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Transferrin-Mediated Cellular Iron Uptake —Special Implication of Endothelium in Hepatic Iron Uptake—

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ABSTRACT : Transferrin (Tf) is thought to play a pivotal role in iron metabolism of various kinds of cells. Tf has specific receptors on the surface of the cells that require iron. Tf-receptor binding is followed by internalization through a system of coated pits and vesicles. The rapid decline of pH of these vesicles leads to the release and sequestration of iron by the cell. Apotransferrin-receptor complex returns to the cell surface, where under neutral pH conditions, apotransferrin is dissociated from the receptor. Recent advances in cellular and molecular biology, gene cloning and monoclonal antibody technique have elucidated many features of these processes at a molecular level. These advances are briefly reviewed, and particularly, our own observations concerning endothelial mediation of uptake of Tf by hepatocytes are discussed.

Key words : Iron uptake, Transferrin, Receptor-Mediated Endocytosis, Desialation, Endothelium

Iron (Fe) is a prerequisite element of energy-generating systems of every life form. To maintain the iron in soluble form available for the biosynthesis of essential iron enzymes and proteins, all organisms have had to evolve specific iron-sequestering mechanisms to chelate iron in its most soluble and stable form[1]. In the vertebrate world, these functions are played by iron-chelating proteins, transferrins, of which the best known is serum transferrin (Tf). Probably, the most important and most intensely studied role of serum Tf is the transport of iron between sites of absorption, storage, utilization and excretion.

Mechanism of Cellular Iron Uptake

Endocytosis : Theoretically, Tf can deliver iron into the cell via three endocytic mechanisms[2].

1. Fluid-phase Endocytosis. This does not require binding of Tf to the cell surface. The magnitude of cellular uptake of iron via this route varies from one cell type to the other and also depends on the functional state of the cell, the cell cycle and Tf concentration in the medium. However, it generally does not exceed 50% of total iron delivery.

2. Specific Receptor-Mediated Mechanism.

This accounts for the highest proportion of transmembranous iron transport (described below in detail).

3. Adsorptive Mechanism. This, like the receptor-mediated mechanism, requires membrane binding followed by internalization of Tf but involves a number of low affinity membrane acceptor sites, which lack the specificity of the true receptors[3].

Release of Ligand at the Cell Surface : This mechanism is proposed to be present both for the reticulocyte[4] and particularly for the hepatocyte[5,6,7]. In these cells, diferric Tf binds to its specific receptors on the cell membrane[5,8,9,10,11]. The iron may then be extracted from Tf by some as yet unknown mechanisms, which might include conformational changes in the receptor after the binding of the ligand, regional changes in the membrane pH, or the reduction of ferric iron on the Tf by a functional group localized on the receptor. The iron is then transferred to a membrane binder[4] and from there into the cell, and Tf is dissociated from the receptor to bind Fe elsewhere in the body.

Transferrin Structure

Mammalian Tf consists of two globular domains of a single polypeptide chain with a molecular weight of approximately 80,000 daltons. The molecule has been sequenced and its three-dimensional structure studied, with the use of x-ray crystallography. Recently, a rat Tf gene was cloned by Huggenvik and Idzerda[12].

The molecule posesses two independent metal-binding sites located in the N-and C-terminal halves of the molecule. Each of these can bind a ferric ion together with a bicarbonate ion. The delivery of iron from Tf to the cell is mediated by the binding of Fe-Tf complexes to specific membrane receptors[13,14]. Therefore, Tf molecule posesses a specific receptor recognition site, in addition to the two metal-binding sites.

Amino acid sequencing of human Tf[15,16] indicates that it contains 679 amino acid residues and has an overall molecular weight of 79,570, including the two asparagine(Asn)-linked glycan groups. The polypeptide chain contains two homologous domains (Fig.1), consisting of residues 1 to 336 and 337 to 679. The two domains show some interesting differences, including the presence of both N-linked glycan moieties in the C-terminal domain at position of 413 and 611 and more disulfide bonds in the C-terminal domain (11 versus 8).

