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Review

Mammalian iron transporters: Families SLC11 and SLC40 ☆

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ABSTRACT

This review is focused on the mammalian SLC11 and SLC40 families and their roles in iron homeostasis. The SLC11 family is composed of two members, SLC11A1 and SLC11A2. SLC11A1 is expressed in the lysosomal compartment of macrophages and in the tertiary granules of neutrophils, playing a key role in innate resistance against infection by intracellular microbes. SLC11A2 is a key player in iron metabolism and is ubiquitously expressed, most notably in the proximal duodenum, immature erythroid cells, brain, placenta and kidney. Intestinal iron absorption is mediated by SLC11A2 at the apical membrane of enterocytes, followed by basolateral exit via SLC40A1. To meet the daily requirement for iron, approximately 80% of the iron comes from the breakdown of hemoglobin following macrophage phagocytosis of senescent erythrocytes (iron recycling). Both SLC11A1 and SLC11A2 play an important role in macrophage iron recycling. SLC11A2 also transports iron into the cytosol across the membrane of endocytotic vesicles of the transferrin receptor-cycle. SLC40A1 is the sole member of the SLC40 family and is involved in the only cellular iron efflux mechanism described. SLC40A1 is highly expressed in several tissues and cells that play a critical role in body iron homeostasis. The signaling pathways that regulate SLC11A2 and SLC40A1 expression at transcriptional, post-transcriptional and post-translational levels are discussed. The roles of SLC11A2 and/or SLC40A1 in iron-associated disorders such as hemochromatosis, neurodegenerative diseases, and breast cancer are also summarized.

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Abbreviations: Nramp1, natural resistance-associated macrophage protein-1; DMT1, divalent metal transporter-1; DCT1, divalent cation transporter-1; Nramp2, natural resistance-associated macrophage protein-2; Ireg1, iron regulated-transporter-1; MTP1, metal transporter protein-1; Dcytb, duodenal cytochrome b; Heph, hephaestin; Cp, ceruloplasmin; *sla* mouse, sex-linked anemia mouse; RES, reticuloendothelial system; TfR1, transferrin receptor-1; STEAP, six-transmembrane epithelial antigen of the prostate; IREs, iron responsive elements; IRPs, iron regulatory proteins; UTR, untranslated region; TfR2, transferrin receptor-2; HJV, hemojuvelin; HH, hereditary hemochromatosis; TMDs, transmembrane domains; HIF, hypoxia-inducible factor.

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1. Introduction

Iron is an essential element required for many redox processes in most living organisms. In humans, iron is required for vital functions such as oxidative metabolism, erythropoietic function and cellular immune responses. Since, in mammals, the majority of iron is present as hemoglobin, iron recycling following erythrocyte degradation by macrophages constitutes one of the major regulatory mechanisms for iron homeostasis. However, stores of iron in the body depend almost exclusively on intestinal iron absorption, since there is no efficient pathway for iron excretion. This highlights the importance of regulated intestinal transport.

Intracellular iron levels must be precisely balanced to supply enough iron for metabolism while avoiding excessive toxic levels. Oxidative stress and organ damage can result as a consequence of cellular iron-loading. Iron homeostasis requires an overall balance between transport and storage to ensure appropriate and non-toxic cellular iron levels.

In this review we focus on the mammalian iron transporters from the SLC11 and SLC40 families and their roles in intestinal iron absorption as well as whole body iron homeostasis. We also summarize the molecular mechanisms that regulate these transporters in physiological and pathophysiological conditions.

2. The mammalian SLC11 family: SLC11A1 and SLC11A2

The mammalian SLC11 family is comprised of two members; SLC11A1 and SLC11A2 (Table 1). These proteins share 66% identity and 82% similarity at the amino acid sequence level, and are part of the large SLC11 family of integral membrane proteins expressed in great diversity across organisms. In general, SLC11 proteins are transporters that use the H^+-electrochemical gradient as the driving force to transport a rather broad range of divalent metal ions, including Mn^{2+}, Fe^{2+}, Cd^{2+}, Co^{2+}, Zn^{2+}, Ni^{2+}, and Pb^{2+} (Gunshin et al., 1997; Nevo and Nelson, 2006), although the transport properties of some of the family members (e.g. SLC11A1) are poorly understood.

Mammalian members of the SLC11 family are thought to have 12 transmembrane domains (TMDs) (Czachorowski et al., 2009) with a conserved hydrophobic core of 10 TMDs (Cellier et al., 1996; Cellier et al., 1995) that plays an important role in H^+-dependent metal transport (Chaloupka et al., 2005; Courville et al., 2008). A highly conserved metal transport signature was found within the cytoplasmic loop between TMD 8 and 9, although the exact role of this sequence motif remains unclear. A DPGN motif between TMD 1 and 2, which is nearly 100% conserved across species, may form part of a metal binding site and is essential for the transport function of these proteins. The loop between TMD 7 and 8 has been reported to be extracellular (Forbes and Gros, 2003; Picard et al., 2000) and the presence of a glycosylated loop in this region is preserved in almost all sequences. Fig. 1 shows a schematic representation of the secondary structure of SLC11A1 and SLC11A2. Although mutagenesis studies of bacterial, yeast, and mammalian SLC11 proteins has begun to uncover key residues and motifs critical for metal and proton translocation, high-resolution structural information will be needed to delineate the structure/function relationship of this protein family.

2.1. SLC11A1: Natural resistance-associated macrophage protein-1 (Nramp1)

The mouse *Slc11a1* gene coding for SLC11A1, also known as Nramp1, was identified in 1993 by positional cloning of the mouse chromosome 1 locus *Bcg*/*Lsh*/*Ity* (Vidal et al., 1993). SLC11A1 plays a key role in mouse innate resistance to infection by intracellular microbes, such as *Mycobacterium*, *Salmonella* and *Leishmania* (Blackwell et al., 2003; Johnson and Wessling-Resnick, 2012). SLC11A1 is a 90–100 kDa integral transmembrane protein expressed in the lysosomal compartment of macrophages and in tertiary granules of neutrophils. The human *SLC11A1* gene was cloned, and localized to the long arm of chromosome 2 (2q35). Human SLC11A1 displays an expression profile similar to the mouse ortholog and was subsequently shown to be associated with resistance to infections by a variety of intracellular pathogens. SLC11A1 colocalizes with the