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Familial manganese-induced neurotoxicity due to mutations in *SLC30A10* or *SLC39A14*

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Abstract

Over the last few years, two rare, familial diseases that lead to the onset of manganese (Mn)-induced neurotoxicity have been discovered. Loss-of-function mutations in SLC30A10, a Mn efflux transporter, or SLC39A14, a Mn influx transporter, increase Mn levels in blood and brain, and induce severe neurotoxicity. The discoveries of these genetic diseases have transformed our understanding of Mn homeostasis, detoxification, and neurotoxicity. Current knowledge about the mechanisms by which mutations in these transporters alter Mn homeostasis to induce human disease is reviewed here.

Keywords

SLC30A10; SLC39A14; ZnT10; ZIP14; manganese neurotoxicity; parkinsonism; metal homeostasis

Introduction

Manganese (Mn) is an essential metal that is required for the activities of numerous enzymes (Aschner et al., 2009). However, at elevated cellular levels, Mn is toxic and induces cell death (Leyva-Illades et al., 2014; Milatovic et al., 2009; Mukhopadhyay and Linstedt, 2011). When levels increase in the body, Mn accumulates in the brain, primarily in the basal ganglia, and leads to the onset of a parkinsonian-like movement disorder (Aschner et al., 2009; Olanow, 2004; Perl and Olanow, 2007). Historically, Mn-induced parkinsonism was reported to occur due to occupational over-exposure to the metal (Aschner et al., 2009). In more recent studies, elevated Mn exposure from environmental sources has also been implicated in the onset of motor deficits (Lucchini et al., 2014; Lucchini et al., 2012). Moreover, transport into bile is the primary mode of Mn excretion; consequently, individuals with defective liver function, due to diseases, such as cirrhosis, fail to excrete Mn and may

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Conflict of Interest Statement

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develop Mn-induced parkinsonism in the absence of exposure to elevated Mn (Butterworth, 2013). Finally, epidemiological studies suggest that elevated Mn exposure in children and adolescents is associated with behavioral and cognitive defects (Bhang et al., 2013; Bouchard et al., 2007; Bouchard et al., 2011; Claus Henn et al., 2010; Khan et al., 2011; Khan et al., 2012; Oulhote et al., 2014; Riojas-Rodriguez et al., 2010; Wasserman et al., 2006). Overall, intracellular levels of Mn need to be maintained within a narrow physiologic range so that the metal may perform its essential function without inducing toxicity.

Over the last few years, our understanding of the mechanisms by which homeostatic control of Mn is maintained in mammalian systems has been revolutionized with the discoveries of two inherited disorders of Mn metabolism. We now know that individuals harboring loss-of-function mutations in *SLC30A10* or *SLC39A14* develop inherited forms of Mn-induced neurotoxicity (Lechpammer et al., 2014; Quadri et al., 2012; Tuschl et al., 2012; Tuschl et al., 2016; Tuschl et al., 2008). Both these genes code for Mn transporters, and disease biology is linked to direct alterations in cellular and tissue Mn levels. The mechanisms by which loss-of-function mutations in these genes impact Mn metabolism are described in more detail below.

SLC30A10

Clinical studies

In 2008, a clinical report described findings from a patient later shown to carry homozygous mutations in *SLC30A10* (Tuschl et al., 2008) (Table 1). The individual was born to consanguineous parents, which raised the possibility of an autosomal recessive disease. Major clinical findings included signs of an extrapyramidal motor defect, ~10-fold increase in blood Mn levels, and, by magnetic resonance imaging, evidence of Mn deposition in the basal ganglia (Tuschl et al., 2008). Liver biopsy provided evidence of cirrhosis and elevated hepatic Mn levels (Tuschl et al., 2008). The patient also had polycythemia (Tuschl et al., 2008). Importantly, there was no history of exposure to elevated Mn from the environment, and levels of other essential metals in plasma [copper (Cu) and zinc (Zn)] were normal (Tuschl et al., 2008).

