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Heme Mobilization in Animals: A Metallolipid's Journey

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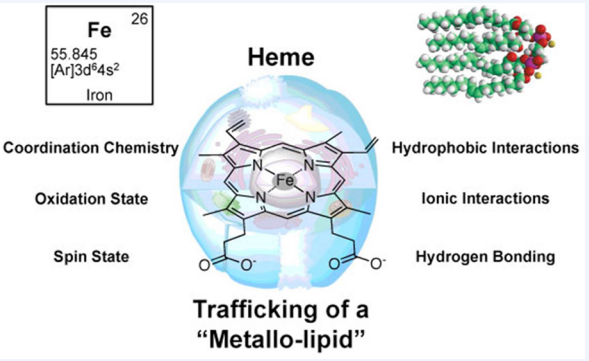
CONSPECTUS: Heme is universally recognized as an essential and ubiquitous prosthetic group that enables proteins to carry out a diverse array of functions. All heme-dependent processes, from protein hemylation to heme signaling, require the dynamic and rapid mobilization of heme to hemoproteins present in virtually every subcellular compartment. The cytotoxicity and hydrophobicity of heme necessitates that heme mobilization is carefully controlled at the cellular and systemic level. However, the molecules and mechanisms that mediate heme homeostasis are poorly understood. In this Account, we provide a heuristic paradigm with which to conceptualize heme trafficking and highlight the most recent developments in the mechanisms underlying heme trafficking.



As an iron-containing tetrapyrrole, heme exhibits properties of both transition metals and lipids. Accordingly, we propose its transport and trafficking will reflect principles gleaned from the trafficking of both metals and lipids. Using this conceptual framework, we follow the flow of heme from the final step of heme synthesis in the mitochondria to hemoproteins present in various subcellular organelles. Further, given that many cells and animals that cannot make heme can assimilate it intact from nutritional sources, we propose that intercellular heme trafficking pathways must exist. This necessitates that heme be able to be imported and exported from cells, escorted between cells and organs, and regulated at the organismal level via a coordinated systemic process. In this Account, we highlight recently discovered heme transport and trafficking factors and provide the biochemical foundation for the cell and systems biology of heme. Altogether, we seek to reconceptualize heme from an exchange inert cofactor buried in hemoprotein active sites to an exchange labile and mobile metallonutrient.

1. INTRODUCTION

Heme (iron protoporphyrin IX) is an essential metallonutrient that serves roles as a vital protein cofactor and signaling molecule.[1−7] As a hydrophobic and cytotoxic species, heme concentration and availability must be tightly regulated.[4,8] This has contributed to the dogmatic belief that (1) heme is a static cofactor buried in the active sites of exchange-inert proteins, and (2) all cellular hemoproteins acquire heme exclusively from de novo synthesis whereas exogenously supplied heme is primarily degraded. However, these long-held views are incompatible with the fact that (a) exogenous heme can be utilized by normal cells and mutants that cannot make it, and (b) heme-dependent signaling necessitates that heme is rapidly mobilized from existing stores. Both processes require that there is a pool of exchange-labile heme and molecules and mechanisms in place that can safely and dynamically distribute heme to a multitude of heme-dependent processes. Although the biosynthesis and degradation of heme are relatively well-understood pathways, there is comparatively little known about heme transport and trafficking.[1]

In most metazoans, heme is synthesized via a highly conserved eight-step process.[1] The first and the last three reactions take place in the mitochondria, and the remaining reactions occur in the cytosol. The first step of heme synthesis begins with the condensation of glycine with succinyl-coenzyme A to form δ-aminolevulinic acid (ALA), the first committed precursor. The last step of heme synthesis is iron insertion into protophorphyrin IX on the matrix side of the mitochondrial inner membrane. In this Account, we focus exclusively on the trafficking of heme once it has been synthesized or acquired from exogenous sources.

