streamlines workflows, and accelerates processing - while capturing cells without damage and enabling incredibly high viability.

Learn More About CellCelector
Iron in blood cells: Function, relation to disease, and potential for magnetic separation

Sowrav Barua1 | Stefano Ciannella1 | Lukman Tijani2 | Jenifer Gomez-Pastora1

1Department of Chemical Engineering, Texas Tech University, Lubbock, Texas, USA
2Department of Medical Oncology, Division of Hematology and Medical Oncology, Texas Tech University Health Sciences Center, Lubbock, Texas, USA

Abstract

Iron in blood cells has several physiological functions like transporting oxygen to cells and maintaining iron homeostasis. Iron is primarily contained in red blood cells (RBCs), but monocytes also store iron as these cells are responsible for the recycling of senescent RBCs. Iron also serves an important role related to the function of different leukocytes. In inflammation, iron homeostasis is dependent on cytokines derived from T cells and macrophages. Fluctuations of iron content in the body lead to different diseases. Iron deficiency, which is also known as anemia, hampers different physiological processes in the human body. On the other hand, genetic or acquired hemochromatosis ultimately results in iron overload and leads to the failure of different vital organs. Different diagnoses and treatments are developed for these kinds of disorders, but the majority are costly and suffer from side effects. To address this issue, magnetophoresis could be an attractive technology for the diagnosis (and in some cases treatment) of these pathologies due to the paramagnetic character of the cells containing iron. In this review, we discuss the main functions of iron in blood cells and iron-related diseases in humans and highlight the potential of magnetophoresis for diagnosing and treating some of these disorders.

KEYWORDS

anemia, iron, magnetophoresis, red blood cells (RBC)

1 | INTRODUCTION

Iron is one of the most vital micronutrients in human organisms as it plays an important role in oxygen transport, nucleic acid replication and repair, host defense, cellular proliferation, oxidative metabolism, and many catalytic reactions (Camaschella, Nai et al., 2020; Yiannikourides & Latunde-Dada, 2019). Approximately 75% of the iron in the human body is associated with erythrocytes as hemoglobin (Hb), a molecule composed of four units, each containing one heme group and one protein chain, which transports oxygen (Gupta, 2014; Nagababu et al., 2008). Part of the remaining iron in the human body is present as free iron, which has the potential to become cytotoxic and acts as a catalyst in the production of reactive oxygen species (ROS), such as superoxide (O$_2^-$), hydroxyl (OH$^-$), hydrogen peroxide (H$_2$O$_2$), and hypochlorous acid (HOCl); these are linked to various kind of diseases like cancer, insulin resistance, diabetes mellitus, and cardiovascular diseases (Alfadda & Sallam, 2012; Bayr, 2005; Soares & Hamza, 2016). The mechanism of iron homeostasis maintains an adequate iron level in the body, avoiding accumulating iron in excess and limiting its uptake from the environment (Camaschella, 2019). Leukocytes have different roles in iron homeostasis. For example, monocytes can uptake iron through different pathways and control its export (Sukhbaatar & Weichhart, 2018; Weiss, 2002). On the other hand, iron is needed for the correct function of leukocytes like T cells, B cells, natural killer (NK) cells, and neutrophils (Cronin et al., 2019). During an infection, the functions of iron uptake, storage, and removal in cells and tissues are controlled by the secretion of cytokines (Ganz & Nemeth, 2015).
Cytokines derived from T cells and monocytes regulate cellular iron homeostasis by affecting the expression of proteins involved in the uptake and storage of iron molecules (Ludwiczek et al., 2003).

Both iron deficiency and excess iron are harmful to the human body and may lead to different disorders, like anemia and hemochromatosis, respectively. In anemia, the concentration of Hb is insufficient to meet the human’s physiological needs and affects roughly one-third of the world’s population (Chaparro & Suchdev, 2019). The most common cause of anemia is iron deficiency, which affects mainly growing children, and premenopausal and pregnant women (Cappellini et al., 2020). Disturbance of iron homeostasis can also cause anemia of chronic disease (ACD), in which uptake and retention of iron increase in the cells of the reticuloendothelial system and thus, limit the availability of iron for erythropoiesis (Weiss & Goodnough, 2005). Autosomal recessive disorders like thalassemia and sickle cell disease can also lead to anemia (Huang et al., 2020; Muncie HL & Campbell, 2009; Xu & Their, 2019). Deficiency of vitamins like vitamins A, B12, C, E, riboflavin, and folic acid is also linked to anemia (Fishman et al., 2000). Differently, hemochromatosis is a group of disorders in which intestinal iron absorption becomes uncontrolled and leads to iron overload, which can cause arthritis, diabetes, heart failure, hepatic cirrhosis, and hepatocellular carcinoma (Girelli et al., 2022). Causes of hemochromatosis may be genetic or acquired, like frequent blood transfusions or excess dietary intake of iron (Chacon et al., 2013). Considering the importance of iron in several different physiological processes in the body, research on iron functions and iron-related diseases in the human body is constantly needed.

Because of the magnetic character of iron, some blood cells (e.g., deoxyhemoglobin red blood cells (RBCs) and some monocytes) show paramagnetism instead of diamagnetism (Furlani, 2007; Gómez-Pastora et al., 2021). This means that these cells are susceptible to manipulation using magnetic fields. As such, magnetophoresis can serve as an attractive technique for the diagnosis and treatment of iron-related diseases. Magnetophoresis, a term used as an analogy to electrophoresis, describes particle and/or cell motion in a viscous medium under the influence of magnetic fields (Gómez-Pastora, Moore et al., 2022; Zborowski et al., 2002). Magnetophoretic-based techniques are presented as simple, low-cost, and portable technologies that can be used to manipulate biological material, in comparison to other methods for blood cell manipulation such as electrophoresis, thermophoresis, electrophoresis, optical trapping, and acoustophoresis (Karampelas & Gómez-Pastora, 2022; Zhu & Trung Nguyen, 2010). Even at a low volume fraction, the paramagnetic constituents of a cell (in this case, iron) control the cell’s volume magnetic susceptibility, as they have a high magnetic susceptibility relative to the diamagnetic constituents of the cell (Xue et al., 2019). Therefore, magnetophoresis can be a promising tool to diagnose and treat different blood diseases (Bessis & Weed, 1973; D’alessandro et al., 2017). Indeed, recent studies have shown how magnetophoresis can be applied not only for blood cell separation but also for diagnosing and treating different blood disorders. For example, Chalmers et al. and Kim et al. presented a novel method in which the RBC magnetic properties (i.e., magnetic susceptibility) can be used to detect iron deficiency anemia (IDA) via magnetophoresis (Chalmers et al., 1999; Kim, Gómez-Pastora, Gilbert, et al., 2019). The studies of McCloskey et al. and Munaz et al. evaluated the possibility of using magnetic fields for the separation of healthy and unhealthy blood cells (McCloskey et al., 2003; Munaz et al., 2018). Moreover, other works have also presented how permanent magnet-based devices could be used for the diagnosis of other anemias like sickle cell disease (Ge & Whitesides, 2018; Kumar, Patton, et al., 2014; M. Weigand, Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022).

