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An Introduction to Divalent Metal Transporter 1

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Description

Iron is required for a number of vital bodily functions. The role of the Divalent Metal Transporter 1 (DMT1), which is required for iron uptake in most cells, is discussed in this study. DMT1 is found on cellular and endosomal membranes, where it plays a role in non-transferrin bound iron intake as well as transfer in bound iron uptake. DMT1 comes in four different isoforms, each with its own set of features involving sophisticated cell-specific regulatory mechanisms that all control iron transport across these membranes. This complication reflects the delicate balance necessary in iron homeostasis, as iron is required for many cell processes but is highly poisonous when present in excess. DMT1 is highly expressed in neurons in the brain. The expression of DMT1 in non-neuronal cells is a point of contention. According to recent research, DMT1 is found in the endosomes of brain capillary endothelial cells, indicating the blood-brain barrier. This adds to the growing body of data showing iron intake at the BBB is mediated *via* transferrin-receptor-mediated endocytosis, followed by iron dissociation from transferrin inside the endosome's acidic compartment and DMT1-mediated iron pumping into the cytosol.

Ferroportin is most likely responsible for iron transfer over the abluminal membrane and into the brain. The lack of transferrin receptors and DMT1 expression in glial cells, including as astrocytes, microglia, and oligodendrocytes, suggests that steady-state iron uptake in glia is significantly lower than in neurons, and/or that different mechanisms for iron uptake in these cell types predominate. DMT1, also known as Nramp2, SLC11A2, and DCT1, is a protein that transports iron between two compartments of the cell: (1) It facilitates iron uptake at the apical cell membrane in cells such as duodenal enterocytes, and (2) It carries iron throughout the endosomal membrane in nearly all cellular processes that take iron *via* the transferrin-transferrin receptor 1 pathway, such as erythroid precursors in the bone marrow and most cells in peripheral tissue. DMT1 works best at a slightly acidic pH of around 5.5, which corresponds to the pH in the duodenum and inside the endosome.

DMT1 belongs to the family of natural resistance associated macrophage proteins. A diverse range of membrane-bound divalent cation transporters makes up this highly conserved protein family. In bacteria, functional homologues of the Nramp proteins can be discovered. In return for one proton, DMT1 transports divalent cations. DMT1's substrate profile contains metals other than iron. For example, membrane-located 1A/(+IRE) DMT1 transports Fe^{2+}, Cd^{2+}, Co^{2+}, Mn^{2+} (group 1) and Ni^{2+}, VO^{2+}, Pb^{2+} (group 2), albeit at a lower efficiency, with group 1 being significantly more effective than group 2. DMT1 does not transport $Zn^{2+.}$ DMT1 transports a variety of cations, including Cu^{1+} and $Cu^{2+.}$ Twelve transmembrane domains, membrane targeting motifs, one consensus transport motif, and two asparagine-linked glycosylation signals in an additional cytoplasmic loop make up the DMT1 protein. The protein's N and C-termini are both found in the cytoplasm. The structure-function link of Nramp.

H^+coupled divalent metal transport has been revealed in several studies: TMD1 and TMD6 are critical for Nramp metal ion and H^+ ion symport. DMT1 was discovered in the mouse in 1995 and cloned from a cDNA library made from duodenal mRNA in rats on a low-iron diet.

The DMT1 gene is made up of 17 exons and extends over 36 kb. The 30 UTR has two alternative transcripts, one with an iron response element (+IRE; Type 1) and the other without an IRE, which were later identified. The IRE is a conserved stem loop structure that modifies the stability or translation efficiency of a certain mRNA by binding specific iron-response proteins in the cell. DMT1 differs at the 50 region in two other transcripts: One mRNA transcript begins in exon 1A, bypasses exon 1B, and splices with exon 2 directly. The first discovered mRNA transcript skips exon 1A, starts in exon 1B, and splices with exon 2. In contrast to variant 1B, where the initiation codon is placed in exon 2, exon 1A has an initiation codon (AUG), and variant 1A has a 29–31 amino acid extension. Each IRE variant's 30 end is different, and it consists of 25 (IRE) and 18 (+IRE) amino acids, respectively. The 30 UTR of the (–IRE) DMT1 isoforms contains a miRNA target region for let-7d. In erythroid cells, Let-7d binds to and regulates the (–IRE) DMT1 isoform.

The translational efficiency of the four isoforms differs, and the IRE isoforms' protein degradation routes differ. The ubiquitin E3-ligase parkin degrades the 1B isoforms, but not the 1A isoforms. Different organ-specific expression patterns are seen in the four DMT1 isoforms. 1A transcripts are virtually exclusively found in polarised cells in the duodenum and kidney, whereas 1B transcripts are found elsewhere. The expression of both IRE types can be detected in most tissues to some extent. As a result, organ-specific DMT1 expression appears to be influenced by components in the 1A variant's promoter or the 1A region itself. Anti-DMT1 immunocytochemistry on Xenopus oocytes transfected with each of the four DMT1 variations revealed that the subcellular distribution of the four isoforms differs. (+IRE) variants are found on the cell membrane, whereas (IRE) variants are not. The fact that DMT1 comes in four distinct isoforms could indicate different functional features. The four isoforms, on the other hand, transport Fe^{2+} at the same rate and have no changes in functional characteristics, permeant ions, or rate limiting steps. Other investigations have likewise found no functional differences between the different isoforms. As a result, the existence of the four isoforms is suggested to address the necessity for subcellular localization and regulation specific to cell types.