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Review On Transferrin: Structure, Function And As Therapeutic Agent

[1]Mr.Nilesh Kothare,[2]Miss.Madhuri Pawar,[3]Miss.Shital Khandagale,[4]Dr.Hemant Kamble,[5]Mr.Santosh Waghmare

[1]Student,[2] Student,[3] Student

[1]Pharmacology,

[1]LSDP College of Pharmacy

Abstract: There has been a lot of work done to understand transferrin-mediated iron uptake since it was identified more than 50 years ago. Our understanding, however, did not significantly develop until the discovery and characterisation of a number of new iron homeostasis-related genes, including the hemochromatosis protein HFE and the iron transporter DMT1. Internalisation of the combination of iron-bound transferrin and the transferrin receptor, which is adversely regulated by HFE, a protein associated with hereditary hemochromatosis, is a significant mechanism for cellular iron uptake. Because of the endosome's acidic pH, iron is liberated from transferrin and then transferred to the cytosol by DMT1. The iron is subsequently either stored in ferritin or used as a cofactor by heme and ribonucleotide reductase. In addition to iron, numerous other metal ions of therapeutic and diagnostic value can bind to transferrin at the iron sites, and many cells can recognise these transferrin complexes. As a result, transferrin has been described as a "delivery system" for both detrimental and beneficial metal ions into cells. The active targeting of anticancer medications, proteins, and genes to primary proliferating malignant cells that overexpress transferrin receptors has also made extensive use of transferrin as a targeting ligand. The iron is subsequently either stored in ferritin or used as a cofactor by heme and ribonucleotide reductase. In addition to iron, numerous other metal ions of therapeutic and diagnostic value can bind to transferrin at the iron sites, and many cells can recognise these transferrin complexes. As a result, transferrin has been described as a "delivery system" for both detrimental and beneficial metal ions into cells. The active targeting of anticancer medications, proteins, and genes to primary proliferating malignant cells that overexpress transferrin receptors has also made extensive use of transferrin as a targeting ligand.

Key words: transferrin; transferrin receptor; drug delivery; gene delivery

INTRODUCTION

Millions of people throughout the world experience neurological problems, and in the next years, even more people will be impacted by cerebrovascular diseases, such as Alzheimer's and Parkinson's disease. The blood-brain barrier (BBB), which prevents drugs from reaching the brain, limits the options for treating neurological illnesses.(1) The BBB controls the flow of chemicals between the brain and the rest of the body creation of effective methods to undermine the integrity of thus, the BBB is essential for developing tools that will enable the treatment of central nervous system (CNS) illnesses. It is crucial to comprehend the morphological and physiological characteristics of the BBB in order to create such bypassing techniques.(2) Delivering these molecules selectively to the identified target cells can increase the therapeutic index of medications while lowering their adverse consequences. Numerous initiatives are being made to investigate the possibilities of site-specific and target-oriented delivery systems, such as drug delivery systems based on polymers and liposomes. Since naturally occurring proteins (like transferrin) are biodegradable, nontoxic, and nonimmunogenic, these proteins have also attracted significant attention in the field of drug targeting(8). Additionally, they are able to target cells specifically because of the abundance of their receptors on the cell surface. Anticancer medications, proteins, and therapeutic genes could be delivered to proliferating malignant cells that overexpress transferrin receptors through the efficient cellular absorption of transferrin (Tf1) pathway. Targeting CNS-active medicines to BBB-associated carrier and receptor proteins is a potential tactic.(5) The transferrin receptor (TfR), which is expressed by brain capillary endothelial cells (BCECs), is the most frequently targeted of these. The state of our understanding regarding the TfR's function in brain iron uptake is summarised in this review. Thereafter, comprehensive coverage of the detailed summaries of studies looking at the delivery of TfR-targeted antibodies and the roles of the TfR and its ligands the brain parenchyma with nanomedicines. The difficulties of the TfR targeting approach are reviewed, with a focus on the potential for developing this method of brain drug delivery into the brain medications of the future.(5)

Transferrins

In-depth research has been done over the last few decades to comprehend these special iron-binding proteins. A wide range of information about Tf and TfR functional characteristics, structures, metal binding properties, and their potential in biomedical processes has been covered in a number of reviews.(6)