The above work was extended by two companion manuscripts in 2012, which identified additional patients that presented with the clinical findings described in the 2008 patient (Quadri et al., 2012; Tuschl et al., 2012) (Table 1). Importantly, now the study was taken a step forward, and whole genome homozygosity mapping and exome sequencing were performed. These assays revealed that affected patients harbored homozygous mutations in *SLC30A10* (Quadri et al., 2012; Tuschl et al., 2012). Inheritance was autosomal recessive; unaffected siblings and parents were heterozygous for *SLC30A10* mutations (Quadri et al., 2012; Tuschl et al., 2012). Notably, cases described in 2008 and 2012 recapitulated findings from a prior report published in 2000 (Gospe et al., 2000). The patient described in 2000 was also included in the 2012 studies. Genetic analyses identified homozygous *SLC30A10* mutations in this patient as well (Lechpammer et al., 2014; Tuschl et al., 2012), and results of a complete autopsy performed on this individual are now available (Lechpammer et al., 2014) (Table 1). Analyses of the brain revealed that there was extensive neuronal loss in the globus pallidus (Lechpammer et al., 2014). This is noteworthy because a similar pattern of

injury is evident in individuals exposed to elevated Mn from occupational sources (Olanow, 2004; Perl and Olanow, 2007). In the liver, there was evidence of hepatomegaly and cirrhosis with portal hypertension (Lechpammer et al., 2014). Finally, Mn levels were elevated, ~16-fold in the basal ganglia and ~9-fold in the liver (Lechpammer et al., 2014).

The clinical studies suggest that mutations in *SLC30A10* enhance Mn levels in the body, and that the observed neurotoxicity likely develops as a secondary consequence of Mn accumulation in the brain. Liver injury and polycythemia, other hallmarks of this disease, may also be direct consequences of Mn toxicity. Hepatic damage may be induced by Mn that deposits in the liver. Polycythemia may occur due to the hypoxia-mimetic effects of Mn that increase erythropoietin expression (Ebert and Bunn, 1999).

Mechanistic assays in cell culture

The SLC30 family has 10 members, SLC30A1-A10 (Huang and Tepaamorndech, 2013; Kambe et al., 2015; Kolaj-Robin et al., 2015). SLC30A1-A8 mediate efflux of Zn from the cytosol to the exterior of the cell or into the lumen of intracellular organelles, and classification of SLC30A9 as a transporter is likely incorrect (Huang and Tepaamorndech, 2013; Kambe et al., 2015; Kolaj-Robin et al., 2015). SLC30A10 was initially thought to act as a Zn efflux transporter (Bosomworth et al., 2012). However, the fact that patients harboring mutations in this gene had elevated Mn levels led us to hypothesize that SLC30A10 may mediate efflux of Mn, instead of Zn, and that disease-causing mutations may interfere with its Mn efflux function. We have rigorously tested this hypothesis over the last few years (Hutchens et al., 2017; Leyva-Illades et al., 2014; Zogzas et al., 2016) (Table 1). Quantitative colocalization analyses using confocal microscopy and surface biotinylation assays revealed that $SLC30A10_{\text{wild-type (WT)}}$ trafficked to the cell surface, while disease-causing mutants tested were trapped in the endoplasmic reticulum (Leyva-Illades et al., 2014). In cell culture, over-expression of $SLC30A10_{WT}$, but not a disease-causing mutant, enhanced Mn efflux, leading to a reduction in intracellular Mn levels (Leyva-Illades et al., 2014). The reduction of cellular Mn was physiologically relevant because over-expression of $SLC30A10_{WT}$, but not a disease-causing mutant, protected HeLa and GABAergic AF5 cells, and primary mouse midbrain neurons against Mn toxicity (Leyva-Illades et al., 2014). Moreover, depletion of SLC30A10, using a specific siRNA, in AF5 cells increased intracellular Mn levels and enhanced sensitivity to Mn toxicity (Leyva-Illades et al., 2014). Finally, in *C. elegans*, expression of $SLC30A10_{WT}$, but not a disease-causing mutant, protected against Mn toxicity (Leyva-Illades et al., 2014). Put together, the above results imply that SLC30A10 functions as a cell surface-localized Mn efflux transporter that mediates Mn efflux, reduces cellular Mn levels, and protects against Mn toxicity (Fig. 1). Disease-causing mutations block the Mn efflux activity of the transporter, leading to increased Mn accumulation within cells and subsequent toxicity (Fig. 1). In this discussion, it is also noteworthy that, in cell culture and *C. elegans*, over-expression of SLC30A10 did not protect against Zn toxicity (Chen et al., 2015; Leyva-Illades et al., 2014; Nishito et al., 2016; Zogzas et al., 2016) (Table 1), suggesting that the primary function of the transporter is to regulate Mn homeostasis.

