Transferrin polymorphism and its clinical applications

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Abstract

Transferrin is an important factor that is responsible for the transport of iron in the blood. It has got several polymorphisms, out of which there are three major isotypes and the polymorphism vary with different species. Transferrin is also distributed in various living cells and body fluids. Normal plasma concentration is necessary to be maintained and if it found less, then the susceptibility to various infections are more. Transferrin also has the ability to modulate differentiation and growth of cells. Apo-transferrin, a synthetic form of transferrin is highly recommended for the treatment of various clinical conditions. The present review helps in the overviewing of the structure of transferrin, polymorphism, functions of transferrin polymorphism and its clinical applications.

Keywords: Apo-transferrin, clinical applications, iron-binding, polymorphism, redox potential

1. Introduction

Transferrin is responsible for the iron-transporting function of the blood. The transferrin (Tf) protein contains 679 amino acid residues. The molecule is stabilised by 19 intra-chain disulphide bonds and is protected by 3 carbohydrate chains - two are N-linked and third is O-linked. Transferrin molecule is divided into two evolutionary related lobes consist of N-lobe (336 amino acids) and C-lobe (343 amino acids) which are linked by a short spaces sequence. Each lobe contains two domains, α-helices and central β-sheet backbone [1]. Domains interact to form a deep, hydrophilic metal iron binding site. The binding site -both N- and C-terminal lobes - 4 conserved AA (2 tyrosine's, 1 aspartic acid, 1 histidine). Binding site requires 2 further O₂ molecules - donated by carbonate molecule - stabilise the iron atom. Reduction in the pH can cause breakage of hydrogen bond that allows the domain to rotate forming an open conformation that promotes iron release [2].

Transferrin also plays an essential role in correction of various clinical conditions, which is primarily because of the process called transferrin polymorphism. Transferrin polymorphism has got various potential roles in antimicrobial activity and immunity, it can be used to treat various clinical conditions. This mainly includes transferrinemia [11-13], ischemia reperfusion injury [14-18], cardiovascular diseases and also in the clinical procedures like radiotherapy [3, 4, 20], targeted delivery system [3, 5, 21] and cancer therapy [22].

2. Transferrin Polymorphism

Transferrin has several polymorphisms that vary with different species. 3 major isotypes include B, C and D. Majority of the species have C allele. There is a link between transferrin polymorphism and susceptibility to diseases [3].

3. Role of transferrin in binding of iron

Central role of transferrin is in DNA replication. Iron acts as a co-factor for heme. Free iron can be toxic that leads to free radical formation, which causes oxidative damage to tissues [4]. It can also cause lipid peroxidation, i.e., hydroperoxides get converted to reactive peroxide and alkoxyl radicals [1]. Transferrin promotes auto oxidation reactions involving CHO aldehyde groups and protein amino groups leading to the formation of glycated products. Iron is transported in a redox-inactive form. The primary role of transferrin is to transport iron safely around the body to supply growing cells. The binding and release of iron by transferrin involves several factors like pH, temperature and ionic concentration [5].
4. Distribution of transferrin
Transferrin is synthesised predominantly in hepatocytes and also in other tissues like sertoli cells, ependymal, oligodendroglial, metastatic melanoma cell lines [6]. Transferrin is also deducted in various body fluids like plasma, bile, amniotic, cerebrospinal, lymph and milk [7].

5. Concentration & half-life of transferrin
Plasma concentration of transferrin is stable from birth and the range is around 2-3 gram per litre. Half-life of the transferrin is around 18 days and the level of transferrin depends on the healthy growth [3]. Levels below 0.1 gram per litre tends to cause increased incidence of infections, growth retardation and anaemia [8].

6. Functions of transferrin polymorphism
Transferrin polymorphism has potential roles in antimicrobial activity, growth, differentiation and cytoproduction. In animals, bacterial pathogens can sequester free iron by releasing low molecular weight siderophores that actively uptakes heme [3]. High levels of free iron can cause increased incidence of bacterial infection, for example, liver failure, hereditary and secondary chromatosis, premature birth and haematological malignancies [9]. The anti-microbial activity of apo-transferrin might not be simply reducing free iron levels and also reducing the adhesion of gram-positive and gram-negative bacteria to surfaces. Transferrin is also important for growth and differentiation activities including myotrophic, embry-morphogenic proliferative, mitogenic, neurotropic, chemotactic and angiogenic activities [10]. Transferrin is one among the many growth factors that tends to modulate cell growth and differentiation [1].

