Mitochondrial ABC Transporters and Iron Metabolism

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Abstract

Mitochondrial are a key organelle in iron metabolism and many metabolic processes involved in iron homeostasis occur in the mitochondria. Eukaryotic cells have developed different transport mechanisms to deal with coordinating movement of iron and iron-related molecules across membranes. Some of those transport mechanisms involve ATP-binding cassette (ABC) transporters. There are four mitochondrial ABC transporters Abcb6, Abcb7, Abcb8 and Abcb10. Abcb6 is localized to the outer membrane of mitochondria where it is involved in porphyrin transport. Abcb7, Abcb8 and Abcb10 are localized to the inner mitochondrial membrane and the exact molecule transported by each is still unclear. Here, we provide a brief review of what is known about each transporter and its role in mitochondrial iron homeostasis. We describe the human diseases associated with known mutations in the genes encoding these proteins and discuss the possible importance of these transporters in immune cell function.

Keywords: ABC transporters; Mitochondria; Iron; Heme

Introduction

ATP-binding cassette (ABC) transporters belong to a large family of membrane proteins that are found in all kingdoms of life and require ATP hydrolysis to transport substrates across membranes [1,2]. They are involved in a large spectrum of biological processes such as transporting ions, lipids, peptides, metabolites, porphyrins and drugs. ABC transporters that are localized to the mitochondria of metazoans include Abcb6, Abcb7, Abcb8 and Abcb10 (Figure 1). These proteins belong to the half transporter B subfamily, thus the ABCB group [3-5]. They contain an N-terminal transmembrane domain and a C-terminal nucleotide binding domain and form homodimers for transport. The mitochondrial ABC transporters are encoded by nuclear genes and contain a varying length mitochondrial targeting sequence that is clipped off in the mitochondrial matrix. The structures of a few of these transporters has been solved although many of their exact substrates transported remain to be determined clues as to what these transporters export from the mitochondria and the biochemical pathways they affect come from biochemical and genetic studies [6-8]. All mitochondrial Abcb transporters have been linked to oxidative stress and are characterized to be involved in iron and/or heme biological processes [9-12].

Iron and heme are essential co-factors for many biological pathways such as Fe-S clusters synthesis, oxidative phosphorylation pathway in the mitochondria and also DNA synthesis. The heme biosynthesis pathway takes place in both the mitochondria and cytosol requiring tight regulation and transport of iron, porphyrin intermediates and heme across the mitochondrial membrane. In this review, we discuss what is known about each mitochondrial ABC transporter including information learned from eukaryote homologues, potential substrates transported, the relationship to iron metabolism and speculate on how these transporters might affect immune function.

![Figure 1: Model of mitochondrial Abcb transporters and their contribution to mitochondrial iron and heme homeostasis. Mitochondrial Abcb transporters are found at the outer and inner membrane. Abcb6 is localized to the outer membrane and has been localized to the plasma membrane where it functions in porphyrin transport. Abcb7, Abcb8 and Abcb10 are localized to the inner mitochondrial membrane. Abcb7 has been suggested to be involved in Fe-S or Fe-glutathione-SS transport out of mitochondria. Abcb8 has been suggested to transport iron out of mitochondria. The substrate transported out of mitochondria by Abcb10 is unknown, but Abcb10 is known to bind Mfn1 and stabilize it for increased iron import. Abbreviations used: CopgenIII=Coproporphyrinogen III, PPgenIII=Protoporphyrinogen III, PPIX=Protoporphyrin IX.](image)

**Abcb6**

Abcb6 was originally identified in a screen for genes associated with drug resistance in the liver [13]. Abcb6 has been localized to the outer...
mitochondrial membrane [14-16], the plasma membrane [16], Golgi apparatus [17], endoplasmic reticulum [18] and the endocytic Pathway [19,20]. Its function at each of these locations has been a source of much controversy. Abcb6 was first described as a mitochondrial porphyrin transporter that imports coproporphyrinogen III (CPGenIII) from the cytosol into the mitochondrion but is also capable of binding heme and protoporphyrin IX (PPIX) [15]. That Abcb6 is important in red cell heme biosynthesis was further supported by studies done in the Abcb6 knockout mouse, however, the importance was only revealed under conditions of hematopoietic stress [21]. These studies further demonstrated that ATP-driven porphyrin import into mitochondria was completely lost in the absence of Abcb6 but that non-ATP-dependent porphyrin import was unaffected. This suggests that under “steady-state” porphyrin synthesis, red cells can compensate for the loss of Abcb6 by increased expression of other porphyrin synthesis and iron acquisition genes.