Assays performed in cell culture, combined with the clinical data, suggest a simple model for onset of neurotoxicity in individuals carrying mutations in *SLC30A10* (Fig. 2). SLC30A10 was detected in the liver as well as in neurons, including in the globus pallidus (Lechpammer et al., 2014; Quadri et al., 2012). In affected patients, loss of the Mn efflux function of SLC30A10 in the liver may block biliary excretion of Mn, and increase Mn levels in liver, blood, and brain (Fig. 2). Additional increase in brain Mn levels may occur due to loss of SLC30A10 function in neuronal cells. Accumulation of Mn in brain may eventually induce neuronal injury, and lead to the development of observed neurological signs and symptoms.

Unexpected hypothyroidism in Slc30a10 knockout mice

Earlier this year, we provided the first detailed phenotypic characterization of *Slc30a10* knockout mice (Hutchens et al., 2017) (Table 1). Our motivation was to use *Slc30a10* knockout mice as a model to better understand the consequences of loss of function of SLC30A10 at the organism level. The mutant strain was a constitutive, full-body *Slc30a10* knockout [details in (Hutchens et al., 2017)]. The expectation was that these knockout mice would develop motor deficits. Instead, we made the surprising discovery that *Slc30a10* knockout mice developed severe hypothyroidism (Hutchens et al., 2017). To elaborate, during early development, knockouts were indistinguishable from littermate controls. However, after weaning, unlike controls, knockouts failed to gain weight, were smaller in size, and died prematurely (by ~6–8 weeks of age) (Hutchens et al., 2017). Compared to controls, Mn levels in the brain, liver, and blood of the knockouts were substantially elevated (~20–60-fold) (Hutchens et al., 2017). Despite this, we did not find evidence of extensive injury in the brain or liver of the knockout animals (Hutchens et al., 2017). Instead, histological analyses demonstrated that there were obvious alterations in the thyroid gland of the knockouts; their follicular epithelial cells were hypertrophic and there was less colloid in the lumen of the thyroid follicles (Hutchens et al., 2017). These changes raised the possibility that the animals were suffering from hypothyroidism. The reduction in follicular colloid could represent decreased production of thyroxine, the major thyroid hormone, and hypertrophic changes in the epithelial cells could be a compensatory response to increase thyroxine production. To test this idea, we measured hormone levels in 6-week old animals, and discovered that, compared to controls, in the knockouts, levels of thyroxine were significantly lower (~50–80%), and thyroid stimulating hormone, profoundly higher (~800–1000-fold) (Hutchens et al., 2017). Importantly, a low Mn diet reduced tissue Mn levels in the knockouts, and rescued the hypothyroidism and failure-to-thrive phenotype, implying that Mn toxicity was the cause (Hutchens et al., 2017).

Thus far, the role of thyroid dysfunction in Mn toxicity has received little attention. However, thyroid hormone plays a fundamental role in neuronal development and function, and hypothyroidism may lead to severe neurological sequelae (Hall, 2016). An important ramification of the unexpected phenotype of *Slc30a10* knockout mice is that alterations in thyroid function may be an unappreciated feature of Mn toxicity in humans, and that it is important to assay for the thyroid hormone status of human patients suffering from Mn toxicity. If evidence of hypothyroidism is detected, thyroxine supplementation may provide a simple means to mitigate some of the observed neurological deficits. In this discussion, we

note that, so far, our studies focused on 16–42 day old animals; therefore, our current findings likely have more relevance to early life Mn toxicity. Assays using tamoxifen-inducible *Slc30a10* knockout animals are necessary to determine whether hypothyroidism is evident when Mn toxicity develops in adult life; these assays are already in progress in our laboratory.