Occurrence and Biological Function

A family of large (molecular mass around 80 kDa) nonheme iron-binding glycoproteins known as transferrins is thought to have evolved with vertebrates or prevertebrates. Transferrins can be classified into three main categories. Blood and other mammalian fluids, such as bile, contain serum Tf, which is mostly produced by hepatocytes. Lactoferrin (Lf), which has a concentration of 2.5 mg/ml and is 30% occupied with iron in blood plasma, is present in milk, tears, saliva, and other secretions,milk, lymph, colostrom, amniotic fluid, cerebrospinal fluid, and lymph. (10)The protein ovotransferrin (oTf) is present in avian and both in avian egg white and reptile oviduct secretions Except for melanotransferrin, the main biological function of transferrins is assumed to be connected to their capacity to bind iron. Iron is transported to cells and tissues by serum Tf from the sites of ingestion into the systemic circulation. Other than iron, a large variety of other metal ions, such as those used for medicinal purposes, radiodiagnostic purposes, and some poisonous metal ions, are also likely to be transported by it. Contrarily, lactoferrin is thought to function primarily as a bacteriostat by chelating iron, which is necessary for the development of microorganism antibacterial action.(12,11) Unrelated to its iron-binding abilities, lactoferrin may potentially influence immunological and inflammatory responses as well as function as a growth factor. Ovotransferrin demonstrates antibacterial action as well. Melanotransferrin's purpose is not yet fully understood. It appears to have a negligible impact on iron absorption. Alternatively, it could promote the rapid growth of tumour cells and function as an iron scavenger at the cell surface to stop lipid peroxidation.(15)

Structure

The majority of the iron circulating in plasma under healthy conditions is attached to Tf, a 78 kDa monomeric glycoprotein that belongs to a family of glycoproteins that also includes ovoTf, melanoTf, and lactoferrin. Tf is one of the most prevalent plasma proteins, with levels ranging from 25 to 50 M (2-4 g/ml) in the blood plasma of healthy adult humans.(17,18) It is largely produced in the liver, but it is also produced locally in the oligodendrocytes and choroid plexus epithelial cells of the CNS. Only around 30% of the Tf molecules are saturated with iron because of how common Tf is in plasma. The accumulation of toxic non-Tf bound iron (NTBI), which can be seriously harmful over time as shown in hemochromatosis, is thus prevented by the role of Tf as a buffer molecule if the plasma concentration of iron grows quickly. The N and C terminal domains of a single polypeptide chain, which makes up the Tf molecule, are both of similar size. Due to the presence of iron-binding sites in each domain, each Tf molecule can transport two iron molecules in their ferric form. These sites have an unusually high binding affinity for a single iron atom. (20)Different Tf forms occur because it has two iron-binding sites. Tf that has not been bonded to iron is known as apo-Tf, whereas Tf that has been bound to one iron atom is known as mono-ferric Tf and Tf that has been bound to two irons is known as di-ferric Tf or simply holo-Tf. Therefore, each Tf molecule has the capacity to transport two iron molecules in their ferric form. Different Tf forms occur because it has two iron-binding sites. Tf that has not been bonded to iron is known as apo-Tf, whereas Tf that has been bound to one iron atom is known as mono-ferric Tf and Tf that has been bound to two irons is known as di-ferric Tf or simply holo-Tf. Iron binds to Tf in a pH-dependent manner.(21) The maximum binding affinity of Tf to iron exists at a physiological pH of 7.4, where the association is nearly irreversible. Iron is released when the binding affinity of Tf to iron is lower than 6.5.

Tf primarily serves as an iron transporter in the body's plasma and interstitial fluids, taking in iron produced from cells and delivering it to other cells. Because of the Tf molecule's hydrophilic character and strong affinity for the TfR, cells that express the TfR are primarily responsible for absorbing Tf-bound iron. Because of the Tf molecule's hydrophilic character and its high affinity for the TfR, cells that express the TfR are primarily responsible for absorbing Tf-bound iron.(23)

There are now two recognised TfRs. These are known as TfR1 and TfR2, with TfR1 having received the most research. In the extracellular domain, they exhibit homologies of 45–66%, but their patterns of expression alter when they are present in the body. The TfR1 is typically present on the surface of the majority of body cells, whereas the TfR2 is mostly expressed in tissues involved in controlling iron metabolism, such as the liver and small intestines.(19)

