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بالرسالة صفحات لم ترد بالأصل

TRANSFERRIN RECEPTOR ON PERIPHERAL BLOOD LYMPHOCYTES IN IRON DEFICIENCY ANAEMIA AND β THALASSEMIA PATIENTS

THESIS

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INTRODUCTION

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Iron is essential for survival of living organisms. Removal of iron from tissue culture media is accompanied by immediate cessation of cell growth and proliferation.[1] iron is required for a variety of biological functions, including oxygen transport, electron transport and DNA synthesis.[2]

Yet although iron is an essential element, excess iron is toxic, through free radical formation with production of reactive oxygen intermediates, with the pathological consequences of iron overloading disorders. Careful maintenance of iron balance is therefore crucial to living organisms.[3]

Intracellular Iron Transport

Role of transferrin

Under physiological conditions, only a small proportion of total body iron daily enters or leaves the body's stores. Consequently, intracellular iron transport is quantitatively more important than intestinal absorption.[4]

Nearly 3 mg of total body iron circulates in the plasma as an unexchangeable pool.[4] In normal individuals, essentially all circulating iron is bound to transferrin. This chelation serves three purposes:

1. it renders iron soluble under physiological pH,

2. it prevents iron-mediated free radical toxicity,

and 3. it facilitates iron transport into the cells.[5]

Transferrin is an 80-KDa glycoprotein that has homologous N-terminal and C-terminal iron binding domains.[6]

Approximately 80% of iron bound to transferrin is delivered to the bone marrow for use in the production of hemoglobin. The remainder is exchanged with non-erythroid cells, which utilize it for production of iron containing proteins.[6]

Holotransferrin is recognized by transferrin receptors, which are present on the surface of most if not all non intestinal cells; the highest expression of the receptors is found on erythroid precursors, placenta, and rapidly dividing cells.[2] Apotransferrin (iron free) binds transferrin receptor with 500-fold lower affinity than diferric transferrin. In the classical transferrin pathway, the holotransferrin binds to the transferrin receptor on the surface of the cell. A pit is formed that invaginates to be incorporated in the cytosol of the cell. The interior of the vesicle is acidified to release iron from the transferrin so that iron can exit the vesicle, possibly facilitated by H^+-ATPase activity. Some or all of this iron associates with the mobilferrin pathway for delivery to cellular organelles in a form that inhibits free radical formation. The apotransferrin remaining in the endosome is delivered to the cell surface

by exocytosis, thereby returning the apotransferrin to the plasma.[2] (Figure 1)

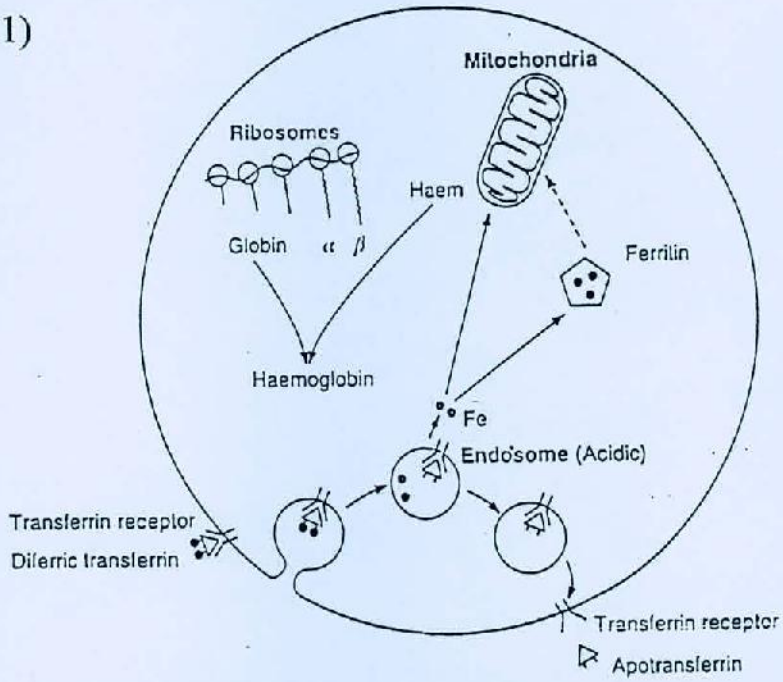

Figure 1: The endocytotic transferrin cycle.[4]