The molecular mechanisms that induce hypothyroidism in *Slc30a10* knockout mice remain to be investigated. Mn levels were elevated in the thyroid gland of knockout mice (Hutchens et al., 2017), raising the possibility that Mn may directly injure thyroid epithelial cells, and alter thyroxine synthesis or secretion. However, Mn levels were also elevated in the brain and pituitary of knockouts (Hutchens et al., 2017), and it is possible that functional changes in these organs play a role in the onset and/or progression of hypothyroidism. Tissue-specific *Slc30a10* knockouts may shed light into the mechanisms of hypothyroidism.

We also discovered that there was a sex-difference in the phenotype of *Slc30a10* knockout mice. Compared to females, male knockouts had lower thyroxine levels and normalized body weights (Hutchens et al., 2017). A protective effect of estrogen against Mn toxicity was previously reported in primary neuronal and astroglial cells and in mice (Lee et al., 2009a; Lee et al., 2009b; Moreno et al., 2011). *Slc30a10* knockout mice may emerge as a useful model to study sex differences in Mn toxicity, and castration, overiectomy, and hormone replacement assays in the knockout mice may be informative.

An important goal of our laboratory is to develop genetically-modified mouse models to study Mn-induced neurotoxicity. When full-body *Slc30a10* knockout mice were fed a low Mn diet (this diet had ~ 11 μg Mn/g chow compared to regular rodent chow, which had ~84 μg Mn/g chow), Mn levels in the brain of the knockouts were still ~10 fold greater than littermate controls. Importantly, however, under these conditions, knockouts did not develop hypothyroidism (Hutchens et al., 2017). On-going assays suggest that life-span of the knockouts may be enhanced by the low Mn diet. Thus, it may be possible to use the full-body knockouts on a low Mn diet as a model to study the neurotoxic effects of Mn, independent of effects on the thyroid.

Overall, the unanticipated phenotype of *Slc30a10* knockout mice raises the intriguing possibility that thyroid dysfunction may have a role in the pathogenesis of Mn-induced disease in humans, opens exciting new avenues for research that bridge endocrinology and metal toxicology, and identifies *Slc30a10* knockout animals as a new model for studying thyroid biology.

SLC39A14

Clinical studies

In 2016, it was reported that homozygous mutations in *SLC39A14* also lead to the development of Mn-induced neurotoxicity in humans (Tuschl et al., 2016) (Table 1). Unlike the SLC30 family of efflux transporters, proteins that belong to the SLC39 family mediate influx of metals into the cytoplasm from the cell exterior or lumen of intracellular organelles (Jeong and Eide, 2013). Most members of the SLC39 family mediate Zn influx; however, in

addition to Zn, SLC39A14 has the capacity to transport Mn, iron (Fe), and cadmium (Cd) as well (Girijashanker et al., 2008; Jenkitkasemwong et al., 2012; Jeong and Eide, 2013; Liuzzi et al., 2006; Pinilla-Tenas et al., 2011; Taylor et al., 2005). In patients harboring *SLC39A14* mutations, loss of developmental milestones, progressive dystonia, and bulbar dysfunction were evident in early life (Tuschl et al., 2016). Towards the end of the first decade, patients developed generalized dystonia, spasticity, limb contractures, and scoliosis (Tuschl et al., 2016). Parkinsonian features, such as hypomimia, tremor, and bradykinesia were present in some individuals (Tuschl et al., 2016). Assays to quantify metal amounts revealed that blood Mn levels were substantially elevated in affected patients, but in two patients tested, levels of Fe, Zn and Cd were normal (Tuschl et al., 2016). By magnetic resonance imaging, there was evidence of Mn deposition in the basal ganglia, extensive white matter involvement, and in some patients, evidence of cerebral or cerebellar atrophy (Tuschl et al., 2016). Autopsy performed on one patient revealed severe neuronal loss in the globus pallidus (Tuschl et al., 2016) (Table 1). An important distinction with *SLC30A10* mutations was that, in patients carrying *SLC39A14* mutations, there was no evidence of Mn deposition in the liver or hepatic dysfunction (Tuschl et al., 2016). Intriguingly, polycythemia was also absent (Tuschl et al., 2016).