This review is structured as follows. After this introduction, Section 2 describes the main functions of iron in RBCs and white blood cells (WBCs) through a more detailed discussion of the previous paragraphs. In Section 3, we present a comprehensive characterization of the various types of diseases linked to unbalanced levels of iron in blood cells. Next, Section 4 brings the fundamentals of magnetophoresis and its potential application to the diagnosis and treatment of blood-related medical conditions. This review finishes with the main conclusions obtained from gathering the current knowledge of this promising field of study.

2 | FUNCTION OF IRON IN BLOOD CELLS

2.1 | Iron in RBCs

RBCs, also known as erythrocytes, play the main role in transporting O2 from the lungs to other cells and tissues and CO2 back from cells/tissues to the lungs. Human RBCs have a biconcave disc shape and red color because of the large amount of Hb in their cytoplasm (Bessis & Weed, 1973). Hb is the protein responsible for the transport of O2 and CO2. Every RBC contains around 270 million Hb molecules (D’alessandro et al., 2017). Hb consists of four polypeptide globin chains and every chain contains one non-protein or prosthetic heme group that binds reversibly to O2 (Perutz, 1979; Thomas & Lumb, 2012). Each Hb molecule is structured by two α and two β polypeptide chains as seen in Figure 1 (Jensen et al., 1998). The heme group is composed of a ringlike porphyrin to which an iron atom is attached (Perutz, 1979). The iron atom’s coordination number is 6, which means that it can receive 6 pairs of electrons (Ha & Bhagavan, 2015). Iron receives five electron pairs from the four nitrogen atoms of the porphyrin and another pair from the nitrogen in the histidine (Jensen et al., 1998). The remaining is used for transporting O2 or CO2 (Ha & Bhagavan, 2015).

Hb is very efficient in the transport of O2 and CO2. It can transport up to 50 times the O2 amount that can be delivered to adults artificially (Klinken, 2002). The valence electron of iron in the heme group remains unchanged during oxygenation and deoxygenation of Hb (Gordon-Smith, 2013; Jensen et al., 1998; Perutz, 1979). The deoxygenated heme group is referred to as the tense state (T-state) and the oxygenated heme group is referred to as the relaxed state (R-state) (Ha & Bhagavan, 2015; Jensen et al., 1998;
The allosteric model describes the transition between these states of the heme group (Gordon-Smith, 2013; Monod et al., 1965). When the first oxygen molecule binds to the T-state heme group, its structure dramatically changes, and the α and β chains rotate at about 15° angle relative to each other (Gordon-Smith, 2013; Jensen et al., 1998; Perutz, 1970), as presented in Figure 2. This rotation loosens the salt bridge between them and thus, it becomes R-state (Perutz, 1970). This state helps to bind the four oxygen molecules to each Hb unit (Ha & Bhagavan, 2015).

The transport of O₂ is also governed by the partial pressure of oxygen (pO₂) in the solution and the pH (Gordon-Smith, 2013). The collection of O₂ molecules by Hb in the lungs is favored by a high partial pressure (pO₂) and a high pH (Ha & Bhagavan, 2015). For this reason, it can bind to O₂ easily and the Hb-O₂ dissociation curve, which is a curve that relates oxygen saturation and pO₂ in blood (Ha & Bhagavan, 2015; Scrima et al., 2019), shifts left (Mairbäurl, 2013), as in Figure 3. When it reaches the cell/tissue where O₂ is delivered, O₂ is released because of the low pO₂ and low pH; the disassociation
curve of oxygen shifts right (Mairbäurl, 2013). This is called the Bohr effect (Ha & Bhagavan, 2015).

2.2 Iron in white blood cells

WBCs, also known as leukocytes, are produced in the bone marrow and found in the blood and lymph tissue (Institute N.C., 2022). The normal concentration of WBCs is 4000–10,000 cells per µL of blood (Blumenreich, 1990). Their main goal is to help the body fight against infections and other diseases through phagocytosis. For this reason, they are an integral part of the immune system (Institute N.C., 2022). Based on the presence of granules in their cytoplasm, WBCs can be classified into two types: granulocytes and agranulocytes. Granulocytes include basophils, eosinophils, and neutrophils, while agranulocytes include lymphocytes (T cells, B cells, and NK cells) and monocytes (LaRosa & Orange, 2008; Sahlol et al., 2020), the latter being an integral part of the recycling of iron in the blood.

Every day, approximately 200 billion Hb molecules are produced in the human body. To produce this amount, the human body requires 20 mg of iron, but only 1–2 mg of iron is absorbed daily in the guts (Camaschella & Girelli, 2020; Hentze et al., 2004). Monocytes (and macrophages) play a major role in this regard by phagocytosing senescent RBCs and supplying iron to the bone marrow, thus being critical in iron recycling and iron homeostasis (Moura et al., 1998). They are the largest WBCs and approximately, 2%–8% of leukocytes are monocytes. Their kidney-shaped nucleus distinguishes them from other WBCs (Ashton, 2007). Monocytes are derived from the bone marrow and spend approximately 24 h in the circulation. After that, they enter the tissue and differentiate to become macrophages (Kim, Gómez-Pastora, Weigand, et al., 2019).