The role of Abcb6 at the plasma membrane has been associated with the new blood type Langereis (Lan) [22]. Individuals lacking Abcb6 at the plasma membrane show increased porphyrin accumulation supporting studies that suggest that Abcb6 functions as a plasma membrane porphyrin exporter [23,24]. Additionally, using a mouse model of porphyria, Fukuda et al. demonstrated that the loss of Abcb6 in combination with a ferrochelatase-deficient mouse resulted in increased PPIX accumulation [24].

The role of Abcb6 at other locations remains unknown. The fact that Abcb6 is found in the ER and Golgi may simply reflect its transit during biosynthesis and its presence in the endocytic pathway may reflect mechanisms to downregulate plasma membrane porphyrin export or some level of mitophagy where damaged mitochondria are degraded by the lysosome. Boswell-Casteel et al. provide a more detailed review of the role of Abcb6 in iron and heme processes and its impact in human disease and drug Treatments [25]. Further studies will be necessary to determine if the other locations for Abcb6 are important in heme or porphyrin homeostasis.

**Abcb7**

The first identification of Abcb7 was as a candidate gene for X-linked sideroblastic anemia with spinocerebellar ataxia [26-28], suggesting a role for Abcb7 in iron/heme biological processes. Abcb7 is localized to the inner mitochondrial membrane and studies have directly shown that reductions in Abcb7 give rise to reduced heme levels in developing red cells [29]. Studies on the Abcb7 yeast homologue Atm1 have provided a great deal of insights into its function. Lack of Atm1 results in accumulation of iron in the mitochondria and decreased cytosolic Fe-S clusters while mitochondrial Fe-S cluster are unaffected [30,31]. That cytosolic Fe-S clusters were affected in human Abcb7 mutants was confirmed by Bekri et al. [26] These studies as well as others suggest that Atm1/Abcb7 may be a Fe/S cluster exporter [31].

In yeast, Fe-S clusters are made in the mitochondria and require Atm1 to deliver Fe-S to the cytosol for assembling cytosolic and nuclear Fe-S cluster proteins [32-34]. These results support a role for Atm1/Abcb7 in cytosolic Fe-S cluster assembly, but what Atm1/Abcb7 transports is not clearly defined. In *in vitro* vesicle and crystal structure studies using Abcb7 homologues suggest that a substrate for Abcb7 is glutathione and possibly glutathione-disulfide [7,8,35], which correlates with a cytosolic defect in Fe-S clusters in the absence of Abcb7 as glutathione is used for Fe-S cluster maturation in the cytosol.

What has yet to be determined is if Fe-S clusters are also transported by Abcb7 and its homologues or if another mitochondrial protein is responsible for this process.

**Abcb8**

Abcb8 was first described as a mitochondrial ABC transporter in 1999 [36], however, its role in mitochondrial homeostasis and iron metabolism was not elucidated until Ichikawa et al. deleted *Abcb8* in the mouse heart [37]. Loss of Abcb8 resulted in severe cardiomyopathy, increased mitochondrial iron accumulation and increased reactive oxygen species. Moreover, mitochondrial isolated from *Abcb8* cardiomyocytes exhibited increased iron levels concomitant with decreased activity of cytosolic Fe-S clusters proteins including xanthine oxidase, glycerol-3-phosphate and cytosolic aconitase suggesting a role for *Abcb8* in iron homeostasis and possibly iron export. Further evidence for *Abcb8* as a mitochondrial iron exporter was observed in doxorubicin-mediated cardiotoxicity studies where overexpression of Abcb8 could reduce both mitochondrial iron accumulation and reactive oxygen species [38]. A role for *Abcb8* in red blood cells or other tissues has not been determined.