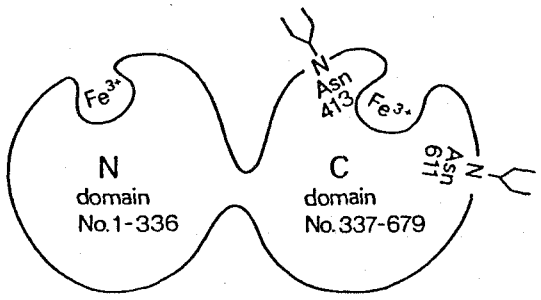

Fig. 1 Human transferrin molecule contains two globular domains (N and C), which are considerably homologous, indicating gene duplication. Each domain has a single Fe-binding site. Both biantennary glycan chains are located in C domain on asparagine residues of 413 and 611.

Glycan moieties consist of two identical and nearly symmetric branched heterosaccharide chains. The monosaccharide sequence of each chain has also been elucidated[17,18]. It is a biantennary structure, demonstrating the

frequently occurring structural element of glycans in plasma glycoproteins.

Despite considerable knowledge of their structure, we know little about the function of the carbohydrate moieties of Tf. Tf differs from most other serum glycoproteins in that enzymatic cleavage of its sialic acid residues has little effect on its survival in the circulation[19]. However, when human Tf is administered as a heterologous protein to rabbits or rats, desialation results in a 3.5-fold increase in catabolic rate[20]. Clearance of mammalian asialoglycoproteins from the circulation depends on specific hepatocyte receptors. These galactosyl receptors recognize the penultimate galactosyl residues that are exposed by enzymatic removal of sialic acid[21]. There is no explanation for the particular vulnerability of asialotransferrin. It may be that the carbohydrate of Tf has a recognition function for receptors of non-erythroid cells.

Heterogeneity of Transferrin

Human Tf is a glycoprotein with two glycan chains in the C-terminal domain linked to Asn residues 413 and 611. The most frequent structure is a biantennary glycan, but a triantennary glycan may also be present[22], linked to Asn at position 611 (Fig.2).

The heterogeneity of human Tf, as shown by isoelectrofocusing, is not caused by its protein moiety, because its amino acid sequence remains constant. It is probably caused by varying amounts of iron and/or varying amounts of sialic acids and other monosaccharides in the glycan groups.

Although the glycan chains of Tf appear to play a minor role in the iron-binding and iron-donating properties, they may have a role in determining the rate of clearance of the protein from the circulation, particularly by the liver, through the interaction of penultimate galactosyl residues of Tf with asialoglycoprotein receptors on the hepatocyte membrane. That the rate of clearance of asialotransferrin is not as rapid as that of other asialoglycoproteins may be related to the relative paucity of penultimate galactosyl residues in Tf, compared with other glycoproteins. Preferential uptake of Tf by certain tissues, such as bone marrow, that do not possess asialoglycoprotein receptors may also play a role.

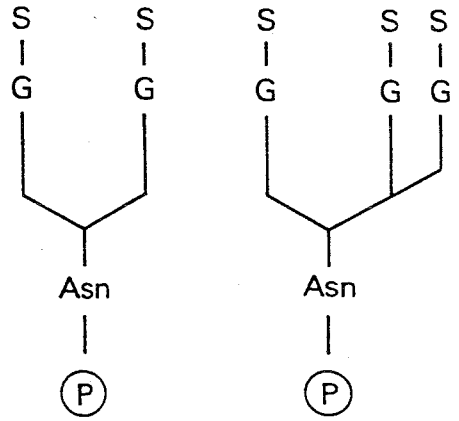

Fig. 2 The structure of bi-and triantennary glycan chains of human transferrin. S, sialic acid (N-acetylneuraminic acid) ; G, galactose ; P, protein.

Initially, it was thought that only the second glycosylation site (611 Asn) can bind triantennary glycan[22]. Recently, however, it has been documented that the first glycosylation site (413 Asn) can also have triantennary glycan[23].