Human monocytes are classified based on the expression of CD14 and CD16 receptors: classical (CD14+ and CD16–), intermediate (CD14+ and CD16+), and nonclassical (CD14– and CD16+) monocytes (Ziegler-Heitbrock et al., 2010). Monocytes use different mechanisms to acquire iron: transferrin-mediated iron uptake, transmembrane uptake of iron ions, iron uptake by lactoferrin receptors, ferritin receptors, or via erythrophagocytosis (Weiss, 2002). Different pathways for iron uptake and iron release are represented by a schematic diagram in Figure 4. In some pathological conditions, nontransferrin-bound iron (NTBI) and free heme accumulate in the serum, which can lead to organ and cell damage and can be easily utilized by microbes (Haschka et al., 2019). In this regard, classical and intermediate monocytes can uptake NTBI and damaged erythrocytes by the CD163 receptor (Haschka et al., 2019; Rubio-Navarro et al., 2015). Monocytes also express CD91 (Hudig et al., 2014), which can capture heme by the iron-binding protein hemopexin (Hvidberg et al., 2005).

Besides, ferroportin, which is the only iron exporter known to date (Hentze et al., 2004), is also expressed in macrophages/monocytes (Kim, Gómez-Pastora, Weigand, et al., 2019). That indicates that monocytes can also release iron, making it available for erythropoiesis (Kim, Gómez-Pastora, Weigand, et al., 2019).

Furthermore, hepcidin, which is produced in the liver in response to iron overload and inflammation (Ganz & Nemeth, 2006), controls iron export in monocytes (Weiss, 2009). Hepcidin binds to ferroportin
and degrades it (Nemeth et al., 2004), and thus, decreases iron export from the cell (De Domenico et al., 2007). On the other hand, if plasma iron decreases, it leads to a reduction in hepcidin synthesis, increasing iron delivery to plasma (De Domenico et al., 2007). Iron uptake and release in monocytes are controlled by different steps which can be thwarted by different diseases like hemochromatosis (Kim, Gómez-Pastora, Weigand, et al., 2019). Moreover, different receptors are expressed on monocytes by which they can sense any infection or tissue inflammation (Yang et al., 2014). If monocytes sense any damage or infection in tissue cells, they get rapidly recruited to the damaged or infected tissue and there they become macrophages (Yang et al., 2014). Macrophages can phagocytize three times more erythrocytes than monocytes (Weiss, 2009).

Also, iron is essential for producing ROS. ROS are byproducts of cellular metabolism that have different physiological functions in the body (Bardaweel et al., 2018) and are produced in neutrophils using iron (Barbusiński, 2009; Bystrom et al., 2014; Renassia et al., 2020). Neutrophils can also secrete lipocalin-2 and lactoferrin, which chelate iron in the case of iron increase in the body (Flo et al., 2004; Nakashige et al., 2015). Additionally, lymphocytes (B, T, and NK cells) need iron to perform their functions. NK cells' activation and activity against viruses are solely dependent on sufficient iron absorption (Littwitz-Salomon et al., 2021). B cells, which produce antibodies against bacteria (Althuwaiqeb & Bordoni, 2021), need iron for maturation (Jiang et al., 2019). Finally, the function and differentiation of T cells are solely dependent on iron (Bonaccorsi-Riani et al., 2015). Activation of T cells depends on the acquisition of iron through the transferrin receptor 2 (TFR-2) via the interleukin-2 (IL-2) pathway (Macedo et al., 2004; S. H. Ross & Cantrell, 2018). There are two main subsets of T cells: CD4+ T helper cells (Th cells), and CD8+ cytotoxic T cells (Sauls et al., 2018). Five major CD4+Th cells have been identified to date (Th1, Th2, Th17, Treg (T regulatory), and Tfh (follicular T helper)), whereas CD8+ T cells differentiate into stem cell memory cells (TSCM), T central memory cells (TCM), T effector memory cells (TEM), and T effector cells, (TEFF) (Golubovskaya & Wu, 2016). Even though iron inhibits differentiation, iron oxide adjuvant increases the activity of Th1 cells (Knofloch et al., 2020; Neto et al., 2018). A similar effect of iron has been found for Th2 cells (Cronin et al., 2019). On the other hand, there is a disagreement about iron's effect on Th17 cells (Ni et al., 2022). Upregulation of transferrin receptor 1 (TFR-1) increases intracellular iron transport and leads to Treg cells to death (Feng et al., 2021). Moreover, iron promotes the differentiation of CD8+ cytotoxic T cells (Wang et al., 2021).

As presented above, iron is an important player in immunosurveillance because it has a pivotal role in differentiating immune cells and can interfere with the cytokines secreted by these cells (Hassan et al., 2016). Also, some leukocytes like monocytes are crucial for maintaining correct iron levels in the body. These cells uptake most of the iron from RBCs and are responsible for releasing it for future erythropoiesis. Therefore, even though iron is mostly associated with RBCs, the presence of the metal in WBCs and the effect that it poses on the immune system cannot be neglected.

3 DISORDERS CHARACTERIZED BY ABNORMAL IRON LEVELS IN BLOOD CELLS

3.1 Anemia

The most prevalent condition characterized by low iron levels in the blood is anemia. There are different types of anemia, as schematized in Figure 5. In this subsection, the main types will be briefly explained.
and the relationship between the iron levels in the cells and the development of the disease will be introduced.

### 3.1.1 | IDA

IDA is the most common anemia and most prevalent nutritional deficiency in the world (Camaschella, 2015; Lopez et al., 2016; Miller, 2013). This disease arises when the iron stores are not enough to support the normal production of erythrocytes (Miller, 2013). Individuals with low Hb levels in the blood (<13 g/dL for males and <12 g/dL for females), low transferrin saturation (<20%), and low ferritin concentrations (<30 ng/mL) should be evaluated for IDA (Cook, 2005; Johnson-Wimbley & Graham, 2011). Globally, there were 1.2 billion cases of IDA diagnosed in 2016 (Pasricha et al., 2021). According to the World Health Organization (WHO), the prevalence of anemia in the developing world is 39% for adults, 48% for children (ages from 5 to 14), and 52% for pregnant women, with IDA accounting for nearly 50% of the total cases (Zimmermann & Hurrell, 2007). Due to blood loss during their menstrual cycles, women are 10 times more susceptible to developing IDA than men of the same age (Garzon et al., 2020). Anemia is more common in the elderly; current research indicates that 10% of people over the age of 65 are anemic, with IDA accounting for half of these cases (Guralnik et al., 2004). IDA occurs due to chronic diseases (inflammation and chronic kidney disease) or nutritional deficiencies (Busti et al., 2014). IDA is present in two forms: functional and absolute. In absolute IDA, the amount of iron is insufficient to support the production of RBCs, whereas, in functional IDA, the amount of iron is sufficient, but the body fails to supply it to the bone marrow to produce RBCs (Busti et al., 2014; Camaschella & Girelli, 2020).