Biological Function

In order to maintain iron availability and prevent the formation of insoluble ferric hydroxide aggregates, transferrins' primary function is to regulate the quantities of free iron in bodily fluids by binding, securing, and moving Fe3 ions. The function of serum transferrin is to move iron between the sites of absorption, storage, and utilisation.(22) It might control how much iron is metabolised and safeguard against free iron's hazardous side effects, which can harm cells by causing the production of free radicals. In addition to iron, it is expected to transport a wide variety of other metal ions, including certain poisonous metal ions, radio diagnostic metal ions, and therapeutic metal ions.Additionally, ovotransferrin and lactoferrin might exhibit antibacterial properties, which appears to depend more on direct touch with the bacteria than just a lack of iron.It has been suggested that lactoferrin functions as a growth factor and may be crucial in controlling immunological and inflammatory reactions as well as iron absorption.

Transferrin Receptor

There are transfemn receptors on practically all mammalian cells. The receptor takes involved in receptor-mediated endocytosis, which is how cells take up iron from transferrin. The abundance of receptors is typically controlled by two variables: cell growth and cellular iron status. The use of transfemn receptor determination as a diagnostic tool is supported by these two elements.(19)

Regulation of Transferrin Receptor 1 Expression

All of the body's nucleated cells, including hepatocytes, intestinal cells, monocytes (macrophages), erythroid cells, red blood cells, and hepatocytes, appear to express the TfR1. Additionally, some insects and specific bacteria can be found in the brain, blood-brain barrier, blood-testis, and blood-placenta barriers, as well as other organs. 10,000 to 100,000 molecules per cell, which are typically detected on tumour cells or cell lines in vitro, express it on rapidly dividing cells. TfR1 expression, in contrast, is typically low or absent in nonproliferating cells. Iron-responsive elements (IREs) and iron-regulatory proteins (IRPs) interact in the 3-untranslated region of TfR1 mRNA to control TfR1 expression in nonerythroid cells at the post-transcriptional stage.(16)Numerous investigations have demonstrated that when the cells developed in the presence of iron salt, their Tf-binding capacity decreased in a concentration- and time-dependent manner. In contrast, treatment of the cells with iron chelators resulted in a decrease in the amount of ferritin and an increase in the number of receptors, which depends on a faster rate of receptor synthesis.(14)

Transferrin Receptor 2 (TfR2)

TfR2, a new member of the TfR-like family, was recently cloned and sequenced. TfR2 and TfR have extracellular domains that are 45% identical and 66% similar. There are two transcripts available. The transmembrane protein that results from the a-transcript is mainly expressed in the TfR2 b-transcript and the liver of humans and mice, respectively, are the products of alternative splicing. Although it may produce an intracellular protein that is broadly dispersed, its expression is minimal.Regarding Tf binding and Tf-mediated iron absorption, TfR2 performs a comparable role as TfR. Two TfRs were created for unknown reasons, which are still not fully understood(19). The high amount of TfR2 expression in the liver points to a specific function for this receptor; it's possible that TfR2 makes a significant contribution to the liver's capacity to absorb and retain iron. Additionally, it has recently been hypothesised that TfR2 may be crucial for controlling hepcifin expression, which would affect the control of dietary iron absorption.(13)