By affinity chromatography on Concanavalin A(Con A) -Sepharose, human Tf displays three components[24]. It is postulated that the first component contains two triantennary glycan chains, whereas Component II bears

one bi-and one tri-antennary glycan chain and Component Ⅲ has two biantennary chains[25]. The iron uptake by hepatocytes from desialated Component Ⅰ is about ten times higher than that of desialated Components Ⅱ and Ⅲ. Thus the increase in Component Ⅰ observed in cirrhosis[26]. may explain the iron overload in the liver of cirrhotic patients.

However, similar peaks are obtained when rat Tf, which has a single glycan chain, is subjected to Con A-Sepharose chromatography[27]. Furthermore, unpublished data from our own laboratory indicate that component Ⅰ of rat Tf has more than three sialic acid residues, indicating the presence of tetraantennary glycan moiety as well. Further studies are needed to determine the exact proportions of different glycans in various types of Tf and the contribution of different types of glycan chain to the iron delivery.

Transferrin Receptor

Fe-Tf complex binds to specific receptors at the cell membrane. The receptor number on the cell surface is an index of the cell's requirement of iron, being largest on rapidly growing cells and hemoglobin-synthesizing cells and much lower on resting cells[28,29,30,31]. Recently, capillary endothelial cells also were shown to possess Tf receptors. In these cells, iron is not used by the cell itself, but Fe-Tf complex is transported via endothelium to the tissue. Thus the endothelium mediates the uptake of iron by the tissue.

The development of monoclonal antibodies, such as OKT9 and B3／25, prompted the isolation and characterization of Tf receptors.

Binding, Internalization and Recycling of Transferrin Receptos

Receptor-mediated endocytosis (Fig.3) is considered to be the major route for the cellular iron uptake. On the cell membrane Tf binds to the receptor. This step is followed by internalization. The binding occurs at 4℃ and is dependent on pH and the iron content of Tf. At pH 7.4, it has a much higher affinity for diferric Tf than for apotransferrin[32]. ; at pH values below 7.0, the affinity for apotranaferrin increases to that of diferric Tf[33,34]. After interaction with Tf, the receptors move laterally in the plane of cell membrane to segregate into clathrin-coated pits.

Eighteen years ago, Morgan[35]first suggested that Fe-Tf complex moves into the cell to deliver its iron. Evidence for this phenomenon now seems to be conclusive. A group of such complexes produces invaginations of the cell membrane (coated pits), leading to the vesicle formation in the cytoplasm (coated vesicles). At this point, the fate of Tf depends on the cell type. In most cells, of which K562 cell is a prototype, coated vesicles soon lose their clathrin coat ; this is followed by a drop in the pH of vesicles. Vesicles with low pH are generally recognized as endosomes. Consequent to the fall in the pH, iron is released from Tf. Meanwhile, the apotransferrin, still tightly bound to the receptor at a pH of about 5, returns within the vesicle to the cell surface, where apotransferrin is released at a neutral pH of about 7.4.

In other cell types, such as endothelium, Fe and Tf remain associated and are externalized to the medium with or without some modification (discussed below in detail).