IDA arises from different physiological and pathological reasons, including inadequate iron uptake (deficient diet, inadequate iron absorption), an increased iron requirement for growth and/or pregnancy, blood loss due to several diseases, or different physiological reasons like menstrual cycles (Camaschella, 2015; Clark, 2008; Lopez et al., 2016; Pasricha et al., 2021). This disease can also be developed after treatment with several drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), which are the most common medication used for treating pain, fever, and other inflammatory diseases (Wongrakpanich et al., 2018). NSAIDs include diclofenac, ibuprofen, ketoprofen, and naproxen, to name but a few (Ghlichloo & Gerrets, 2019). Finally, it should be noted that genetic disorders may also cause IDA (Camaschella, 2015). Development of IDA has three stages: storage iron deficiency (or decreased iron stores), iron deficient erythropoiesis (iron depletion in the bone marrow), and IDA (low Hb level and development of anemia) (Scott & Stockham, 2013). It should be noted that iron reserves are initially prioritized for increased erythropoiesis during blood loss (Naigamwalla et al., 2012). Erythropoiesis and the creation of other iron-containing proteins (such as myoglobin) are restricted once the body’s iron reserves are depleted, which causes IDA (Feldman et al., 2000).

The main symptoms of IDA are fatigue, headaches, paleness, and cold intolerance (DeLoughery, 2017; Lopez et al., 2016). Sometimes symptoms like tachycardia, lack of endurance, pica (an eating disorder that includes eating nonfood items), and koilonychia, are also observed (DeLoughery, 2017; Gao & Monaghan, 2018). IDA has extensive negative consequences on immunity, including impaired B-cell and T-cell activity, as well as reduced phagocytosis and macrophage-killing ability (Scrimshaw & SanGiovanni, 1997). It is also linked to an increased risk of malaria and infection (Oppenheimer, 2001). IDA diagnosis entails determining the underlying condition or cause through a thorough review of the patient’s medical history and physical examination. A thorough examination of the patient’s medications, nutrition, concurrent medical conditions, fecal features, exposure to fleas and ticks, and careful questioning regarding potential sources of blood loss should be performed (Naigamwalla et al., 2012). Generally, diagnostic testing includes performing a complete blood count test, peripheral smear, reticulocyte count, and serum iron indices testing (Johnson-Wimbley & Graham, 2011). Hb determination has been the most extensively used screening tool for iron deficiency, however, it has limitations for the diagnosis of IDA when employed as the sole laboratory test due to its low specificity and sensitivity (Cook, 2005). For the determination of IDA, the central parameter is ferritin (Miller, 2013). In most cases, ferrus sulfate is used to treat this condition (DeLoughery, 2017). However, other iron supplements (iron dextran, iron gluconate, and iron sucrose) are also widely used for IDA management (Cook, 2005).

### 3.1.2 | ACD

ACD is the second most common anemia after IDA (Weiss & Goodnough, 2005). It occurs due to the inability of the bone marrow to produce enough RBCs (also called hypoproliferative anemia) even though there is enough reticuloendothelial iron available (Means RTMeans, 2003). Recent studies have shown that ACD is linked to obesity, aging, kidney failure, and chronic inflammatory diseases like cancer, chronic infection, and autoimmune diseases (Fraenkel, 2015). In patients who suffer from chronic inflammatory states like cancer and autoimmune diseases, ACD is also found (Weiss, 2009). For this reason, this disease is also referred to as anemia of inflammation (Fraenkel, 2015). As presented above, the level of hepcidin is controlled by a complex interaction between bone morphogenic proteins, its coreceptor hemojuvelin, proteases, and inflammatory cytokines, like IL-1 and IL-6 (Fraenkel, 2015; Lee et al., 2005). In the case of inflammation, IL-1 and IL-6 increase the production of hepcidin (Lee et al., 2005). Due to the increase of hepcidin levels in serum, macrophages engulf senescent and old erythrocytes and thus, acquire iron, but it is not released, which causes ACD (Agarwal & Prchal, 2009).

Measuring Hb levels is not enough for the correct diagnosis of ACD since the exclusion of other kinds of anemia (particularly IDA) is needed for the diagnosis of ACD (Wiciński et al., 2020). Some other
parameters like serum iron levels and transferrin saturation are key for distinguishing ACD from other anemias (in ACD iron levels and transferrin saturation are decreased whereas transferrin levels are increased in IDA but they remain almost normal or decreased in ACD) (J. Cullis, 2013; Wicinski et al., 2020). With regard to therapy, the main treatment of ACD evolves around eradicating the underneath disease that promotes its development (Fraenkel, 2015). If that is not possible, blood transfusions or iron supplements can be used to treat this disorder (Nemeth & Ganz, 2014). In this regard, treatment of the underlying inflammatory or malignant process associated with ACD will often result in an improvement in the degree of anemia; examples include the use of corticosteroids in polymyalgia rheumatica, tumor necrosis factor inhibitors in rheumatoid arthritis or inflammatory bowel disease as well as the use of antiretroviral medications in the treatment of human immunodeficiency virus infection (J. O. Cullis, 2011).