**Abcb10**

*Abcb10* was first identified as a downstream target of *GATA1*, a major transcription factor for terminal erythroid differentiation and named ABC-me (for mitochondrial erythroid) [39]. *Abcb10* knockout in mouse is embryonic lethal due to anemia, supporting an essential role in erythropoiesis [40], however, *Abcb10* is expressed ubiquitously suggesting a broader function than erythropoiesis. *Abcb10* is localized to the inner mitochondrial membrane and has been shown to form a complex with Mitoferrin1 (Mfrn1) and Ferrochelatase (Fech) to enhance heme synthesis [41,42]. Decreases in *Abcb10* levels lead to reduced Mfrn1 protein levels and decreased iron import into mitochondria and consequently a reduction in heme biosynthesis. *Abcb10* has also been shown to have a protective effect against oxidative stress [11,40]. There has been some controversy regarding the role of *Abcb10* and the possible substrate transported. Yamamoto et al. reported increased protoporphyrin IX (PPIX) accumulation in hematopoietic cells in a hematopoietic-specific targeted deletion of *Abcb10* [43] suggesting a defect in iron import or a defect in ferrochelatase function. In contrast, other groups have not observed PPIX accumulation when *Abcb10* levels are greatly reduced [40,44-46]. One study suggested that *Abcb10* was a delta-aminolevulinic acid (ALA) exporter, the product of the first reaction in heme synthesis that occurs in the mitochondria [44].

Recent studies, however, demonstrated that *Abcb10* is not the ALA exporter [45,46]. Seguin et al. determined that significant reductions in *Abcb10* in zebrafish and murine erythroleukemia cells did not result in a defect in ALA transport but rather total ALA synthesis was decreased due to reduced levels of *Alas2* activity [45]. Further, it was shown that loss of *Abcb10* resulted in a decrease in hemoglobinization transcripts due to increased occupation of Bach1 (a transcriptional repressor [47]) on the beta-Globin promoter. Overexpression of Gata1 or Alas2 was able to suppress Bach1 repression and partially rescue hemoglobinization transcripts levels in *Abcb10*-silenced MEL cells. Surprisingly, hemin or ALA addition did not have an effect on the transcripts levels, suggesting that the substrate transported by *Abcb10* is an important signal for hemoglobinization optimization. The substrate for *Abcb10* has yet to be identified. Qui et al. determined that glutathione was able to regulate *Abcb10* ATP binding and hydrolysis.
activity; oxidized glutathione GSSG activated while reduced glutathione GSH inhibited Abcb10 ATP hydrolysis activity [46]. Further studies are necessary to determine the substrate transported by Abcb10 to define its role in mitochondrial iron and heme homeostasis and red cell hemoglobinization induction.

**Mitochondrial ABC Transports and Human Disease**

Almost all organisms require iron for life as Fe-S clusters and heme synthesis, all processes that occur in the mitochondria, are essential. Because of this fact, the inability to regulate mitochondrial iron homeostasis would be predicted to affect all mammalian cells. Evidence to support the importance of mitochondrial Abcb transporters has been shown for Abcb8 and Abcb10 in cardiomyocytes [37,44]. Abcb6 and Abcb10 in red cells [21,40-43,45,46,48,49] and for Abcb6 in liver [23,24]. In addition, Abcb6 is highly expressed in megakaryocytes and platelet production is elevated in the absence of Abcb6 [49]. Furthermore, Abcb6 null platelets are hyperactive in platelet-mediated development of atherosclerosis and show increased leukocyte interactions without changes in peripheral leukocyte numbers [50-55]. Deletion of Abcb7 in mouse leads to a decrease in platelets and white blood cells. These results suggest some regulatory mechanism for porphyrin/heme synthesis is important in immune cell function although no studies have addressed this possibility. Human disease that are associated with the loss of the Abcb mitochondrial transporters are listed in Table 1 [5].

<table>
<thead>
<tr>
<th>Gene</th>
<th>Human disease</th>
<th>Reference</th>
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<tbody>
<tr>
<td>ABCB6</td>
<td>Familial pseudohyperkalemia</td>
<td>[56,57]</td>
</tr>
<tr>
<td></td>
<td>Dyschromatosis universalsis hereditaria</td>
<td>[58,59]</td>
</tr>
<tr>
<td></td>
<td>Microphthalmia, isolated with coloboma</td>
<td>[60]</td>
</tr>
<tr>
<td>ABCB7</td>
<td>X-linked sideroblastic anemia with cerebella ataxia (XLS/A)</td>
<td>[26,27]</td>
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<tr>
<td></td>
<td>Refractory Anemia with Ring Sideroblasts (RARS)</td>
<td>[61]</td>
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</tbody>
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**Table 1:** Human diseases associated with mutations in mitochondrial Abcb transporters.

**Conclusion**

To our knowledge, a role for Abcb transporters in other organ systems or cellular functions has not been reported. A role for ABC transporters has been suggested for immune cell functions including antigen processing and presentation, natural killer and T cell development transporters. Cells that are highly proliferative such as ABC transporters. Science 293: 1782-1784.

**Conflict of Interest**

The authors declare no conflicts of interest.

**References**


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