Mechanistic assays in cell culture

To gain insight into the underlying molecular mechanisms, assays in cell culture were performed. In HEK-293 cells, $SLC39A14_{WT}$ and disease-causing mutants trafficked to the cell surface (Tuschl et al., 2016). Thus, unlike SLC30A10, disease-causing mutations did not alter trafficking of SLC39A14. Importantly, however, the Mn influx capacity of disease-causing SLC39A14 mutants was lesser than WT, implying that the mutations inhibited Mn transport activity (Tuschl et al., 2016).

Slc39a14 knockout mice

Slc39a14 knockout mice were described as early as 2010 (Tang et al., 2010) and 2011 (Hojyo et al., 2011), but tissue Mn levels were not measured at that time. In 2017, three separate groups characterized changes in Mn levels in mice lacking *Slc39a14* (Aydemir et al., 2017; Mitchell D Knutson, 2017; Yongjuan Xin, 2017) (Table 1). Consistent with the human phenotype, depletion of *Slc39a14* increased Mn levels in the blood and brain, but not in the liver, and induced neuromotor deficits (Aydemir et al., 2017; Mitchell D Knutson, 2017; Yongjuan Xin, 2017). Treatment with a chelator reduced serum manganese levels and rescued the motor deficits, suggesting that Mn toxicity may be the underlying cause (Yongjuan Xin, 2017). We are currently characterizing thyroid function of *Slc39a14* knockout mice.

Disease model

Expression studies revealed that SLC39A14 was detected in the liver (Girijashanker et al., 2008; Tuschl et al., 2016), suggesting that the function of SLC39A14 may be to transport Mn into hepatocytes from blood (Fig. 2). A straight-forward model to explain disease onset is that SLC39A14 and SLC30A10 may act co-operatively to mediate biliary Mn excretion – SLC39A14 may transport Mn from blood into hepatocytes, and SLC30A10 may subsequently transport Mn from within hepatocytes into bile (Fig. 2). This model has to be

experimentally tested, and requires generation of a mouse strain in which both *Slc39a14* and *Slc30a10* are depleted. We are working on generating and characterizing this double knockout strain. However, the fact that patients and mice with SLC30A10, but not SLC39A14, mutations had elevated liver Mn supports the above idea. Additional support comes from assays in zebrafish lacking SLC30A10 or SLC39A14 (Table 1). Indirect evidence for hepatic manganese accumulation was evident in fish lacking SLC30A10 (liver Mn levels were not directly measured in this study) (Xia et al., 2017). In contrast, zebrafish lacking SLC39A14 accumulated Mn in the brain, but not in abdominal viscera (liver, pancreas, intestines, and spleen) (Tuschl et al., 2016). Thus, in the absence of functional SLC39A14, Mn may fail to be transported into hepatocytes (Fig. 2); consequently, Mn levels may increase in blood and brain, and neurotoxicity may eventually ensue. In this discussion it is important to note two additional issues. Blood and brain Mn levels were not elevated in a liver-specific knockout of *Slc39a14* that was also recently generated (Yongjuan Xin, 2017), suggesting that the gastrointestinal tract and pancreas also likely play a role in mediating Mn excretion. Finally, elevations in brain Mn levels reported in patients, mice and zebrafish lacking SLC39A14 imply that SLC39A14 is not required for the import of Mn into neuronal cells.

