frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 14 March 2025
DOI 10.3389/fphar.2025.1584190

OPEN ACCESS

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RECEIVED 26 February 2025
ACCEPTED 03 March 2025
PUBLISHED 14 March 2025

CITATION
Carrilho P, Chopra S, Pichika MR, Fleming RE and Parrow NL (2025) Editorial: The potential of transferrin as a drug target and drug delivery system.
Front. Pharmacol. 16:1584190.
doi: 10.3389/fphar.2025.1584190

Editorial: The potential of transferrin as a drug target and drug delivery system

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KEYWORDS

transferrin, hepcidin, erythropoiesis, targeted drug delivery, transferrin receptor (TfR)

Editorial on the Research Topic
The potential of transferrin as a drug target and drug delivery system

Transferrin (Tf), the major iron-binding protein in plasma, appears to have both cargo and signaling functions. It has two homologous lobes, N and C, each of which can bind one iron molecule. Clefts in these lobes close upon binding iron (Luck and Mason, 2012), resulting in a conformational shift that alters the affinity for transferrin receptors and may have additional consequences for protein-protein interactions. The ability of each lobe to independently bind an iron atom results in four circulating species of Tf: apoTf, monoferric N, monoferric C, and holoTf. The monoferric forms of transferrin influence erythropoietin sensitivity and iron homeostasis (Parrow et al., 2019). Thus, targeting them may have therapeutic potential in diseases characterized by erythropoietin resistance or dysfunctional hepcidin levels.

Transferrin has two receptors: transferrin receptor 1 (TFR1) and transferrin receptor 2 (TFR2). TFR1 is ubiquitously expressed, including in the brain endothelium (Roberts et al., 1993), and primarily serves to deliver iron from transferrin to cells. At serum pH, iron-loaded Tf binds TFR1 with high affinity and the complex undergoes endocytosis. A decrease in endosomal pH promotes the release of iron from Tf and the apo-Tf-TfR1 complex is recycled to the cell surface where apoTf is released (Steere et al., 2012). TFR1 is upregulated in highly proliferative cells (Zhang et al., 2024) and in response to iron deficiency (Tong et al., 2002; O'Donnell et al., 2006; Meyron-Holtz et al., 2004).

TFR2 is thought to primarily serve as a signaling receptor. In mice (Fleming et al., 2002) and humans (Camaschella et al., 2000), loss of TFR2 results in hereditary hemochromatosis, a disorder characterized by excessive iron absorption secondary to inappropriately low hepcidin levels.

This Research Topic focuses on Tf as a therapeutic target and a drug delivery system. Li et al. present a review of the potential therapeutic applications of Tf (*Pathophysiological aspects of transferrin-A potential nano-based drug delivery signaling molecule in therapeutic target for varied diseases*). They provide an overview of the use of TF as a therapeutic agent in various clinical conditions. One of these is transferrin replacement therapy in the rare transferrin deficiency disease, atransferrinemia. Another is the use of transferrin therapies, such as the administration of ApoTf, to neutralize free iron in

ischemia reperfusion injury models. This review also covers an array of studies where chemotherapeutics or imaging agents are delivered via transferrin-conjugated moieties or are otherwise directed to TfR1 by an antibody or peptide. These approaches leverage the upregulation of TfR1 that characterizes proliferating tumor cells.

He et al. also present studies investigating transferrin-conjugated therapies or TfR1-targeting in the context of reviewing the potential for natural products to alleviate chemotherapy-related cognitive impairment (*Natural products for the treatment of chemotherapy-related cognitive impairment and prospects of nose-to-brain drug delivery*). One such study indicates that targeting nanocarrier-wrapped ginsenoside RG1 (an active constituent of ginseng) to TfR1 increased penetration of the blood brain barrier and decreased brain infarct volume in a cerebral ischemia model (Shen et al., 2019). He et al. also propose nose-to-brain delivery as a mechanism to bypass the blood-brain barrier. Proof of principle is provided by at least one study that generated and investigated transferrin-conjugated chitosan nanoparticles (Gabold et al., 2023). Nanoparticles with the highest surface expression of transferrin had the highest uptake in a human nasal epithelial cell line and transferrin-conjugated nanoparticles passed more quickly through an epithelial layer to glioblastoma cells in co-culture model systems.

In a specific study of transferrin as a delivery system, Alrouji et al. present a primary investigation of the binding mechanism of capsaicin with human transferrin (*Evaluation of binding mechanism of dietary phytochemical, capsaicin, with human transferrin: targeting neurodegenerative diseases therapeutics*). Capsaicin is the primary component of chili pepper. Recent studies suggest dietary capsaicin may have neuroprotective properties, with specific therapeutic potential for Alzheimer's disease (Wang et al., 2020; Xu et al., 2017). Transferrin provides a potential means to deliver capsaicin across the blood-brain barrier via TfR1. Using a combination of approaches, their studies indicate that capsaicin binds transferrin in the iron-binding pocket without significant structural alterations. They report a binding constant of 3.99×10^6 M^{-1}, indicating that transferrin has a considerably lower affinity for capsaicin compared to Fe^{3+} (Aisen et al., 1978). *In vivo* studies comparing the efficacy of transferrin-mediated capsaicin delivery to dietary capsaicin in mouse models of disease will be useful in evaluating the feasibility of this approach.

Ren et al. present an umbrella review of meta-analyses of the effects of the prolyl hydroxylase inhibitors (PHI) on anemia in chronic kidney disease (*Efficacy and safety of hypoxia-inducible factor-prolyl hydroxylase inhibitor treatment for anemia in chronic kidney disease: an umbrella review of meta-analyses*). This class of drugs inhibits the oxygen-dependent prolyl hydroxylases responsible for degradation of hypoxia inducible factor (HIF) (Haase, 2021). HIF controls the myriad responses to hypoxia (Semenza, 2012), and transferrin itself is upregulated in response to hypoxia (Li et al., 2022). Their meta-analysis confirms an increase of ~ 1 g of hemoglobin per deciliter in studies of PHIs. As expected, the increase is more pronounced compared to placebo than to erythropoiesis-stimulating agents (ESAs). Treatment with PHIs decreases levels of the hepatic iron-regulatory hormone hepcidin, also demonstrating a stronger effect compared to placebo than to ESAs. Surprisingly, 7 of 11 studies analyzed did not show a significant difference in serum iron concentration compared to ESA or placebo. There was, however, evidence of increased total iron-binding capacity, a surrogate measure of transferrin, and transferrin level itself. A corresponding decrease in transferrin saturation was also observed. Based on the demonstrated capacity of lobe occupancy of transferrin to influence erythropoietin responsiveness and iron homeostasis, it is tempting to speculate that the upregulation of transferrin by the prolyl hydroxylase inhibitors may have previously unrecognized effects on the distribution of iron-bound transferrin species that contribute to the efficacy of these therapeutics in the anemia of chronic kidney disease.

In total, this Research Topic provides exciting evidence that transferrin has therapeutic utility in a variety of diseases. Additionally, targeting TfR1 may provide specific mechanisms for delivering chemotherapeutics and imaging modalities to rapidly proliferating cells, as well as bypassing the blood-brain barrier. We look forward to the continued development of drugs based on transferrin.

Author contributions

PC: Conceptualization, Writing–original draft, Writing–review and editing. SC: Writing–original draft, Writing–review and editing, Conceptualization. MP: Writing–original draft, Writing–review and editing, Conceptualization. RF: Writing–original draft, Writing–review and editing, Conceptualization. NP: Conceptualization, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. RF and NP are supported in part by NIH NIDDK grant R01DK095112 to RF.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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