The limited understanding of heme transport and trafficking, and its dynamics, is in large part due to the lack of tractable genetic and biophysical tools to study these processes. The last 10 years have witnessed a renaissance in our understanding of the cell biology of heme, including the identification of eukaryotic heme transporters and chaperones. This is because of the characterization of genetic mutants in conventional model systems that have been typically used to identify iron metabolism pathways, e.g., yeast, zebrafish, and mice, as well as the exploitation of atypical model systems that do not synthesize heme, e.g., the roundworm *C. elegans* and trypanosomatids.[9,10] *C. elegans* in particular is unique because

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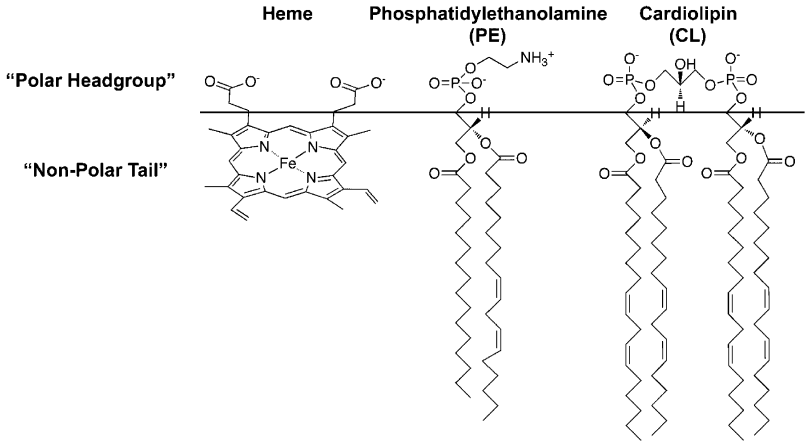

Figure 1. Lipid-like properties of heme. The "phospholipid-like" structure of heme is depicted alongside the other mitochondrial-derived lipids phosphatidylethanolamine (PE) and cardiolipin (CL).

it is a heme auxotroph that requires environmental heme to survive. Thus, heme transport and trafficking can be studied within the context of a live animal without confounding contributions from heme synthesis.[9] Another key development is the generation of fluorescent and enzymatic reporters to probe the dynamics and distribution of heme in cells and animals.[11−13]

In this Account, we provide a general framework to contemplate heme mobilization and dynamics in animals. In mammals, cells may have specialized pathways to deal with excessive heme. For example, (a) erythroblasts differentiate into mature red blood cells in which hemoglobin is the major protein; (b) hepatocytes have specialized receptors to detoxify heme during pathophysiological conditions of hemolysis; (c) reticuloendothelial macrophages phagocytose effete red cells to recycle heme and iron; and (d) enterocytes absorb heme from a heme-rich diet such as red meat. Each of these cells has specific mechanisms for heme uptake/transport and heme degradation/detoxification. However, heme synthesis occurs in virtually all cells in the body, and these cells contain a variety of hemoproteins residing in numerous subcellular compartments. Thus, a priori, one would expect that cellular transport and trafficking of heme must obey specific generalized principles. Although a fair amount is known about how certain bacteria can capture and utilize exogenous heme, this review elaborates a comprehensive scheme for heme homeostasis in animals. In particular, we discuss intra- and intercellular heme trafficking as well as the biochemical cues that may initiate the mobilization of heme. We will highlight both recent advances in our understanding of heme mobilization as well as outstanding questions.

2. PRINCIPLES OF HEME TRAFFICKING: PERSPECTIVES ON AN EXCHANGE-LABILE "METALLOLIPID"

A useful formalism with which to contemplate cellular heme is as exchange-inert and -labile pools. Inert and labile heme may be operationally defined as heme that is unavailable or available for new heme-dependent functions, respectively. The nature (concentration, speciation, oxidation state, and localization) and dynamics of these heme pools are poorly understood. By definition, inert heme does not contribute toward new protein hemylation and signaling and corresponds to heme buried in the active sites of hemoproteins like globins and cytochromes. Labile heme (LH) is readily accessible for protein hemylation and heme signaling and corresponds to heme that is buffered by exchange-labile small molecules, peptides, or proteins. LH in various cell lines and subcellular compartments, including the nucleus, cytosol, and mitochondria, has been estimated to be between approximately 25 and 300 nM,[11−13] which is ∼10% of the total cellular heme concentration.[11]