Hemoglobin iron remains with the erythrocyte for its 120 day life span, after which the red cell is phagocytosed in the reticulendothelial system. Iron is again released into the plasma, where it is bound to transferrin and made available for the synthesis of heme and other iron-containing proteins. If iron stores are adequate, some iron may be stored in the reticuloendothelial system as ferritin or hemosiderin.[7]

At the cellular level, two uptake processes are available when transferrin is presented to the cell. At low diferric transferrin concentrations, uptake occurs via the classical receptor-mediated pathway. At high diferric transferrin concentrations, iron enters the cell via a "transferrin receptor-independent pathway" (TRIP)".[8] This has

been shown in experiments that specifically block each pathway. Iron entering the cell via the trip pathway seems to be donated to the mobilferrin-integrin pathway. However, it is not clear whether the iron is released near the cell surface with subsequent entry via the mobilferrin-integrin pathway, or if there is an additional step involving pinocytosis.[8]

Transferrin receptor

Cellular transferrin receptor

The biology and biochemistry of cellular transferrin receptor and the origin of transferrin receptor in the circulation have been the subject of excellent reviews in the past decade.[9]

The cellular transferrin receptor is the gateway for iron entering all body cells.[9] It is a transmembrane glycoprotein that contains two identical subunits, each weighing 95 KDa, linked by disulphide bridges.[10] It is firmly anchored in the cell membrane, the major portion of the protein being external to the cell.[10] The receptor are expressed on the surface of all body cells, with the largest number found in rapidly dividing cells, erythroid precursor, and the developing placenta.[11] Because more than 80% of body iron is used for erythropoiesis, a proportionate number (75-80%) of total transferrin receptors in the body are in the erythroid marrow.[12] The affinity of transferrin receptor for its ligand depends on the iron content of the circulating transferrin it is

maximal for diferric transferrin, moderate for monoferric transferrin, and negligible for iron-free apotransferrin.[9] Once iron-containing transferrin is bound to its surface receptor, the complex is internalized by endocytosis. The small non lysosomal vesicular structures that are formed (called endosomes) become acidified by protonation to a pH of about 5.5, at which point iron loses its affinity for transferrin and diffuse across the vesicular membrane to the cytosol. The apotransferrin, still bound to its receptor, is routed back to the cell surface within a few minutes, where the transferrin is released on return to physiological pH.[10]

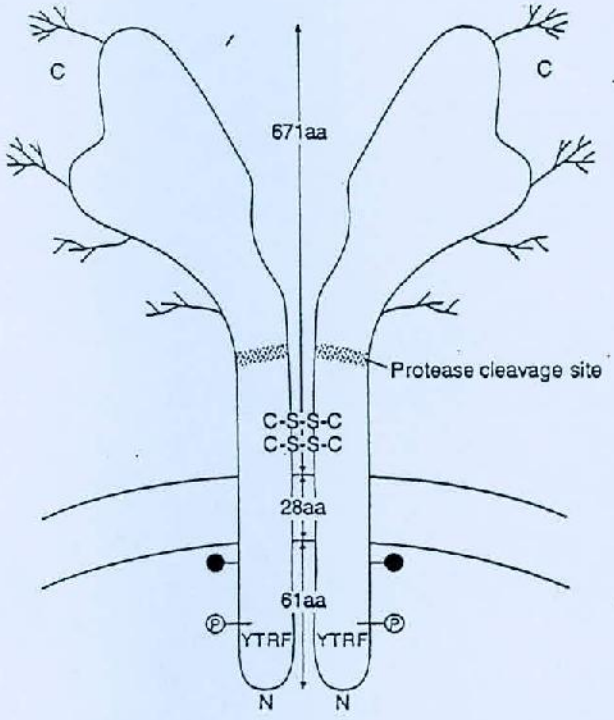

Figure 2: Structure of dimeric transferrin receptor[10]