3.1.3 | Thalassemia

Thalassemia is a type of anemia caused by a genetic disorder, which reduces the adequate production of the α or β chains of the Hb (Aydinok, 2012; Muncie HL & Campbell, 2009; Vij & Machado, 2010). This disease is prevalent in Indian, Mediterranean, South Chinese, Middle Eastern, and Southeast Asian descent (Li, 2017). As it is an autosomal recessive disorder, both parents must be affected by or be carriers of the gene to pass it to their offspring (Bajwa & Basit, 2019). Thalassemia can be divided into two major groups: α-thalassemia, which occurs when there is a decrease in the production of the α-globin chain, thus leading to an increase in the production of the β-globin chain in Hb, and β-thalassemia, in which the production of the β-globin chain is decreased and leads to the increase of the α-globin chain in the molecule (Helmi et al., 2017; Muncie HL & Campbell, 2009; Rund & Rachmilewitz, 2001). Mutation or deletion of one or more of the genes responsible to produce α-globin chains (situated in chromosome 16) causes α-thalassemia (Bajwa & Basit, 2019; Li, 2017; Muncie HL & Campbell, 2009). The four clinically recognized forms of α-thalassemia are: silent carrier, α-thalassemia trait, Hb H (HbH) disease, and hydrops fetalis syndrome (Marengo-Rowe, 2007). α-thalassemia silent carrier status is caused by a single gene loss and is asymptomatic with normal hematologic findings (Muncie HL & Campbell, 2009). α-thalassemia trait is associated with microcytosis and typically, no anemia is presented by this two-gene deletion (Hartevelt & Higgs, 2010). However, the three-gene loss leads to considerable HbH synthesis, which contains four β-chains (Songdej & Fucharoen, 2022). HbH can cause chronic hypochromic microcytic anemia and hemolytic anemia (Harewood & Azevedo, 2017). Hb Barts, which has four gamma chains, is significantly produced as a result of the four-gene deletion. Usually, α-thalassemia major with Hb Barts causes fatal hydrops fetalis (Chui et al., 1998). On the other hand, mutation of the β-globin gene cluster in any of its 200 regions (since deletion of the gene is rare) in chromosome 11 results in the development of β-thalassemia (Aydinok, 2012; Bajwa & Basit, 2019; Galanello & Origa, 2010; Marengo-Rowe, 2007; Muncie HL & Campbell, 2009). The synthesis of β-chains is completely absent in β-thalassemia patients; in β+-thalassemia there is a partial shortage in the formation of β-chains (Marengo-Rowe, 2007).

The symptoms of thalassemia are dependent on its severity and type. Common symptoms include: pale skin, deformed facial or skeletal bones, and arrhythmias (Bajwa & Basit, 2019). Symptoms may be absent in silent carriers of α-thalassemia (Shaﬁque et al., 2021). For diagnosis, measurements of the mean corpuscular volume (MCV) of individual RBCs are used to differentiate between IDA and thalassemia (Galanello & Origa, 2010; Muncie HL & Campbell, 2009). More specifically, the Mentzer index, which is the MCV divided by the RBC count, is used to differentiate thalassemia from iron deﬁciency (indexes with a value of <13 serve to diagnose the person with thalassemia, whereas a value of >13 is found in patients with iron deﬁciency) (Siswandari et al., 2019). As for the therapy, patients with thalassemia traits do not need any treatment (Ali et al., 2021). On the other hand, supplements of folic acid (2–5 mg/day) are prescribed to HbH patients (Vichinsky, 2012). However, during times of potential oxidative stress, such as infections or the use of oxidative drugs, blood counts should be monitored and transfusional intervention may be necessary (Harewood & Azevedo, 2017). Also, for mild thalassemia, occasional blood transfusions may be needed, whereas for moderate to severe thalassemia, frequent blood transfusions, the use of chelation therapy, stem cell transplants, and even gene therapy may be required (Bajwa & Basit, 2019).

3.1.4 | Sickle cell anemia (SCA)

SCA is an autosomal recessive disorder caused by a mutation in the β-globin gene of the Hb. In this mutation, the substitution of glutamic acid by valine occurs, resulting in the production of sickle Hb (HbS) molecules, which interact with adjacent HbS molecules under deoxygenation conditions and create HbS polymers (M. R. H. Weigand et al., 2021). These aggregates form lengthy chains, distorting the RBC into a sickled shape and impeding the cell's passage through blood vessels (Lonergan et al., 2001). Furthermore, the malformed RBCs tend to attach to the endothelium, which results in the reduction of the cell deformability and hindrance in blood vessels, promoting the development of excruciatingly painful vaso-occlusive crisis (VOC) (Darbari et al., 2020; Eaton et al., 2006; Jang et al., 2021). Polymerization also increases the permeability of the cell's membrane for cations (sodium, potassium, magnesium, and calcium) in a nonselective manner. When these cations reach the RBCs, numerous cell membrane transport processes are triggered, with the most significant consequence being the water outflow from the RBCs, which in turn, increases the density of the cells (Lonergan et al., 2001).

Apart from VOC, SCA patients suffer from invasive infections, acute chest syndrome, strokes, and chronic pulmonary hypertension (Mehta et al., 2006; Shah et al., 2019). The median life expectancy of
SCA patients is between 42 and 47 years (Hematology, 2016). This mutation is common in sub-Saharan Africa and every year almost 300,000 individuals are born with the disease (Mburu & Odame, 2019). The inheritance of both HbA (normal Hb) and HbS (or HbAS) corresponds to sickle cell trait; strictly not a form of SCA but that may be associated with adverse health outcomes (M. Weigand, Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022) Sickle cell trait affects between 1 and 3 million Americans, 8%–10% of African Americans, and more than 100 million people worldwide (Hematology). It should be noted that there is no recommended approach for diagnosing SCD (Smith & Kinney, 1997). Nevertheless, the Agency for Health Care Policy and Research has proposed combining three newborn screening methods: Hb electrophoresis, isoelectric focusing, and high-performance liquid chromatography (HPLC) (Koch et al., 2000). Apart from those, other diagnostic techniques have been developed to determine SCA (Ilyas et al., 2020; Ware et al., 2017). Moreover, microfluidic systems and other point-of-care (POC) devices have been successfully tested for the diagnosis of SCA (Hasan, 2017; Knowlton et al., 2015). Modern treatment options for SCA emphasize optimum supportive care, such as blood transfusions and pain relievers (Tisdale et al., 2020). Drugs like hydroxyurea or voxelotor are widely used for treating SCA patients (Eaton & Bunn, 2017; Platt et al., 1984). Other treatments for SCA include hydroxyurea, L-glutamine, and bone marrow transplantation (Agrawal et al., 2014; Inusa et al., 2019; Lonergan et al., 2001). Significant improvements in SCA understanding have enabled the development of curative therapeutics via allogeneic stem cell transplantation, with the prospect of gene therapy-based treatments in the future (Tisdale et al., 2020).

### 3.1.5 Vitamin deficiency anemia

Vitamin deficiency or nutritional anemia is considered the most common nutritional disorder in the world, mainly prevalent in developing countries (Ahmed, 2000; Hercberg & Rouaud, 1981). To ensure the normal production of blood cells, some vitamins like vitamin A, folic acid, vitamin B12, vitamin B6, and riboflavin (vitamin B2) play a vital role, where vitamin C and E work as antioxidants by diminishing the presence of free radicals (Fishman et al., 2000). Vitamin A appears to be involved in the pathogenesis of anemia through diverse biological mechanisms, but these are not fully understood yet (Semba & Bloem, 2002). The deficiency of folate and vitamin B12 impairs DNA synthesis and causes megaloblastic anemia (Ayodele, 2018). On the other hand, riboflavin deficiency leads to anemia by impairing iron absorption and iron metabolism (Mahabadi et al., 2022; Meier et al., 1981). Finally, vitamin B6 is used for treating sideroblastic anemia but deficiency of this vitamin is rare (Fishman et al., 2000; Meier et al., 1981).