As an iron-containing tetrapyrrole, heme has characteristics of both a metal and a lipid. Accordingly, we propose a heuristic paradigm that predicts LH is trafficked in a manner that is a hybrid of both transition metals and lipids. From the perspective of a transition metal, heme can be viewed as a voluminous "alloy" of iron. As such, heme transport and trafficking is in part dictated by its coordination chemistry and oxidation state. This evokes the existence of chaperones, buffers, and transporters analogous to those identified for Cu(I).[14] Indeed, over the last 10 years, molecular genetic approaches in a range of cell types and model organisms, and most notably in the heme auxotroph *C. elegans*, have revealed a number of heme homeostatic factors, including transporters and chaperones.

From a lipid-centric viewpoint, ferrous heme can be considered as a phospholipid-like molecule containing a headgroup consisting of a pair of negatively charged hydrophilic propionates and a tail comprising a formally neutral hydrophobic porphyrin core, $[Fe^{2+}por^{-2}]^0$ (Figure 1). As such, heme trafficking may be dictated by hydrophobic, ionic, and hydrogen bonding interactions between heme and surrounding protein matrices or membranes. This suggests that heme may be trafficked like other mitochondrial-derived lipids such as cardiolipin and phosphatidylethanolamine (PE) via membrane-tethering complexes, lipid transfer proteins, vesicular trafficking, or lipid transporters (Figure 2).[15,16]

3. MOBILIZATION FROM THE MITOCHONDRIA

The last step of heme biosynthesis occurs with ferrochelatase inserting ferrous iron into protoporphyrin IX in the matrix side of the inner membrane. At this point, heme can follow one of four fates; it can be trafficked (1) to the mitochondrial matrix, where hemoproteins like cholesterol side-chain cleavage enzyme (cytochrome p450scc) reside, 2) to respiratory complexes in the inner membrane, 3) to the intermembrane space (IMS), where hemoproteins like cytochrome *c* peroxidase resides, or 4) out of the mitochondria to hemoproteins present

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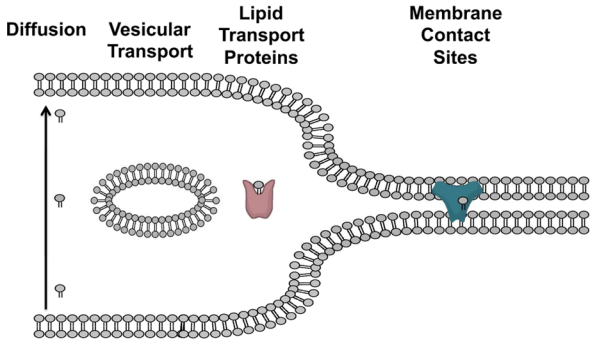

Figure 2. Mechanisms of lipid trafficking. Heme may be trafficked by mechanisms analogous to that of other lipids, including by diffusion, vesicular transport, carrier proteins, and at membrane contact sites. Sites of membrane contact are facilitated by supramolecular protein assemblies, e.g., the endoplasmic reticulum-mitochondria encounter structure (ERMES) complex, that are located at the interface of two organelles and act to tether them together.

in virtually every subcellular compartment (Figure 3).[1] The factors that dictate directionality of mobilization and the

