Bol Med Hosp Infant Mex. 2016;73(6):372–379

Boletín Médico del
Hospital Infantil de México

www.elsevier.es/bmhim

REVIEW ARTICLE

Antibody-mediated targeting of the transferrin receptor in cancer cells

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Received 22 September 2016; accepted 23 November 2016
Available online 13 December 2016

KEYWORDS
TfR1;
Anti-TfR1;
Immunoconjugate;
Immunotherapy;
Cancer therapy

Abstract Iron is essential for cell growth and is imported into cells in part through the action of transferrin (Tf), a protein that binds its receptor (TfR1 or CD71) on the surface of a cell, and then releases iron into endosomes. TfR1 is a single pass type-II transmembrane protein expressed at basal levels in most tissues. High expression of TfR1 is typically associated with rapidly proliferating cells, including various types of cancer. TfR1 is targeted by experimental therapeutics for several reasons: its cell surface accessibility, constitutive endocytosis into cells, essential role in cell growth and proliferation, and its overexpression by cancer cells. Among the therapeutic agents used to target TfR1, antibodies stand out due to their remarkable specificity and affinity. Clinical trials are being conducted to evaluate the safety and efficacy of agents targeting TfR1 in cancer patients with promising results. These observations suggest that therapies targeting TfR1 as direct therapeutics or delivery conduits remain an attractive alternative for the treatment of cancers that overexpress the receptor.

PALABRAS CLAVE
TfR1;
Anti-TfR1;
Inmunoconjugados;
Inmunoterapia;
Terapia contra el cáncer

Anticuerpos que reconocen el receptor de transferrina en células tumorales

Resumen El hierro es esencial para el crecimiento celular. Es transportado dentro de las células con la ayuda de la transferrina (Tf), proteína que se une a su receptor (TfR1 o CD71) en la superficie celular y libera el hierro dentro de los endosomas. El TfR1 es una proteína de membrana tipo II que se sobreexpresa en muchos tejidos debido al requerimiento de las células para importar hierro unido a Tf. La sobreexpresión de TfR1 se ha asociado con células que proliferan rápidamente, incluyendo los diferentes tipos de cáncer. El TfR1 se ha empleado como blanco

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http://dx.doi.org/10.1016/j.bmhimx.2016.11.004

terapéutico por diversos motivos: su accesibilidad a la superficie celular, su capacidad de internalizarse constitutivamente en las células, su papel esencial en el crecimiento y la proliferación celular, así como por su sobreexpresión en las células tumorales proliferantes. Entre los agentes terapéuticos dirigidos contra el TfR1 destacan los anticuerpos, por su alta especificidad, estabilidad y propiedades estructurales. Se han realizado diversos ensayos clínicos para evaluar la seguridad y la eficacia de los anticuerpos que reconocen el TfR1 en pacientes con cáncer y se han obtenido resultados prometedores. Estas observaciones sugieren que las terapias con fundamento en el reconocimiento de TfR1, ya sea como terapia directa o empleados como acarreadores, representan una alternativa muy atractiva de tratamiento contra los diferentes tipos de cáncer que sobreexpresan este receptor.

1. Introduction

As an essential cofactor for life, iron facilitates several enzymatic reactions critical for DNA replication and cellular respiration. The cellular processes that rely on iron include nucleotide synthesis and electron transport. However, free ferrous iron can be toxic to living systems.[1] To avoid this toxicity, organisms have evolved iron transport and storage systems such as carrier proteins (transferrin and ferritin), heme, and iron-sulfur clusters.[1] Transferrin (Tf) is found in the blood of mammals as a two-lobed protein.[2] Under neutral physiological conditions, each transferrin molecule is capable of binding two ferric iron atoms. Tf releases its iron cargo at low pH, with maximal release observed near pH 5.[3] Definitive evidence of a transferrin receptor (TfR1) was found first in rabbit reticulocytes,[4] and later confirmed in a variety of species and cell types, including human placenta, a rich source of TfR1.[5,6] TfR1 is a cell surface protein that binds Tf and facilitates its endocytosis from plasma.[2] The receptor exists on the cell surface as a homodimeric type-II glycoprotein receptor; the extracellular domain (ECD) of the homodimer can bind up to two molecules of transferrin. The ECD of TfR1 contains three subdomains: a helical, protease-like, and apical domain (Figure 1).