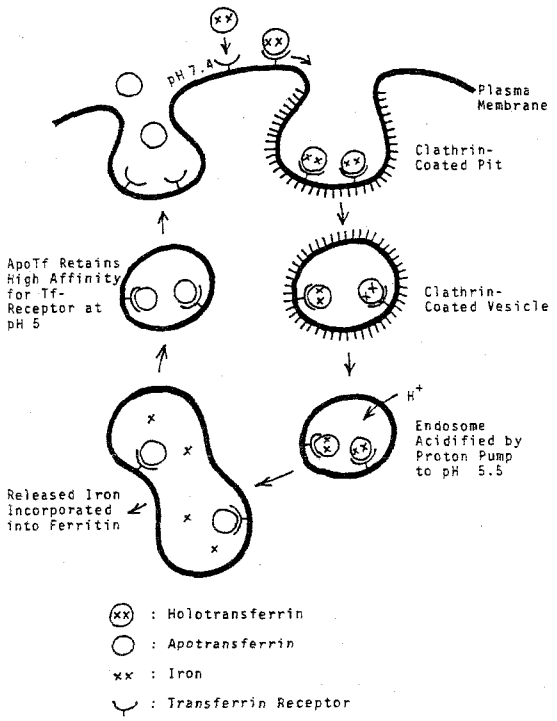

Fig. 3 Cellular iron uptake and transferrin-receptor recycling. The iron-transferrin complex moves laterally in the plane of membrane into the area of clathrin-coated pits. Membrane fusion results in transformation of these pits into clathrin-coated vesicles, which rapidly shed their clathrin coat. Consequent to the function of their hydrogen pump, their pH is rapidly lowered to 5. At this stage, they are known as endosomes. In this pH, iron is dissociated from transferrin to be incorporated into ferritin. The transferrin-receptor complex moves to the cell surface, where endosome becomes integrated with plasma membrane. Here, in the pH of about 7.4, the apotransferrin has a low affinity for the receptor. They become dissociated so that transferrin can circulate and chelate iron elsewhere. (Modified from Bomford Munro : Hepatology 5 : 870-875, 1985.)

Endothelial Mediation of Transferrin Uptake by Hepatocytes

Recently, interesting observations concerning endothelial mediation of uptake of Tf by hepatocytes have been accumulated (Fig. 4) L iver endothelium has high number of Tf receptors, but the presence of a significant number of Tf receptor on the hepatocyte has been questioned[36,37]. On the other hand, hepatocytes do bear many asialoglycoprotein receptors, which can recognize terminal galactosyl residues of glycoproteins[38]. When rat liver endothelial cells are incubated with rat diferric Tf, the internalized protein is desialated and externalized, with a negligible loss of iron[39].

Subsequently, asialotransferrin, which bears terminal galactosyl residues, is bound by asialoglycoprotein receptor on the hepatocyte. Part of this asialotransferrin is degraded in the lysosome after removal of iron, and the rest may possibly be resialated to recycle back into the circulation[40,41,42]. More recently, we have obtained the evidence indicating that the endothelium selectively desialates triantennary but not biantennary glycan chain of the molecule[43]. Interestingly, asialoglycoprotein receptors on the hepatocytes have been shown to possess selectivity for triantennary chain of asialoglycoproteins[44]. On the other hand, Tf molecules containing only biantennary glycan chain (s) are not desialated by the endothelium and could be recognized by hepatocytes through Tf receptors. This endothelial mediation of iron

uptake by the liver may provide a control mechanism whereby the endothelium can modulate the rate of iron uptake by the liver, and this may be an important factor in the pathogenesis of certain iron overload states, such as hemochromatosis and cirrhosis-associated siderosis.