Concluding perspectives

While Mn-induced neurotoxicity due to elevated exposure from occupational sources was first reported over 150 years ago, genetic disorders of Mn metabolism that enhance brain Mn levels and induce neurotoxicity have only recently been discovered. However, work on these diseases has already transformed our understanding of the mechanisms of homeostatic regulation of Mn in cells and organisms. Continued rapid progress is expected as numerous laboratories world-wide are now working on better understanding the functions of SLC30A10 and SLC39A14. Mutations in *SLC30A10* or *SLC39A14* are rare, but there is substantial overlap in the neurological presentation of patients who suffer from Mn toxicity caused by *SLC30A10 or SLC39A14* mutations and those that develop toxicity due to elevated Mn exposure or hepatic dysfunction. Thus, work on these genetic diseases may enhance our understanding of the mechanisms by which Mn induces neurotoxicity in general. Additionally, recent population-based studies suggest that single nucleotide polymorphisms in these genes may be associated with altered blood metal levels. Indeed, in 2016, a single nucleotide polymorphism in *SLC30A10* that associated with increased Mn levels in blood, altered neurological function, and decreased *SLC30A10* expression was identified (Wahlberg et al., 2016). Single nucleotide polymorphisms in *SLC39A14* have also been associated with increased Cd levels in humans (Rentschler et al., 2014). These studies raise the possibility that polymorphisms in *SLC30A10* or *SLC39A14* may alter the risk for developing toxicity from Mn or other metals in the general population. Finally, there is significant interest in developing small molecules to protect against or treat Mn neurotoxicity. Studies suggest that increasing Mn efflux may be an effective strategy for protection (Leyva-Illades et al., 2014; Mukhopadhyay and Linstedt, 2011). As SLC30A10 and SLC39A14 appear to be the primary transporters responsible for Mn detoxification, further study of these proteins and their mechanisms of action may make valuable contributions towards the generation of effective Mn detoxifying agents.

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Highlights

- Mechanisms of Mn toxicity due to *SLC30A10* or *SLC39A14* mutations are described.

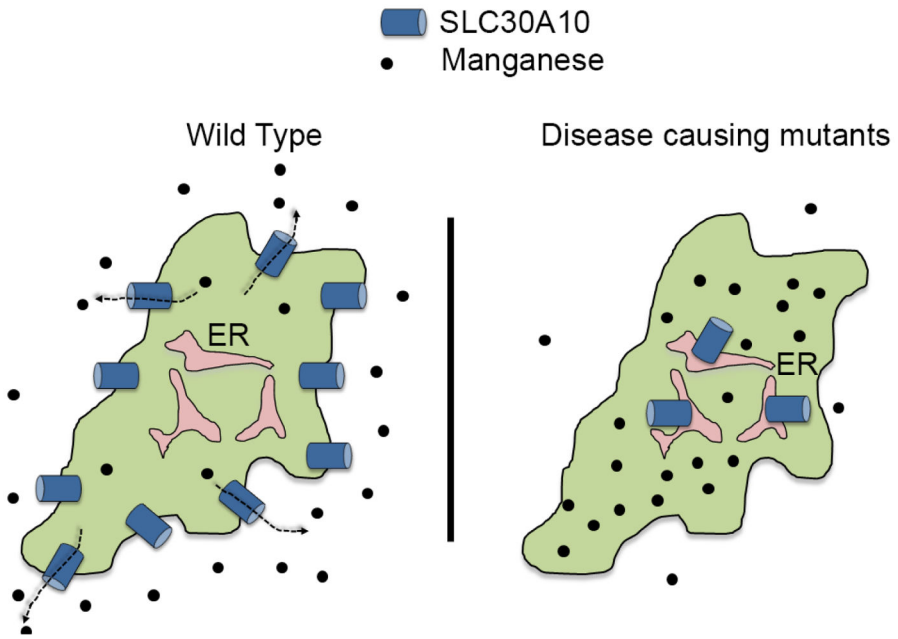

Figure 1.