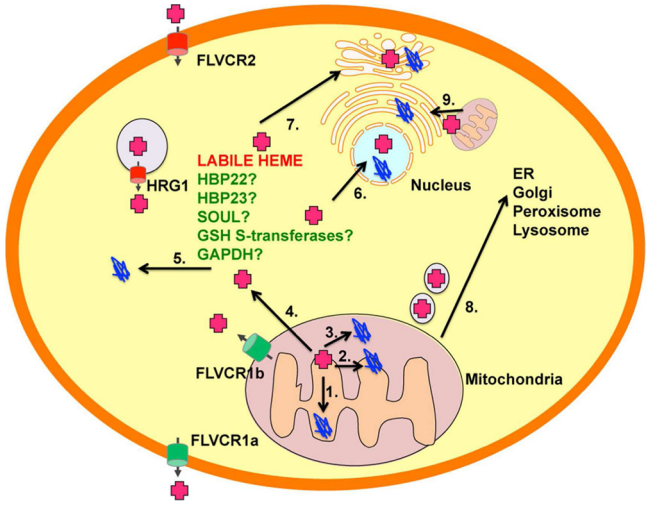

Figure 3. Intracellular heme transport and trafficking in eukaryotes. Once heme (red crosses) is biosynthesized on the matrix side of the mitochondrial inner membrane, it must transit to (1) soluble matrix proteins, (2) inner membrane proteins, (3) soluble intermembrane space (IMS) proteins, or (4) outside the mitochondria. Once in the cytosol, labile heme, which is buffered in part by the factors indicated in green, must be trafficked to (5) cytosolic, (6) nuclear, and (7) endoplasmic reticulum (ER) and golgi proteins. Alternatively, heme can be trafficked to other locales via (8) mitochondrial-derived vesicles (MDVs) or (9) mitochondria-ER contact points. Known heme transport and trafficking factors are highlighted.

hierarchy for heme allocation, as well as the mechanisms that mediate the trafficking of mitochondrial heme, are largely unknown. The recent identification of a mitochondrial heme metabolism complex that traffics heme biosynthetic intermediates via substrate channeling might suggest similar mechanisms of intramitochondrial heme trafficking.[17] In such a scenario, once heme is synthesized, it would be passed from one protein to another without being released into solution. Alternatively, in analogy to metallochaperones that deliver copper to cytochrome *c* oxidase,[14] there may be as yet to be determined heme chaperones that traffic heme to respiratory complexes or soluble proteins in the matrix or IMS.

Most interestingly, oxidative signals from H_2O_2 can initiate the transfer of heme between hemoproteins. Respiratory chain-derived H_2O_2 can irreversibly oxidize a heme-coordinating His residue in cytochrome *c* peroxidase, causing heme dissociation and transfer to catalase.[18] These types of peroxide-dependent oxidative modifications labilize heme from otherwise exchange-inert hemoproteins, thereby facilitating heme transfer and reallocation. However, whether this mode of peroxide-based heme transfer only occurs under pathophysiological conditions of oxidative stress or not remains to be determined.

Trafficking of heme out of the mitochondria and into the cytosol necessitates that it must cross the inner and outer membranes (Figure 2). Although heme is lipophilic, the negatively charged propionates pose an energetic barrier to cross a lipid bilayer, albeit local pH or metal cation concentrations in the vicinity of the membrane may shield this charge.[19] Alternatively, there may be specific heme transporters analogous to those for other metals or lipids. For instance, Flvcr1b,[20] a member of the major facilitator superfamily (MFS) of secondary active transporters, is postulated to export heme from the mitochondria.

Flvcr1b is derived from Flvcr1a, a 12 transmembrane domain (TMD) plasma membrane heme exporter.[5,21] An alternate transcriptional start-site located within the first intron of *Flvcr1* results in a shorter transcript that is proposed to produce a truncated six TMD isoform termed Flvcr1b. Knocking-down Flvcr1b by siRNA resulted in mitochondrial heme accumulation and termination of erythroid differentiation, whereas overexpression resulted in increased cytosolic heme.[20] *Flvcr1a/b*$^{-/-}$ mice lack both isoforms and die in utereo due to a block in erythroid maturation. However, genetic ablation of *Flvcr1a* alone causes in utero lethality that was attributed to severe hemorrhage and skeletal deformations. Because erythroid differentiation was normal in *Flvcr1a*$^{-/-}$ mice, the erythroid maturation function was therefore attributed to Flvcr1b. Evidence for direct heme transport by Flvcr1 is lacking with gaps in key mechanistic details. For instance, how does Flvcr1 bind and translocate heme, and what drives the energetics of transport on the mitochondrial membranes versus the plasma membrane? Interestingly, Flvcr1a residues implicated in mediating heme transport via interactions with the heme-binding protein hemopexin are located in a segment from amino acids 132−201 (His_{145}, Tyr_{153}, His_{198}) that are missing in Flvcr1b.[22] Further, it is unknown if Flvcr1b is located on the inner or outer mitochondrial membrane, which will have implications for where it acquires, i.e., matrix vs IMS, and transports heme, i.e., IMS vs cytosol. Although Flvcr1b may constitute one way of contributing to LH in the cytosol, it is by no means the only way. Eukaryotes like *S. cerevisiae* lack Flvcr1 homologues altogether, implying the presence of alternative heme transport mechanisms.

