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Diverse relations between ABC transporters and lipids: An overview

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ABSTRACT

It was first discovered in 1992 that P-glycoprotein (Pgp, ABCB1), an ATP binding cassette (ABC) transporter, can transport phospholipids such as phosphatidylcholine, −ethanolamine and -serine as well as glucosylceramide and glycosphingolipids. Subsequently, many other ABC transporters were identified to act as lipid transporters. For substrate transport by ABC transporters, typically a classic, alternating access model with an ATP-dependent conformational switch between a high and a low affinity substrate binding site is evoked. Transport of small hydrophilic substrates can easily be imagined this way, as the molecule can in principle enter and exit the transporter in the same orientation. Lipids on the other hand need to undergo a 180° degree turn as they translocate from one membrane leaflet to the other. Lipids and lipidated molecules are highly diverse, so there may be various ways how to achieve their flipping and flopping. Nonetheless, an increase in biophysical, biochemical and structural data is beginning to shed some light on specific aspects of lipid transport by ABC transporters. In addition, there is now abundant evidence that lipids affect ABC transporter conformation, dynamics as well as transport and ATPase activity in general. In this review, we will discuss different ways in which lipids and ABC transporters interact and how lipid translocation may be achieved with a focus on the techniques used to investigate these processes.

Contents

1. Introduction

Lipids make up about 5–10% of the dry mass of a cell [1], and mammalian cells dedicate about 5% of their genes to the synthesis of lipids [2]. Lipids are chemically much more diverse than implied by

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the simple structural classification into hydrophobic tail and hydrophilic head groups. Significant methodological advances, mainly in mass spectrometry, have given rise to the field of "lipidomics". A 2005 lipidomics survey classified eight basic types of lipids (glycerophospholipids, glycerolipids, sphingolipids, saccharolipids, fatty acyls, sterol lipids, prenol lipids and polyketides), which are present in cellular membranes [3]. These main categories can then be further subdivided into classes and subclasses. For the most abundant lipid category in mammalian cells, glycerophospholipids, at least 20 additional subcategories exist. A single cell, with its ability to create diverse lipid chains and head groups, may therefore well contain more than a thousand chemically different lipids [2] and in entire tissues or organisms this number may rise to tens of thousands [4].

However, complexity does not end there. Lipids are not homogenously distributed across a cell membrane, but compartmentalized, i.e. to different organelles [5]. In addition, the lipid distribution between the two lipid bilayer leaflets is asymmetric. At the plasma membrane, phosphatidylethanolamine, phosphatidylserine or phosphatidic acid are mostly located in the inner (cytosolic) membrane leaflet, while phosphatidylcholine, sphingomyelin or glycolipids have a preference for the outer (exo-cytoplasmic) leaflet [2]. In some cases, these preferences stem from the physical properties of the lipids themselves, i.e. their chain length and degree of saturation, as well as their head group properties that influence membrane curvature and fluidity. Furthermore, proteins are responsible for heterogeneity in lipid distribution (e.g. [5]). Although passive diffusion of lipids from one bilayer leaflet to the other is very slow (~10^{-15} cm^2/s) compared to their lateral movement (~10^{-8} cm^2/s), active transport is required to counteract diffusion-based lipid movement and the resulting homogenization of leaflet content.

Several types of membrane proteins mediate lipid transport: (i) Secondary active transporters belonging to the MOP (multidrug, oligosaccharidyl-lipid, polysaccharide) superfamily require a proton or sodium gradient [6]. (ii) Primary active transporters such as ABC (ATP binding cassette) transporters usually "flop" lipids from the inner membrane leaflet to the outer leaflet, energized by ATP hydrolysis [7]. The reverse "flipping" process from the outer to the inner leaflet is carried out by P4-type ATPases [8,9]. Lipid transport in this direction is also carried out by ABCA4, which is the only eukaryotic ABC transporter described to date to function as a flippase and thereby as an importer (see below, [10]). Finally, (iii) scramblases are not direction-specific and act energy independently [11,12].

In addition to being substrates of transporters, lipids can also serve as scaffolds for membrane proteins, and they can be embedded permanently in a protein's structure. The lipid environment can also influence protein activity, i.e. ATPase or transport activity in the case of ABC transporters. Finally, e.g. for multidrug (ABC) transporters with a strong preference for amphipathic and hydrophobic molecules, lipids can serve as a reservoir for these non-lipid hydrophobic substrates due to their enrichment in the membrane bilayer.