TfR1 is encoded by the TfRC gene that belongs to the transferrin receptor family. The family of receptors includes TfR2 and is derived from ancient carboxypeptidases.[7] The TfR1 homodimer is held together by disulfide linkages and constitutively endocytosed through the canonical clathrin-mediated pathway. Once in acidified endosomes, a receptor carrying iron loaded Tf undergoes a structural rearrangement that promotes the release of iron by Tf. Meanwhile, the iron-free Tf molecule remains bound to the receptor and recycles back to the cell surface where it is released at a neutral pH (Figure 2A). Recycling of TfR can occur hundreds of times during the lifetime of a single receptor.[8] At any given time, a cell can express hundreds of thousands of copies of TfR1[9] with only a small percentage present at the cell surface. More detailed descriptions of Tf trafficking and iron import are available elsewhere.[10,11]

All three subdomains of TfR1 are required for Tf binding. The helical domain of TfR1 is responsible for dimerization.

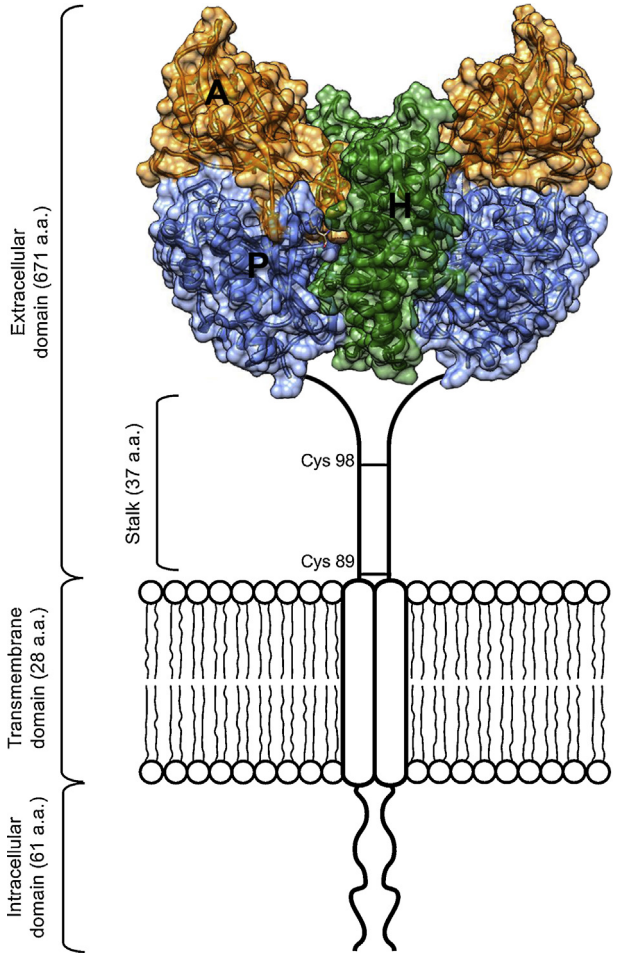

Figure 1 Scheme of the TfR1 homodimer on the cell surface consisting of two monomers linked by disulfide bridges at cysteines 89 and 98. The TfR1 contains an intracellular domain, a transmembrane domain, and a large extracellular domain. Here, the structural model of the extracellular domain of TfR1 was generated with coordinates from PDB ID 1DE4, and consists of three subdomains: apical (A, orange), helical (H, green) and protease-like domain (P, blue).