Schematic depicting the intracellular function of SLC30A10 and the mechanism by which disease-causing mutants induce Mn toxicity. Wild-type SLC30A10 traffics to the cell surface, transports Mn from the cytosol to the cell exterior, and protects against Mn toxicity. Most disease-causing mutants are trapped in the endoplasmic reticulum (ER) and fail to mediate Mn efflux. Consequently, cellular Mn levels increase and toxicity ensues.

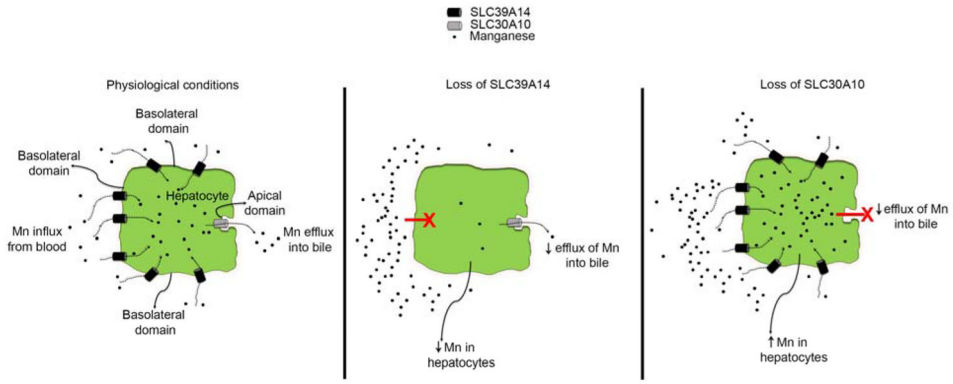

Figure 2.

Proposed model for the role of SLC39A14 and SLC30A10 in regulating Mn homeostasis and detoxification. SLC39A14 may localize to the basolateral aspect of hepatocytes and transport Mn from blood into hepatocytes. Note that a prior study localized SLC39A14 to the basolateral domain of hepatocytes in rats (Nam et al., 2013). SLC30A10 may localize to the canalicular/apical domain of hepatocytes and transport Mn from within hepatocytes into bile. Consistent with available experimental and clinical data, this model predicts that, in the absence of functional SLC39A14, Mn levels will increase in blood and brain, but not in liver, and in the absence of functional SLC30A10, Mn levels will increase in liver, blood, and brain. Increase in brain Mn may induce neurotoxicity. In the case of SLC30A10, loss of efflux function in the brain may play an additional role in inducing neurotoxicity.

Table 1

Time-line of major discoveries on SLC30A10 and SLC39A14.

Year	Event/Finding	Reference
2008	First detailed case report of an individual suffering from Mn-induced neurotoxicity later attributed to mutations in *SLC30A10*.	(Tuschl et al., 2008)
2012	Discovery that homozygous mutations in *SLC30A10* induce familial Mn-induced neurotoxicity	(Quadri et al., 2012; Tuschl et al., 2012)
2014	Discovery that SLC30A10 functions as a Mn efflux transporter	(Leyva-Illades et al., 2014)
2014	Autopsy findings of an individual who harbored *SLC30A10* mutations	(Lechpammer et al., 2014)
2016	Identification of critical amino acid residues required for Mn transport activity of SLC30A10	(Nishito et al., 2016; Zogzas et al., 2016)
2016	Discovery that homozygous mutations in *SLC39A14* induce familial Mn-induced neurotoxicity.	(Tuschl et al., 2016)
2016	Autopsy findings of a patient with *SLC39A14* mutations	(Tuschl et al., 2016)
2016	Findings from zebrafish lacking SLC39A14	(Tuschl et al., 2016)
2017	Generation and characterization of *Slc30a10* knockout mice	(Hutchens et al., 2017)
2017	Characterization of Mn toxicity in *Slc39a14* knockout mice	(Aydemir et al., 2017; Mitchell D Knutson, 2017); (Yongjuan Xin, 2017)
2017	Findings from zebrafish lacking SLC30A10	(Xia et al., 2017)