We will give an overview over human ABC lipid transporters first, followed by a discussion of a few specific questions how lipids influence ABC transporter functions, how ABC transporters may translocate lipids and how this has been studied with different biophysical techniques. Due to the available data, the latter section will also strongly feature bacterial transporters.

2. ABC transporters

ABC transporters are ubiquitous in all three phyla of life. They share the same core structure consisting of two transmembrane regions (TMDs) and two soluble nucleotide binding domains (NBDs). The TMDs bind and translocate substrates across lipid bilayers while the NBDs bind and hydrolyze ATP. ABC transporters can function as exporters (i.e. removing substrates from the cytoplasm) or importers (i.e. translocating substrates into the cytoplasm) [13]. Mammalian ABC proteins belong to seven subfamilies, ABCA-G: Members of the families A-D and G code for membrane transporters (Fig. 1), while the members of the ABCE and ABCF families are soluble proteins consisting only of NBDs, which are involved in, e.g. ribosome recycling and transcription regulation [14,15]. The NBDs of all ABC proteins are highly conserved both on the level of sequence and 3D structure. They consist of a RecA-like domain including the Walker A (P-loop) and B motifs and a helical domain including the ABC signature motif (C-loop) signifying their ABC protein family affiliation. Eukaryotic transporters of the ABCA and C families are expressed with all four domains on a single polypeptide chain (so-called full transporters), while ABCD and G members (as well as the majority of prokaryotic exporters) are "half-transporters" where one TMD is fused to one NBD. A unique feature of the ABCG subfamily is their domain topology with an N-terminally leading NBD followed by the TMD. In the ABCB family, both full and half transporters can be found (Fig. 1). Two half-transporters will homo- or hetero-dimerize to form a full transporter [16]. In bacteria, many other ABC transporter domain organizations, such as all four domains on separate peptides, exist.

3. Human ABC transporters in lipid transport

Twenty out of the 48 human ABC transporter proteins have been implicated in the transport of lipids or lipid-like molecules, such as steroids (including cholesterol and bile acids), phospholipids and sphingolipids (for a detailed description please refer to [17]). These "lipid translocators" belong to all ABC transporter subfamilies (A, B, C, D, G), thus no subfamily specific trait seems to be responsible for lipid recognition and transport. Mutations in these proteins lead to disruptions in lipid metabolism and distribution. Consequences are lipid-associated diseases such as Sitosterolemia [18], Stargardt disease [19] or Tangier disease [20], thus underlining the importance of well-organized cellular lipid translocation.

3.1. Transport of phospholipids and sphingolipids

ABCA1, ABCA3, ABCA4, ABCA7, ABCB1 (Pgp), ABCB4 and ABCC1 can translocate phospholipids across the plasma membrane (Fig. 1) (e.g. [17,21]). ABCA1 and ABCA7 are also important for the formation of high density lipoproteins (HDL) [22,23] required for cholesterol transport to the liver. While the physiological significance of phospholipid and glycosphingolipid transport by ABCB1 remains unclear [24], one putative physiological function may be the secretion of PAF (platelet-activating factor), a phospholipid involved in inflammation and allergic responses [25]. ABCB4 is responsible for phosphatidylcholine extrusion from the liver into the bile [26,27]. ABCC1 was initially identified as a glutathione-conjugate transporter [28], but lipid transport has also been demonstrated (e.g. [29]).

ABCA3 expression peaks before birth and coincides with the expression of surfactant proteins. Its presence is restricted to the lung alveolar type II pneumocytes. These are responsible for the storage and excretion of a phospholipid/cholesterol/protein mixture that acts as the lung surfactant. For this, the lipid/protein mixture is stored in so-called lamellar bodies. ABCA3 is responsible for the uptake of lipids into these specialized organelles [30,31].

Mutations in ABCA12, expressed in epidermal keratinocytes, lead to harlequin-type ichthyosis [32], caused by dysfunctional lipid translocation into lamellar granules, which act as stores for lipids such as ceramides and phospholipids [33–35]. These secretory organelles are released to form a water-impermeable, protective skin barrier. In harlequin-type ichthyosis patients, the dermis cannot properly form (before birth) and at birth newborns display a harlequin-pattern of dried, cracked skin [36]. Patients are extremely vulnerable to pathogens and many newborns die shortly after birth.

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