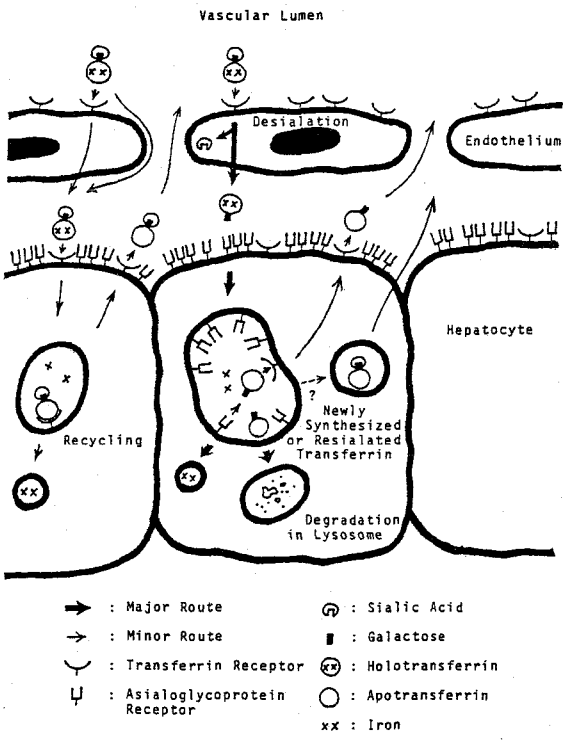

Fig. 4 Endothelial mediation of hepatic uptake of irontransferrin complex. The sialated iron-transferrin complex binds to appropriate receptors on the liver endothelium and is internalized, desialated so that the penultimate galactosyl residues are exposed, and then externalized to the abluminal side. The molecule is then recognized by asialoglycoprotein receptors of the hepatocyte membrane and internalized. Iron is removed in the low pH of endosome to be incorporated into ferritin. Asialoapotransferrin may be degraded in lysosomes or may bind to the vacant transferrin receptors available and recycle back to the cell surface. Part of the asialotransferrin may be resialated to join the newly synthesized transferrin and be externalized to the circulation. Part of the iron-transferrin (probably containing only biantennary glycan chains) complex may not be desialated in the endothelium and be externalized in sialated form. This can be recognized by the transferrin receptor of hepatocyte membrane, and it can follow the same pathway as every other cell, with removal of iron and recycling of transferrin-receptor complex.

Hepatic membrane asialoglycoprotein receptors are lectin-like substances that specifically bind galactose and N-acetylgalactosamine residues. They outnumber Tf receptors on the hepatocyte membrane. Thus the endocytosis of asialotransferrin is mediated by this specific lectin, not by Tf receptors. Although diferric Tf does not affect the binding of asialotransferrin, it does reduce the half-life of the ligand in the liver. This suggests that Tf receptors may play an importhnt role in the exocytic leg of the endocytic-exocytic cycle. Based on this information, Regoeczi and Koj proposed a model[42] in which diferric asialotransferrin enters hepatocytes via asialoglycoprotein receptors. In the acidic environment of endosomes, iron becomes dissociated from asialotransferrin. In this acidic pH, iron-free asialotransferrin also becomes dissociated from asialoglycoprotein receptor but binds to the Tf receptor. This model is based on the data demonstrating that the binding of asialoglycopro-

tein to its receptor is acid labile but not Tf receptor binding.

Summary and Conclusion

The complexity of the Fe-Tf transport system is becoming gradually disclosed. The basic model for iron uptake maintains that under physiologic conditions, Fe-Tf complex is taken up by the cell via receptor-mediated endocytosis. The pH of the endosome then falls, and iron is dissociated in this acidic environment and apotransferrin subsequently recycles back to the cell surface to bind more iron for delivery to the cell. There is also increasing evidence that this process may display variations in different cell types and that this basic model may not apply to all situations.

Moreover, in addition to the specific receptor-mediated mechanism, fluid-phase endocytosis and nonspecific adsorptive mechanisms may play a role in cellular uptake of iron.

With the development of analytic and preparative methods, increasing evidence is being accumulated that Tf consists of heterogeneous variants with regard to its iron and sialic acid content, each of which may play a different role in iron metabolism.

Recent advances in molecular biology, gene cloning and monoclonal antibody technology have led to the elucidation of structural features of Tf and Tf receptors. It is anticipated that these recent developments will rapidly lead to an understanding of abnormalities of iron metabolism at a molecular level, particularly in such disorders collectively known as iron overload.

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トランスフェリンを介する鉄の細胞内取り込み機序
—特に肝細胞への取り込みにおける内皮細胞の関与について—

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簡潔表題：鉄の細胞内取り込み機序
索引用語：鉄の細胞内取り込み，トランスフェリン，脱シアル化，内皮細胞
Key words : Receptor-Mediated endocytosis.

トランスフェリン（Tf）は鉄代謝において重要な役割を担っている。鉄を必要とする細胞の表面には，Tfの特異的受容体が存在し，Ffは受容体との結合に引き続いて，coated pitsとcoated vesiclesを介して細胞内に取り込まれる（internalization）。Vesicle内での急速なpHの低下にともない，鉄はTfから分離し，細胞内で分画される。一方，鉄を失ったTf（アポTf）は受容体と結合したまま細胞表面にもどり，中性のpHのもとで受容体から解離する。最近の細胞・分子生物学の進歩，遺伝子クローニング，ならびにモノクローナル抗体の開発により，分子レベルで鉄代謝経路が解明されつつある。今回，これまでの主要な知見をまとめ，特に，最近筆者らの研究により明らかとなった，肝の鉄代謝における内皮細胞の役割について考察した。