Blood Reviews 31 (2017) 400–405

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Review

Therapeutic use of transferrin to modulate anemia and conditions of iron toxicity

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ARTICLE INFO

Keywords:
Transferrin therapy
Anemia
Hypotransferrinemia
β-thalassemia
Oxidative stress
Non-transferrin bound iron

ABSTRACT

As the main iron transporter, transferrin delivers iron to target tissues like the bone marrow for erythropoiesis. Also, by binding free iron, transferrin prevents formation of reactive oxygen species. Transferrin deficiency due to congenital hypotransferrinemia is characterized by anemia as well as oxidative stress related to toxic free iron. Transferrin supplementation may be beneficial in two ways. First, transferrin can correct anemia by modulating the amount of iron that is available for erythropoiesis. This is obvious for patients that suffer from hypotransferrinemia, but may also have beneficial effects for β-thalassemia patients. Second, under conditions of iron overload, transferrin reduces oxidative stress by binding free iron in the circulation and in tissues. Hereby, transferrin protects the host against the reactive oxygen species that can be formed as a consequence of free iron. This beneficial effect is shown in hematological patients undergoing chemotherapy and stem cell transplantation. Transferrin may also be beneficial in lung injury, ischemia-reperfusion injury and hypomyelination.

This review summarizes the preclinical and clinical data on the efficacy of exogenous transferrin administration to modulate certain forms of anemia and to prevent the toxic effects of free iron. Thereby, we show that transferrin has promising therapeutic potential in a wide variety of conditions.

1. Introduction

Transferrin (Tf) is a 76 kD glycosylated glycoprotein with a half-life of 8–10 days [1]. Tf is mainly synthesized in the liver and has the capacity to bind two atoms of iron in the ferric form (Fe^{3+}) [2]. The main function of Tf is binding and transportation of iron in the circulation, thereby preventing the participation of iron in redox reactions. Tf is present in the circulation in a non-iron bound form, termed apotransferrin (apo-Tf), or in iron bound forms: monoferric Tf or diferric holotransferrin (holo-Tf) [3]. Holo-Tf is taken up by transferrin receptor expressing cells via receptor mediated endocytosis [4]. There are two Tf receptors in humans, transferrin receptor 1 (TfR1) and transferrin receptor 2 (TfR2) [5]. TfR1 is expressed by all cell types, whereas TfR2 is only expressed by hepatocytes, erythroblasts and peripheral blood mononuclear cells [6,7]. Both receptors bind holo-Tf. Upon binding to its receptor, the complex undergoes endocytosis and reaches the lysosome where iron is released from holo-Tf by acidification. The complex of the non-iron bound Tf (apo-Tf) and the receptor is then returned to the cell membrane, where apo-Tf is released in the circulation for reutilization and the receptor can bind another molecule of holo-Tf [2,3]. When plasma iron levels exceed the iron binding capacity of Tf, toxic free iron can appear. This non-transferrin bound iron (NTBI) may catalyze the Fenton reaction in which the highly reactive hydroxyl radical is formed from hydrogen peroxide and superoxide:

$$Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2$$
$$\underline{Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-}$$
$$\cdot O_2^- + H_2O_2 \rightarrow \cdot OH + OH^- + O_2$$

The summation of these reactions is the Haber Weiss reaction. The toxic reactive oxygen species (ROS) that are formed can cause oxidative

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http://dx.doi.org/10.1016/j.blre.2017.07.005

stress and tissue damage [3,8].

Plasma iron levels are mainly regulated by hepcidin, a peptide that is secreted by hepatocytes [9,10]. It has been suggested that during high Tf saturation, Tf binds to TfR2 which induces hepcidin expression [11,12]. Hepcidin acts by reducing iron levels by inhibiting iron absorption from the duodenum and decreasing iron secretion from cells like hepatocytes and macrophages, by degradation of ferroportin, the iron exporter [13]. Production of hepcidin is induced by increased plasma iron levels as well as by inflammation [14,15]. Low iron levels, anemia, hypoxia and accelerated erythropoiesis cause a reduction in hepcidin production [16]. In accelerated erythropoiesis, erythroferrone (ERFE), a hormone produced by erythroblasts, suppresses hepcidin production [17]. This leads to an increase in iron uptake and release, resulting in elevated serum iron levels and Tf saturation, which is required for heme synthesis [18,19]. During inflammatory conditions, iron metabolism is altered. Pro-inflammatory cytokines like interleukin-6 induce the production of hepcidin, resulting in iron sequestration in macrophages and hepatocytes with subsequent low plasma iron levels [13]. This iron sequestration is thought to be an endogenous response of the host, with the aim to restrict iron availability in the circulation for bacterial growth [20]. Also Tf is lowered during inflammatory conditions, therefore Tf is considered to be a negative acute phase protein [21].

Tf supplementation could be beneficial in different patients groups. First, Tf supplementation may correct some causes of anemia by modulating the amount of iron available for erythropoiesis. Second, apo-Tf supplementation may reduce inflammatory reactions by inhibiting oxidative stress by binding free iron (fig. 1). Tf can be isolated from human plasma or expressed by recombinant techniques [22]. Tf that can be used clinically can be purified relatively simply from human plasma by Cohn fractionation, ion exchange chromatography and ultrafiltration [23]. Purified apo-Tf is approved by the European Medicines Agency as orphan drug and is already used as a therapy for patients with hypotransferrinemia. Here, we review preclinical and clinical data on the efficacy of Tf supplementation to either correct anemia due to different causes or to counteract oxidative stress as a consequences of free iron in different diseases.