### 3.2 Hemochromatosis

Hemochromatosis, which can be resulted from both acquired and genetic conditions, is one of the most common hematologic disorders, characterized by iron overload (Yun & Vincelette, 2015). It is also known as ‘bronze diabetes’ as this disease changes the color of the skin and creates pancreas-related disorders (Porter & Rawla, 2021). The different types of hemochromatosis are shown in Figure 6. Hemochromatosis can be divided into two types: primary or hereditary hemochromatosis (HH) and secondary hemochromatosis (Porter & Rawla, 2021; Siddique &

---

**FIGURE 6** Different types of hemochromatosis and their mechanisms.
Kowdley, 2012). It is most prevalent in Caucasian descents who are homozygote or compound heterozygote for genes on chromosome 6p (Barton et al., 1998; Blachier et al., 2013; Zoller & Henninger, 2016). In Celtic and Nordic countries, approximately 1 in 220 people are affected by HH (Bacon et al., 2011). Due to blood loss in menstrual cycles, women are less affected by HH and the ratio between men and women is 3:1 (Porter & Rawla, 2021).

Generally, HH is a genetic condition (Brisso et al., 2008). If the iron levels in plasma are more than enough to support erythropoiesis, NTBI starts accumulating in the liver, heart, and endocrine tissue and eventually causes HH (Hider & Kong, 2013). The extra NTBI can also produce cytotoxic hydroxyl and lipid radicals in the liver, heart, and pancreas and lead to the failure of these organs (Yun & Vincelette, 2015). Recent research has shown that the monocytes of HH patients release twice lower molecular weight iron (LMW-Fe) than what monocytes from healthy individuals release (Kim, Gómez Pastora et al., 2011; Brissot et al., 2008). Major mutation of the HFE gene causes type 1 or HFE-related hemochromatosis, type 3 hemochromatosis, and type 4 hemochromatosis, or ferroportin disease (Bacon et al., 2011; Brissot et al., 2008). Major mutation of the HFE gene causes type 1 or HFE-related hemochromatosis (Milman et al., 2019). This mutation leads to a lower hepcidin expression in these patients, which promotes higher intestinal iron absorption (Bridle et al., 2003). Hepcidin deficiency or hepcidin resistance also results in impaired control of iron storage in macrophages and increased iron release into the circulation (Fillet et al., 1989). Consequently, and despite the fact that iron excess is present in other tissues, individuals with hemochromatosis have inadequate levels of iron in their macrophages (McLaren, 1989). Type 2 or juvenile hemochromatosis is a rare disease that affects mostly young individuals (Brissot et al., 2008) and is caused by hepcidin failure due to the mutation of hemojulenin (Lu et al., 2004) or hepcidin (Roetto et al., 2003). On the other hand, type 3 hemochromatosis is an autosomal recessive disease that occurs due to the mutation of the TFR-2 gene, which is located on chromosome 7 (Roetto et al., 2001). When type 3 HH results in an iron overload comparable to HFE-related hemochromatosis, it can cause aberrant liver function, diabetes, hypogonadism, cardiomyopathy, and arthritis (Lima Santos et al., 2012). Type 4 hemochromatosis results from the mutation of the ferroportin (SLC40A1) gene (Pietrangelo, 2004; Wallace & Subramaniam, 2007). This type of hemochromatosis is more frequent than types 2 and 3 and it has been reported in a wide range of individuals (Bardou-Jacquet & Brissot, 2014); since it affects ferroportin, this disorder causes loss of the iron export function (De Domenico et al., 2006; Drakesmith & Prentice, 2012). As presented above, two types of mechanisms are involved in HH: hepcidin failure and ferroportin failure (Brissot et al., 2008). Hepcidin failure increases NTBI (Hider, 2002) and this is the responsible mechanism behind types 1, 2, and 3 hemochromatoses (Brissot et al., 2008). Type 4 arises from the mutation of the ferroportin gene, which leads to ferroportin failure (Brissot et al., 2008; Hider & Kong, 2013). On the other hand, secondary hemochromatosis arises from repeated transfusions of blood, and may be caused by diseases like thalassemia, myelodysplastic syndromes, SCA, and hereditary spherocytosis (Gattermann, 2009; Hider & Kong, 2013; Porter & Rawla, 2021).

High serum ferritin and transferrin saturation are observed in patients with hemochromatosis (in general, serum ferritin levels above 300 ng/ml in men and 200 ng/ml in women are found (Elsayed et al., 2016)). Nevertheless, other possible disorders such as acute or chronic inflammatory conditions, liver illness, infection, and secondary iron overload, must be taken into account while evaluating hemochromatosis (Murphree et al., 2020). Patients with continuously high ferritin and transferrin saturation levels who do not present any other evident iron overload reason need to be considered for HFE mutation testing. In the absence of tests showing excessive iron levels, it is prudent for individuals with a known family history of hemochromatosis to undertake HFE mutation testing, especially if both parents are Caucasian due to the greater occurrence of HFE mutations in people of European heritage (Bardou-Jacquet & Brissot, 2014). Patients with a recent hemochromatosis diagnosis should be examined for typical signs of organ damage, paying particular attention to the liver, heart, pancreas, anterior pituitary, joints, and skin (Murphree et al., 2020). The most common and general treatment for this condition includes therapeutic phlebotomy (Witte et al., 1996). Clinical evidence shows that iron removal before the development of cirrhosis and diabetes is related to a decreased morbidity and mortality (Niederau et al., 1996), and that some aspects such as hepatic fibrosis, may be alleviated by a phlebotomy treatment (Powell et al., 2006). Nevertheless, if a patient does not have access to a superior vein or if venesection is contraindicated, iron chelators like deferasirox may be recommended for early iron removal (Adams et al., 2000; Phatak et al., 2010).