In analogy to lipid trafficking, direct membrane contacts or vesicular trafficking to other organelles may also mediate mobilization out of the mitochondria (Figure 2). For instance, mitochondria-associated membranes (MAMs), which form contact sites between the mitochondrial outer membrane and the endoplasmic reticulum (ER) via the ER-mitochondria encounter structure (ERMES), are a contiguous interface for the exchange of lipids and may also be an axis for heme exchange.[23] Indeed, factors involved in heme homeostasis, including coproporphyrinogen III oxidase, ferrochelatase, HBP

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1, and HO-2, have been found to associate with MAMs.[24] Because of the extensive network of ER between the nucleus, Golgi, and secretory pathway, heme can gain access to a number of hemoproteins present in these organelles as well as proteins that are targeted to the lysosome, peroxisome, plasma membrane, or are secreted (Figure 3). However, the mechanisms by which hemes are distributed once in the ER or Golgi, including any putative heme chaperones, are currently unknown. Another potential exit strategy for mitochondrial heme is via mitochondrial-derived vesicles (MDVs).[25] MDVs have been found to traffic material to peroxisomes and lysosomes, and it is tempting to speculate that hemes may also be part of the cargo.

4. MOBILIZATION FROM THE CYTOSOL

In principle, all cytosolic heme is derived either from the mitochondria via de novo synthesis or from extracellular sources via uptake at the plasma membrane (discussed in section 5). Cytosolic heme is most likely buffered by any number of factors that constitute a heterogeneous exchange-labile heme pool (Figure 3). These include a number of heme binding proteins (HBPs) defined by their molecular weights, including 22 kDa HBP, 23 kDa HBP, and SOUL, as well as glutathione *S*-transferase.[1] In addition, in analogy to lipid trafficking, fatty acid binding protein (FABP), which functions to traffic fatty acids and lipids, has been suggested to act as a heme trafficking factor on the basis that its affinity for heme is 10-fold greater than that for fatty acids like oleic acid.[1] These putative HBPs were identified on the basis of their interaction with heme-agarose or blue-sepharose columns and submicromolar heme dissociation constants. However, it is unclear if these proteins play a role in heme trafficking beyond simply buffering excess heme. It is also unknown if heme can be mobilized from these factors.

Interestingly, the glycolytic enzyme glyceraldehyde phosphate dehydrogenase (GAPDH), was found to act as a heme chaperone.[26] Stuehr and colleagues noted that nitric oxide (NO) can inhibit heme insertion into a variety of hemoproteins, including nitric oxidase synthase (NOS), hemoglobin, catalase, and cytochrome P450. These observations led to the hypothesis that there was a cellular heme trafficking factor upstream of these diverse hemoproteins that mobilized heme in an NO-dependent manner. Subsequent biochemical studies identified GAPDH as such a factor that interacted with a heme-agarose column in a NO-dependent fashion.[26] This formed the basis for experiments demonstrating that GAPDH is required for heme delivery to NOS enzymes and that this heme transfer is inhibited by nitric oxide (NO). Thus, like H_2O_2, NO may also dynamically regulate heme transfer reactions. Consistent with this notion, treatment of endothelial cells with NO was postulated to release heme from certain hemoproteins.[27] This concept was only recently visualized in yeast using genetically encoded heme sensors.[11]