7. Clinical Applications of Transferrin
7.1. Atransferrinemia
It is a rare condition that is characterised by anaemia, iron overload, growth, retardation and increased incidence of infections [11]. Infusion of apo-transferrin can be done to treat the condition [12]. The individuals affected with atransferrinemia have normal haemoglobin levels and did not develop antibodies to Transferrin [11, 13].

7.2. Ischemia reperfusion (IR) injury
Ischemic reperfusion injury is a condition that promotes oxidative stress [14] resulting in inflammation and ultimately, cell death by apoptosis and necrosis. It is associated with conditions such as stroke, cardiovascular disease and renal failure [15, 16]. Because free iron can able to catalyse the production of free-radicals, the presence of increased concentration of redox reactive iron could potentiate ischemic reperfusion injury [14, 17]. The use of iron chelator like deferoxamine is useful in protective against ischemic reperfusion injury [15]. Apo-transferrin was able to inhibit neutrophil chemotaxis and complement activation and prevent loss of renal function in a dose-dependent manner [18].

7.3. Cardiovascular diseases
Low levels of Transferrin and glycation of amino residues on Transferrin, enhance the pro-oxidative effects of iron [4]. These effects are significant causes underlying lipid peroxidation and the risk of CardioVascular Disease in diabetic animals [19]. Transferrin is a negative acute phase protein that get down regulated in certain cases like diabetes. Oxidative damage and neuropathy in diabetes animals causes increased loss of Transferrin [1]. Transferrin levels in diabetes animals tends to be 10 percentage lower than normal individuals. Intravenous administration of apo-transferrin in diabetic animals can minimise free iron migration and provides a means to control the oxidative damage & to reduce the frequency of Cardiovascular Disease [10].

7.4. Radiotherapy
Levels of transferrin tends to decrease during radiotherapy treatment and it promotes oxidative-stress by increasing the levels of redox reactive iron in the circulation [3, 20]. Infusion of apo-transferrin might bind the iron released during irradiation - minimise oxidative damage [4].

7.5. Targeted drug delivery
The mechanism of iron transport and uptake via transferrin transport system has the potential for site specific delivery of various therapeutic metal ions, drugs, proteins, and genes. Transferrin is only percentage saturated with iron in the body [3]. Thirty other metal ions can also bind to transferrin [21]. It is possible to use transferrin to transport other metals around the body. Gallium and indium can also be transported by transferrin. The cellular uptake of gallium is mainly through the transferrin mechanism and it concentrates in tissues expressing high levels of transferrin such as tumors [3]. Gallium, a low-energy gamma-emitting radionuclide - widespread used as a targeted drug delivery using transferrin pathway. Other examples of anti-cancer compounds that are used in conjunction with transferrin include doxorubicin, chlorambucin and paclitaxen. Transferrin pathway can also be used to deliver small peptides by incorporating the target peptide into the primary sequence of transferrin. Delivery of therapeutic genes can also be done through viral vectors.

7.6. Cancer therapy
Apo-transferrin can be used in the treatment of cancer. Transferrin in combination with other factors like Insulin like Growth Factors-1 and Interleukin-2 can promote cytotoxicity and proliferation in lymphokine-activated killer (LAK) cells and natural killer (NK) cells [22]. The iron binding ability of Transferrin has been used in conjunction with the anti-malarial drug, artemisinin (ART), to improve drug resistance in small cell lung carcinoma (SCLC). Artemisinin, a naturally occurring compound in the presence of iron can get break down into a toxic compound and it can able to kill the SCLC cells at nanomolar concentrations after treatment with transferrin [3]. Leukaemia cells are also more effectively kill when artemisinisin compounds are used in conjunction with transferrin.

8. Conclusion
Transferrin like plasma proteins have additional functions apart from its primary activity of binding and transporting iron. From a therapeutic perspective, this enables one molecule to be used for various treatments. Transferrin is also used to deliver drugs to rapidly growing cells, to activate immune cells and to prevent cell apoptosis. Transferrin, being an abundant plasma protein is an ideal candidate for purification from plasma. Delivery systems could be altered for specific delivery of drugs to rapidly dividing cells. Transferrin is therefore an ideal candidate molecule for companies wishing to pursue new therapeutic options.
Conflict of Interest
The authors declare that they have no conflict of interests.

References