### 4.1 Fundamentals of blood cell magnetophoresis

Magnetophoresis refers to the movement of a magnetic particle (and/or cell or biological matter) in a viscous medium under influence of inhomogeneous magnetic fields (Robert et al., 2011; Watarai & Namba, 2002; Zborowski et al., 2002). Publications on magnetophoresis have increased in recent years due to its versatile application in biomedical research, water treatment, diagnosis of diseases, and therapy (Gómez Pastora et al., 2016; Gómez-Pastora et al., 2020; Lenshof & Laurell, 2010; Wu et al., 2022; Zborowski & Chalmers, 1999).

The primary advantage of magnetophoresis is that it enables the specific manipulation of thousands of particles and cells efficiently over a short period of time (e.g., magnetophoretic-based devices have been able to separate continuously RBCs from WBCs at relatively high volumetric flowrates, comparable to other devices used for magnetic particle...
separation at the microscale) (K. H. Han & Frazier, 2006; Hejazian et al., 2015; Whitesides, 2006). Figure 7 presents the acting forces on blood cells in a magnetophoretic device. The motion of particles and cells in a typical magnetophoretic device depends on several competing forces, such as the drag force ($\vec{F}_D$), magnetophoretic force ($\vec{F}_M$), buoyancy force ($\vec{F}_B$), gravitational force ($\vec{F}_G$), and lift force ($\vec{F}_L$). In most cases, for a shallow channel and a particle/cell suspended in an incompressible fluid, $\vec{F}_B$, $\vec{F}_G$, and $\vec{F}_L$ can be neglected (Alnaimat et al., 2018; Pamme & Manz, 2004; Gómez-Pastora et al.).

Under this scenario, the particle/cell trajectory can be computed according to Newton's second law (González Fernández et al., 2020; González-Fernández et al., 2021; X. Han et al., 2015):

$$m_p \frac{d\vec{v}_p}{dt} = \vec{F}_D + \vec{F}_M$$  \hspace{1cm} (1)

where, $m_p$ represents the mass of the particle (or blood cell) and $\vec{v}_p$ its velocity. Applying Stoke's law, $\vec{F}_D$ can be obtained as (Furlani, 2007; Gijs et al., 2010):

$$\vec{F}_D = 6\pi \mu r (\vec{v}_f - \vec{v}_p) f_0$$  \hspace{1cm} (2)

where, $r$ represents the hydraulic diameter of the particle/cell, $\mu$ is the viscosity of the fluid, $\vec{v}_f$ is the velocity of the fluid, and $f_0$ is the drag coefficient, which can be estimated as:

$$f_0 = \left\{ 1 - \frac{9}{16} \left( \frac{r}{r+z} \right)^2 + \frac{1}{8} \left( \frac{r}{r+z} \right)^3 - \frac{45}{256} \left( \frac{r}{r+z} \right)^4 - \frac{1}{16} \left( \frac{r}{r+z} \right)^5 \right\}$$  \hspace{1cm} (3)

where, $z$ represents the distance of the particle to the solid wall of the channel/device. For small distances (which is generally the case for cell separation in small devices), one may consider $z$ negligible, in which case ($z = 0$), $f_0 = 3$ (Gijs et al., 2010). Following, $\vec{F}_M$ can be calculated as follows (Amiri Roodan et al., 2020; Hejazian et al., 2015; Munaz et al., 2018; Shiriny & Bayareh, 2020; Tarn & Pamme, 2017):

$$\vec{F}_M = \frac{V_p}{\mu_0} (\chi_p - \chi_f)(\vec{B} \cdot \nabla)\vec{B}$$  \hspace{1cm} (4)

where, $V_p$ is the volume of the cell, $\chi_p$ and $\chi_f$ are the dimensionless magnetic susceptibilities of the particle/cell and fluid, respectively, and $\mu_0$ is the magnetic permeability in vacuum ($\mu_0 = 4\pi \times 10^{-7}$ H/m). $\vec{B}$ and $\nabla \vec{B}$ are the magnetic flux density and its gradient. The magnetic susceptibility ($\chi$) value is generally employed to classify materials into ferromagnetic ($\chi > 0$), paramagnetic ($\chi > 0$), and diamagnetic ($\chi < 0$) (Munaz et al., 2018). In whole blood, most WBCs show diamagnetism, whereas RBCs show diamagnetism or paramagnetism depending on their oxygenated state (Furlani, 2007). As oxyhemoglobin has no unpaired electrons, it shows zero magnetic moment and diamagnetic behavior, whereas deoxyhemoglobin is paramagnetic since it has four unpaired electrons (Pauling & Coryell, 1936a). On the other hand, methemoglobin contains five unpaired electrons in its structure and shows paramagnetism (Zborowski et al., 2003). Since monocytes acquire iron from RBCs, some cells have magnetic properties. More specifically, recent research has shown that a subset of monocytes has paramagnetic properties (Gómez-Pastora et al., 2021).

4.2 | Applications of blood cell magnetophoresis

4.2.1 | Diagnosis of anemia

For diagnosing anemia, determination of the RBC count, hematocrit (Hct), and Hb is performed (Gómez-Pastora, Weigand, et al., 2022).
Also, Wintrobe’s parameters such as MCV, mean corpuscular Hb (MCH), and MCH concentration (MCHC) of RBCs can be helpful to find the etiology of the anemia (Sarma, 1990). Some modern blood analyzers use flow cytometry, spectrum absorption, and/or chemical reaction to provide new useful indices like reticulocyte counts, and hypochromic RBC counts (Schaef er & Schaefer, 1999). Although these instruments provide accurate and reproducible data, they are very expensive ($75,000–$200,000) (Sullivan, 2006), present issues in portability, and require trained technicians and costly reagents to operate (Heikali & Di, 2010). According to Pauling and Coryell’s pioneering work on the magnetism of Hb, different states of Hb show different magnetic moments (Pauling & Coryell, 1936a, 1936b), as has been presented above. Under this scenario, the use of magnetophoresis can be a cheaper solution to diagnose anemias since the introduction of powerful and low-cost neodymium magnets and modern computer imaging technologies enable the development of instruments that can determine the magnetic susceptibility of blood cells, which are related to their Hb and iron content (Chalmers et al., 1999, 2017). For example, recent works have suggested the use of a permanent magnet-based microsystem referred to as cell tracking velocimetry (CTV) (Chalmers et al., 1999; Kim, Gómez-Pastora, Gilbert, et al., 2019; Kim, Gómez-Pastora, Weigand, et al., 2019; R. H. Weigand et al., 2021) as a portable and inexpensive hematology analyzer able to measure traditional RBC indices and novel indices such as the percentage of hypochromic RBCs and the red cell distribution width (Gómez-Pastora, Weigand, et al., 2022).