It is unknown if or how cytosolic heme may be mobilized to other organelles, including the nucleus, ER, Golgi, peroxisomes, and so forth. To date, no organelle-specific heme trafficking factors or transporters have been identified. This is particularly important when considering the multitude of signaling roles for heme. For instance, a number of heme-regulated transcription factors, including HAP1 in yeast[28] and Bach1,[29] p53,[2] and REV-ERB[3] in mammals, which collectively control pathways spanning oxygen sensing, iron homeostasis, the antioxidant stress response, mitochondrial respiration and biogenesis, mitophagy, apoptosis, circadian rhythms, cell cycle progression, and proliferation, require the dynamic mobilization of heme to the nucleus. In addition, heme may also act as a retrograde signal between mitochondria and the nucleus or regulate certain kinases and ion channels.[7] In all of these cases, a heme-based signal must be initiated, transmitted, and integrated to affect physiology and metabolism. However, the basic molecular mechanisms, kinetics, and thermodynamics underlying these processes are unknown. For instance, many of the heme-regulated nuclear transcription factors exhibit micromolar dissociation constants for heme,[28] yet labile heme in compartments spanning the cytosol, nucleus, and mitochondria has been estimated to be ∼20−40 nM or less on the basis of imaging experiments with genetically encoded fluorescent sensors.[11,12] This raises fundamental questions about how these transcription factors become heme activated and the nature of the factors that mobilize and traffic heme for signaling.

5. MOBILIZATION OF EXOGENOUS HEME

In addition to de novo synthesis, cellular heme can also be derived from exogenous sources. Molecular genetic approaches in the heme auxotroph *C. elegans* have been instrumental in the discovery of heme transporters. The heme importers HRG-1 and its paralogue HRG-4 were identified as *heme responsive genes* that are transcriptionally upregulated during growth on low heme.[30] They were subsequently determined to be involved in heme uptake in the intestines of worms. HRG-4, which lacks mammalian homologues, localizes to the plasma membrane. On the other hand, HRG-1, which is conserved from arthopods to vertebrates, including mammals, is present in endolysosomal compartments, and mobilizes exogenously-derived endosomal heme into the cytosol (Figure 4).

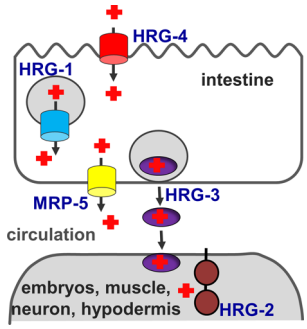

Figure 4. Heme homeostasis pathways identified using the *C. elegans* model. HRG-1 paralogues (HRG-1, HRG-4) import heme into the intestine from the apical surface. Heme export from the basolateral surface of the intestine is mediated by MRP-5, an ABC transporter. The peptide HRG-3 is secreted by the mother's intestine and functions to transport maternal heme to developing oocytes and other extra-intestinal tissues. HRG-2 is a putative heme reductase, which facilitates heme uptake in the hypodermis.

Human HRG1 (Slc48A1), which is 20% identical to the *C. elegans* HRG-1, is predicted to have four TMD-spanning helices.[30,31] HRG1 functions cooperatively with a V-type H^+-ATPase, where intracompartmental acidification can cause the release of heme from hemoproteins, solubilize free heme, and couple heme translocation to a proton gradient.[31] HRG1 was shown to import heme into *Xenopus* oocytes and transport zinc mesoporphyrin (ZnMP) into the *C. elegans* intestine and

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murine cells ectopically expressing HRG1. Indirect measurements for heme transport activity using yeast reporter assays revealed that a number of highly conserved heme-binding His and Tyr residues are critical for HRG1 activity.[32]