2. Tf supplementation to correct anemia

As holo-Tf is the main source of iron for erythropoiesis, sufficient levels of holo-Tf are essential for maintaining a steady production of erythrocytes. The importance of ample holo-Tf for erythropoiesis is best underscored in patients suffering from hypotransferrinemia, who have severely reduced levels of Tf. On the other side of the spectrum there are the β-thalassemia patients, whose increased erythropoiesis can be corrected by Tf therapy. The therapeutic efficacy of Tf for both diseases is discussed below.

2.1. Tf supplementation in patients suffering from hypotransferrinemia

Hypotransferrinemia is a rare, hereditary disorder characterized by microcytic, hypochromic anemia, with very low or undetectable Tf levels and increased ferritin levels. Due to a lack of Tf, and a subsequent lack of iron in erythroid precursors, hypotransferrinemia patients suffer from severe anemia. In addition, these patients display growth retardation and cognitive impairment. Due to the uptake of NTBI in a Tf-independent way, some patients develop severe hemochromatosis and die at a very young age [24]. Since 1972, patients with hypotransferrinemia have been treated with plasma purified apo-Tf. In the first patient, an 8 year old boy with hypotransferrinemia, injection of 1 g of apo-Tf resulted in an increase in hemoglobin and erythrocyte counts, which lasted for several weeks [24,25] (Table 1). After this single injection of 1 g of apo-Tf, Tf levels peaked briefly while erythrocyte counts increased over time. The hemoglobin level increased from 6.4 g/dl to 9–10 g/dl [24,25]. During 5 years of treatment with apo-Tf injections every 3–4 months, the patient began to thrive and his mental development improved remarkably; he went from a special class for developmentally-delayed children to a normal student class [24]. A similar case was described in a girl with hypotransferrinemia, in whom a similar response upon apo-Tf therapy was observed [26] (table 1). Side effects were not observed in these two cases. Also, no antibodies to

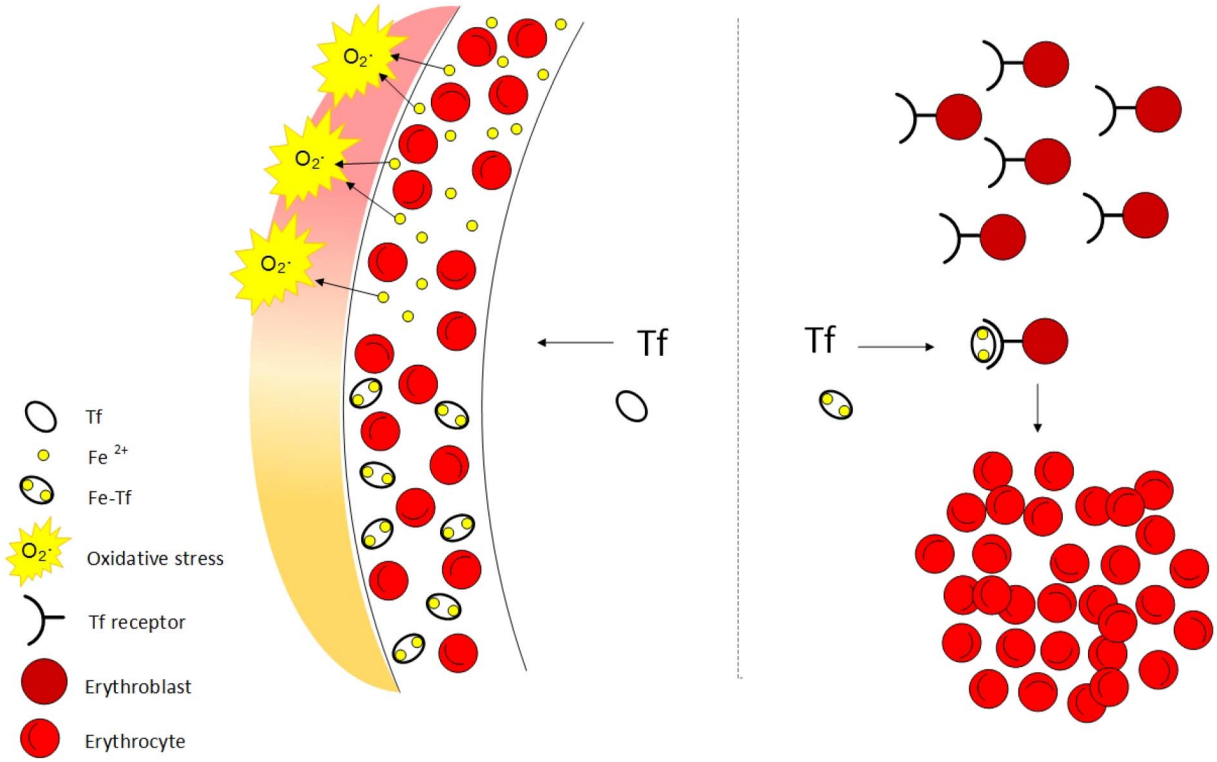

Fig. 1. The two functions of Tf: Tf may correct anemia by modulating the amount of iron available for erythropoiesis and Tf may reduce oxidative stress by binding free iron.