4.2.2 | Separation of healthy and unhealthy cells based on iron content (fractionation)

In the case of surgery, trauma resuscitation, treatment of patients with oncologic diseases, organ transplantation, severe blood loss, and acute anemia, blood transfusions can be considered a lifesaving treatment (Kim, Gómez-Pastora, Gilbert, et al., 2019; W. B. Ross & Yap, 1990). After transfusion, 25% of the transfused RBCs are removed by the spleen even though the ex-vivo damage of the exogenous RBCs is minimal (M. Weigand Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022). Receiving multiple transfusions is associated with several side effects. Due to RBC units shortage problems, some hospitals diluted RBC units during the coronavirus disease 2019 (COVID-19) pandemic (Jacobs & Booth, 2022), which may have alleviated the problems associated with receiving repeated blood transfusions like alloimmunization, iron overload, and delayed hemolytic reactions (Ware et al., 2017). Magnetophoresis can also be a solution to fractionate ex-vivo, stored RBCs, to separate healthy, iron-rich, RBCs from damaged or senescent RBCs, and thus, provide effective and high-quality cells for transfusion (Gómez-Pastora et al., 2018; McCloskey et al., 2003; Munaz et al., 2018). A possible setup for RBC separation based on iron content is shown in Figure 8. A recent study evaluated the possibility of using magnetophoresis (by using a neodymium-iron-boron [NdFeB] permanent magnet in a pressure-driven flow system) to fractionate RBCs based on their iron content (M. Weigand, Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022).

4.2.3 | Sickle cell disease diagnosis and treatment

Diagnosis of SCA requires HPLC, Hb electrophoresis, and/or isoelectric focusing, which are expensive analyses and require trained technicians (Yusuf et al., 2011). Since SCA is the most frequent Hb abnormality in sub-Saharan Africa, where the health care system is inaccessible to the majority of the population (Ngolet et al., 2016), a low-cost, compact, and user-friendly diagnostic device is needed (Knowlton et al., 2015). Since one of the main characteristics of SCA is the presence of high-density RBCs in the bloodstream (Fabry et al., 1984), density-based diagnosis is a cheap alternative to the existing ones (Kumar, Patton, et al., 2014). In this regard, magnetic levitation (MagLev) can be a promising alternative because of its low cost. This technology can distinguish between two diamagnetic objects whose densities differ by 0.0002 g/cm³ (Abrahamsson et al., 2020; Ge & Whitesides, 2018; Mirica et al., 2009). MagLev is performed by suspending the material in a medium; then, a combination of magnetic and gravity forces separates the objects according to their density (Ge et al., 2020). A recent study suggested the potential use of a cheap, portable diagnosis system that incorporates a three-dimensional printed MagLev platform with a cellphone and induces cell dehydration by sodium metabisulfite.
(Knowlton et al., 2015). Other studies have also employed MagLev-based systems as POC diagnostic devices for SCA (Kumar, Chundra-Liyoka, et al., 2014; Song et al., 2014).

Furthermore, for SCA, regular blood transfusions are recommended in the case of acute anemia, splenic sequestration, reticulocytopenia, accelerated hemolysis, stroke, and acute chest syndrome (Telen, 2001). In the case of VOC, many patients need blood transfusion therapy to reduce the concentration of HbS (Boma Muteb et al., 2017). During the procedure, the blood of the patient is discarded through an apheresis device, and replaced by healthy RBCs (Howard, 2016; Quirolo et al., 2015). However, only a small portion of the RBCs in the SCD patients are polymerized (M. Weigand, Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022). In this regard, magnetophoresis is a potential solution to separate the patient’s sickle RBCs from the healthy RBCs due to their different oxygen affinities, which affect the RBC magnetic properties (Eldeniz et al., 2021; M. Weigand, Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022). A recent study evaluated the potential of magnetophoresis using a NdFeB permanent magnet in a pressure-driven flow system to separate healthy RBCs from sickle RBCs and further research in this area may yield future therapeutic interventions (M. Weigand, Gomez-Pastora, Palmer, et al., 2022; M. Weigand, Gomez-Pastora, Strayer, et al., 2022).

5 | CONCLUSIONS

Iron in RBCs plays the main role of transporting oxygen and iron in monocytes/macrophages results from phagocytosing senescent RBCs, recycling it back to the bone marrow. Iron not only helps lymphocytes in performing their functions but also controls cytokines derived from T cells and macrophages. To perform these roles properly, iron content must be strictly regulated in the human body. Imbalances in iron physiology may lead to a wide spectrum of diseases ranging from anemia to hemochromatosis, some of which can be fatal. In this study, we have reviewed explicitly the different roles of iron in blood cells and have introduced several iron-related diseases such as IDA, SCA, thalassemia, ACD, and the different forms of hemochromatosis. Even though several techniques have been developed for the diagnosis and treatment of iron-related disorders, in some cases, they are not cost-effective, portable, or require trained technicians. Since some of the iron-related diseases affect the majority of the population of developing nations where health care resources are limited, combined with the current worldwide limited access to proper health care and treatment, magnetophoretic-based technologies emerge as a cheap, viable, and portable solution for the diagnosis of iron-related diseases, thus becoming a prominent research field. In this review, we have discussed several magnetophoretic devices that may offer a solution to these issues. For example, devices like the CTV have shown a new path in the diagnosis of iron-related diseases, like IDA. Other permanent magnet-based devices allow the fractionation of blood cells based on iron content, which is a promising technology for the treatment of SCA. Finally, we introduce MagLev-based devices, which can be used as POC diagnostic devices for disorders like SCA.

ACKNOWLEDGMENTS

Financial support from Texas Tech University is acknowledged.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Sowrav Barua http://orcid.org/0000-0001-8700-4036
Stefano Ciannella http://orcid.org/0000-0001-8998-2095

REFERENCES


...


Rubio-Nava, A., Amano Villabobos, J. M., Lindholt, J. S., Buendia, I., Egido, J., Blanco-Colio, L. M., Samaniego, R., Meilhac, O., Michel, J. B., Martin-


**How to cite this article:** Barua, S., Ciannella, S., Tijani, L., & Gomez-Pastora, J. (2023). Iron in blood cells: Function, relation to disease, and potential for magnetic separation. *Biotechnology and Bioengineering*, 1–18.

https://doi.org/10.1002/bit.28388