CELLULARIRONUPTAKEVIATRANSFERRIN-RECEPTOR-MEDIATED ENDOCYTOSIS

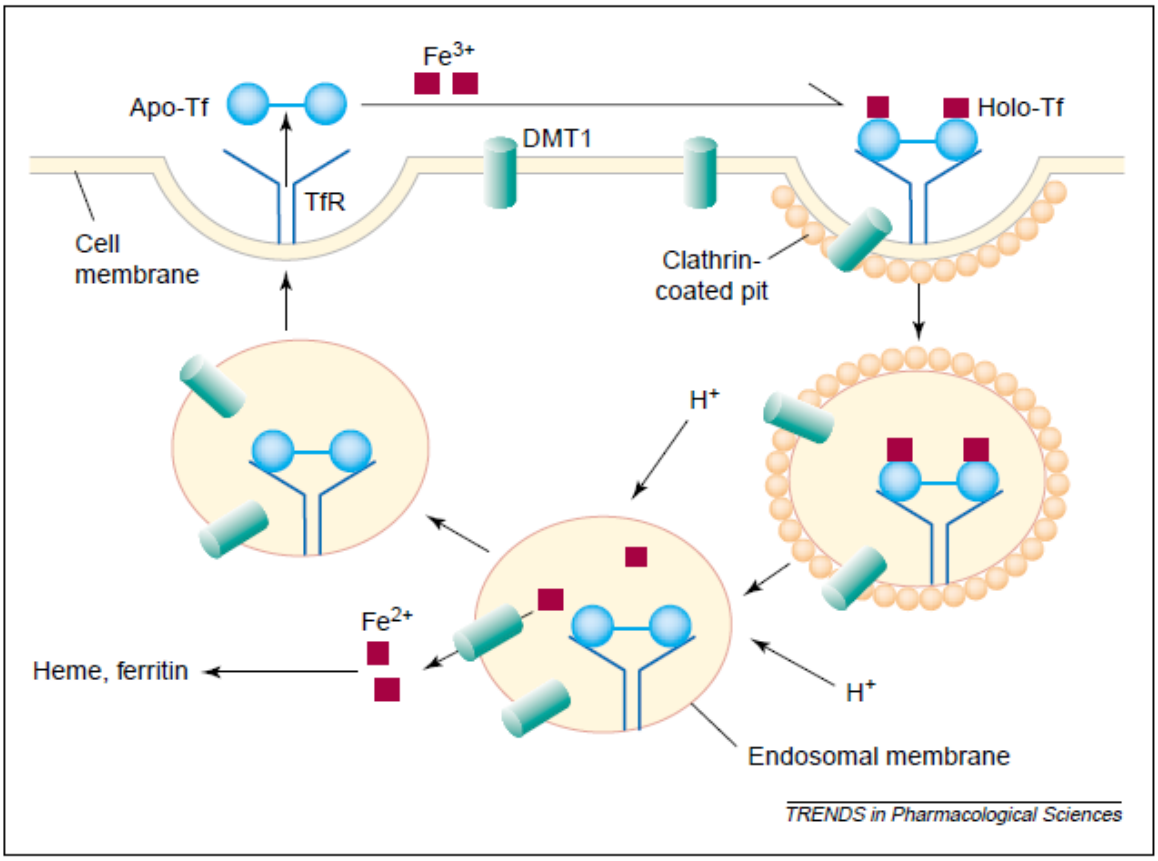
Iron and Diseases

Almost all creatures require iron, which performs a number of biological tasks. Examples include the movement, storage, and activation of oxygen; the creation of energy; the growth of new cells; and a number of catalytic procedures.(23) Iron could be poisonous, though, if it combines with oxygen to form poisonous free radicals that damage DNA, proteins, and cellular membranes. Organisms combat this issue by carefully controlling the amount of iron present in their internal fluids. There is no efficient excretory route in animals like humans. Instead, iron absorption and its export from the enterocytes to the blood are regulated by the cells lining the gut and enterocytes. Typically, an adult human contains 35 to 45 mg of iron per kilogramme of body weight, with more than two thirds of that iron being absorbed into haemoglobin in both developing and mature red blood cells. Dietary iron absorption and body utilisation are typically closely related because the proximal small intestinal tract detects body iron concentrations.(21)

Transferrin-Receptor-Mediated Iron Uptake

The majority of mammalian cells, if not all of them, are capable of absorbing iron through the transferrin receptor-bound differic transferrin's receptor-mediated endocytosis. The recent identification of numerous genes, including HFE96, linked to hereditary hemochromatosis, and divalent metal transporter (DMT1/Nramp2), a membrane iron transporter, has significantly increased our understanding of cellular iron transport. These proteins most likely have a significant impact on the transferrin cycle. The six phases of transferrin endocytosis—binding, internalisation (endocytosis), acidification, dissociation, and reduction—as well as the cytosolic transfer of iron into intracellular molecules like ferritin—are commonly acknowledged.(17)

One of the mechanisms in cell biology with the finest characterization is endocytosis mediated by transferrin and TfR. A family of iron-binding proteins known as transferrins transports iron between its sites of absorption, storage, and utilisation. The internalisation of the complex of iron-bound transferrin and the TfR is a key mechanism for cellular iron absorption. Diferric-transferrin attaches to the TfR on the cell surface, and the complexes are then transported into the endosomal compartment via clathrin-coated pits following endocytosis. Iron is liberated from transferrin and then transferred to the cytosol by the divalent metal transporter (DMT1) as a result of the endosome becoming mature and losing its clathrin coat. The apo-transferrin-TfR complex is then returned to the cell surface via exocytic vesicles, where it is discharged into the circulated and used again. The liberated iron is either retained in ferritin or utilised as a cofactor by heme and ribonucleotide reductase.(16)