FLVCR2 may constitute a cell surface heme transporter. This is based on findings that collectively demonstrate FLVCR2 binds to a heme-agarose column and that overexpression of FLVCR2 in Chinese hamster ovary (CHO) cells and *Xenopus laevis* oocytes exhibit enhanced heme accumulation and greater sensitivity to heme toxicity. Cellular accumulation of ZnMP is reduced upon FLVCR2 depletion by siRNA.[33] However, it is unclear whether FLVCR2 imports heme into the cytosol like HRG1 or exports heme into the lumen of intracellular organelles, which would also result in enhanced cellular heme (Figure 3).[32]

What is the contribution of exogenous heme to the cellular heme repository? The simplistic model is that it is degraded by heme oxygenase (HO), releasing iron for cellular functions including *de novo* heme synthesis. However, it is unclear how exogenous heme makes its way to HO in the ER or if there is a fraction of heme that contributes to the LH in the cytosol. Indeed, with respect to the latter, a number of cells and animal systems that are defective in heme synthesis can be rescued by heme supplementation, suggesting a route for recycling and reusing the heme that is independent of heme degradation.[34−36] The differential allocation and utilization between endogenously synthesized heme and exogenously supplied heme, and their relative contributions to the heme quota, need to be fleshed out.

6. MOBILIZATION BETWEEN CELLS

Disease, inflammation, or intravascular hemolysis can release hemoglobin or heme from red blood cells. Two extracellular heme-scavenging proteins in the serum, haptoglobin and hemopexin, bind hemoglobin and heme, respectively.[37] Haptoglobin is also mainly secreted from hepatocytes and binds free hemoglobin in the plasma. The haptoglobin-hemoglobin dissociation constant has been estimated by fluorimetry to be tighter than a K_D of 10^{-15} M at pH 7.0.[38] This complex is endocytosed by tissue macrophages via the receptor CD163,[39] and the heme released during endosomal acidification is imported into the cytoplasm and recycled by macrophages for subsequent erythropoiesis.[40] Hemopexin, produced predominately by the liver, binds heme in the plasma. The hemopexin-heme K_D was estimated to be 5×10^{-15} M at pH 7.0 by competition titration with hemoglobin followed by UV/vis spectrophotometry.[41] The hemopexin-heme complex is endocytosed after binding to the LRP1/CD91 receptor, which is expressed on several cell types including macrophages, hepatocytes, placental syncytiotrophoblast, and neurons.[41−43] Cell culture studies in primary macrophages have shown that heme, released from the destruction of red cells, can be imported and utilized *in toto* by a Golgi-targeted horseradish peroxidase reporter.[44] Moreover, heme export by FLVCR1 can be enhanced over 100-fold upon binding to hemopexin as demonstrated by competition experiments using hemopexin and a 69 amino acid FLVCR peptide fused to a GST protein.[45] These results suggest that extracellular hemopexin may facilitate heme efflux. The liver itself has mechanisms for heme import, as patients with acute porphyria who are administered intravenous heme complexed to albumin show increased heme-dependent enzyme activity in the liver.[46]

Analogous to the trafficking of lipids, an alternative mechanism for the scavenging of extracellular heme involves its sequestration by lipoprotein particles that can subsequently be endocytosed.[47] Free heme can readily enter lipoprotein particles with 80% of heme that is added to whole plasma partitioning into low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs), despite the presence of haptoglobin, hemopexin, and albumin.[47] This is likely a mechanism that is operative under hemolytic distress.

Recently, heme released during hemolysis was shown to serve as a signal for monocyte differentiation into macrophages.[6] Environmental heme induces the degradation of the transcription factor BACH1, which causes the derepression of SPI-C, another transcription factor required for splenic red pulp macrophage development. These results strongly support the notion that exogenous heme, released from red cells, is not immediately degraded by HO but must remain intact for function in the nucleus of monocytes, implicating that intertissue transport of heme is essential for cellular differentiation.