Transferrin in metallodrug delivery

Because serum transferrin is only partially saturated with iron, it has a high affinity for binding to other metal ions of therapeutic and diagnostic importance. It is commonly accepted that transferrin can carry the anticancer drugs Ga3+ and Ru3+ into tumour cells, while other absorption methods that are not receptor-mediated may also be possible(8) . The first distinct Ti4+-protein complex, Ti4+-transferrin, has recently been characterised and may be relevant to the anticancer activity of titanium complexes . Additional biological research on Ti2-transferrin revealed that Ti2-transferrin can prevent Fe2-transferrin from attaching to membranes and from being taken up by human placental choriocarcinoma cell lines. This discovery is important for our comprehension of how titanium anti-tumor drugs work. (9)Transferrin may be used to carry titanium to cancer cells, where it may then be released into the tumor's acidic microenvironment and target DNA. Transferrin has also been connected to the movement of bismuth anti-ulcer medications.It has been demonstrated that these medications can bind transferrin even in physiologically plausible situations. IEC-6 rat intestinal cells can also recognise bismuth-lactoferrin. This discovery might have effects on bismuth transport as well as bismuth's antibacterial properties. In addition to inhibiting target enzymes necessary for bacterial life, bismuth may also be released within cells and interfere with iron uptake as a result of binding to transferrin or lactoferrin. There is a need for more research in this area.(7)

Transferrin conjugates in drug and gene delivery

Because there are more TfRs on the surface of tumour cells, transferrin has potential as a medication delivery system. Some of the anticipated benefits of transferrin-drug conjugates include a more favourable tissue distribution, an extended plasma half-life, and regulated drug release from the conjugates. Recent research has shown that the transferrin absorption pathway is an extremely powerful tool for treating cancer in both human and animal models. Transferrin has the ability to prevent cardiotoxicity and the emergence of drug resistance when combined with anticancer medicines like doxorubicin.(5) Transferrin-CRM107, a combination of transferrin and a point mutant of diphtheria toxin, specifically kills cells that express a lot of TfRs, including tumour cells. Patients with malignant brain tumours have received intratumoral injections of transferrin-CRM107. Due to the low level of TfRs expressed by capillary endothelial cells in the brain, patients who receive high doses of transferrin-CRM107 may experience neurological deficits that are consistent with endothelial damage, even though approximately half of these patients showed a decrease in tumour volume.(9)

Transferrin receptor in brain drug delivery

The blood-brain barrier (BBB) in vivo, which is made up of the brain capillary endothelial wall, significantly restricts the transport of therapeutic medicines to the brain. However, certain receptor-mediated transport systems are present in brain capillary endothelial cells and may be used to deliver medicines to the brain specific anti-receptor antibodies, such as the rat TfR monoclonal antibody OX26 shows significant promise as a medication for the brain.(5)

transportation arrows the OX26 delivery strategy is less sensitive to blockage by circulating transferrin than the transferrin-drug conjugates because the OX26 antibody binds to the TfR at a place different from the transferrin binding site. (6)Therapeutic conjugates that contain the OX26 antibody are transcytosed via the BBB by the brain capillary endothelial TfR. Antisense radiopharmaceuticals, which enable early changes in gene expression to be visibly caught by imaging and guarantee early diagnosis and treatment of CNS disorders, have been given this delivery mechanism. Therapeutic peptides or proteins have been successfully delivered into the brain using this approach as well. Recent research has shown that brain-derived neurotrophic factor (BDNF), when coupled with OX26, was also transported into the brain, suggesting that this finding may be significant.(20)

Conclusion

Transferrin and the TfR have the potential to be crucial targeting ligands for a variety of therapies, including anticancer medications, peptides, proteins, and even genes, when delivered to malignant cells that overexpress transferrin receptors. The distribution of drugs and genes to the brain is significantly influenced by the TfR in particular. There are just a few clinical uses at the moment due to a number of issues, most notably the poor targeting and transfection effectiveness of gene delivery. It is very likely, nevertheless, that the fundamental research in this field will be transformed into practical applications, notably in the diagnosis and treatment of CNS illnesses, given the tremendous advancements in biology, material science, pharmaceutical science, protein engineering, and these other fields.

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