In addition to the role of macrophages during erythrophagocytosis of red cells, the enterocytes also play an important role in heme absorption derived from the diet. Although most dietary heme is postulated to be degraded by enterocytes to release iron, sufficient evidence exists that some heme could be exported intact from the intestinal basolateral membranes.[48] For example, studies have demonstrated that a portion of heme remains intact and is transported from the basolateral membrane in Caco2 cells.[49]

In *C. elegans*, HRG-3, an 8 kDa protein, binds and delivers maternal heme to developing oocytes, functioning as a heme chaperone.[50] Heme export is mediated by the ABC transporter MRP-5/ABCC5 in *C. elegans*.[51] MRP-5 deficiency leads to embryonic lethality in worms unless rescued by heme supplementation. Embryonic fibroblasts derived from *Mrp5*-deficient mice show reduced heme levels in the secretory pathway, as measured by heme incorporation into Golgi-targeted horseradish peroxidase. Although these results show that MRP5 can export cytosolic heme into the Golgi lumen in isolated cells, $Mrp5^{-/-}$ mice show no overt phenotypes. One possible explanation could be *in vivo* genetic compensation by another related transporter in mice, such as ABCC12/MRP9, which is phylogenetically related to mammalian ABCC5 but is absent in the *C. elegans* genome. In the *C. elegans* hypodermis, HRG-2, a single-pass type I transmembrane protein, facilitates heme utilization.[52] HRG-2 binds heme and may function as an oxidoreductase as it contains a thioredoxin-like fold and a glutathione *S*-transferase domain (Figure 4).

Although these pathways for heme utilization would be expected for *C. elegans*, a heme auxotroph, do vertebrates have interorgan heme delivery pathways? Mouse and zebrafish embryos that are unable to synthesize heme can survive several days postfertilization.[53,54] Because of the high-energy demands of a developing embryo, this suggests a possible maternal heme contribution. Along these lines, FLVCR1 expression in human placenta is correlated with LRP1 expression and neonatal iron status.[55] Moreover, HRG1 is expressed in the placenta.[30] Therefore, the placenta expresses the necessary transporters for heme import from maternal blood and heme export to the fetus, which may become a significant source of iron during development.[56]

Taken together, these studies indicate that interorgan heme transport may not just be limited to obligate heme auxotrophs.

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Direct heme transfer between cells may become more relevant under specific conditions, such as low iron availability or pathogenesis.

7. CONCLUSIONS

Since the discovery of hemoproteins like hemoglobin or myoglobin, we often view heme as a static cofactor buried in hemoprotein active sites. However, its use as an intra- and intercellular signaling molecule and a metallonutrient required in every subcellular compartment necessitates that heme is dynamically and rapidly mobilized. Because of the emergence of new genetic and physical tools, we are just now beginning to uncover the molecules and mechanisms required to traffic heme within and between cells. The next decade promises to further transform and expand our understanding of heme mobilization in cells and animals.

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Notes

The authors declare the following competing financial interest(s): I.H. is the President and Founder of Rakta Therapeutics Inc. (College Park, MD), a company involved in the development of heme transporter-related diagnostics. He declares no other competing financial interests.

Biographies

Amit R. Reddi earned B.A. and Ph.D. degrees in Chemistry from Carleton College (2003) and Columbia University (2008), respectively, both with distinction. Following an NIH postdoctoral fellowship at Johns Hopkins University in the lab of Valeria Culotta (2008–2013), he joined the faculty of the School of Chemistry and Biochemistry at the Georgia Institute of Technology in 2013 as an Assistant Professor. His interests in copper and heme metallobiochemistry have been recognized by a number of awards, including the Arturo Leone Young Investigator Award and an NSF CAREER award.

Iqbal Hamza received his B.Sc. and M.Sc. in Biochemistry from the University of Bombay, India, and a Ph.D. in Biochemistry from the State University of New York at Buffalo. He continued his interests in metallobiology by joining the laboratory of Jonathan Gitlin at Washington University School of Medicine. Combining his previous research experiences in iron biology and copper trafficking, Dr. Hamza deliberately set out to tackle the problem of how heme is trafficked in eukaryotes when he joined the University of Maryland in 2002. His research focuses on the biology of heme across eukaryotic species.

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