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Review

Unravelling the role of sphingolipids in cystic fibrosis lung disease

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ABSTRACT

Cystic fibrosis (CF), one of the most common lethal hereditary diseases of white European populations, is caused by loss-of-function mutations in the CF Transmembrane conductance Regulator (CFTR) gene. One of the main causes of mortality is the onset of CF lung disease, which is characterized by chronic infection and inflammation resulting in the progressive remodelling, irreversible damage and fibrosis of the airways. An increasing number of studies indicate that sphingolipids are crucial players in pulmonary manifestations of CF, even if their direct involvement in CF lung disease is still unclear. In this review, we give an overview of the role of sphingolipids in CF pulmonary disease, focusing on the relationship between glycosphingolipids and lung inflammation, which represents the main hallmark of this disease.

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1. Cystic fibrosis lung disease

Cystic fibrosis (CF) is one of the most common lethal hereditary and monogenic disorders among people of white European descent, although it has been reported in all races. It is an inherited autosomal recessive disease caused by mutations in a single gene, consisting of 27 exons, which codes for the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein (Riordan et al., 1989). It is a large multidomain protein comprising 1480 amino acid residues arranged in two membrane-spanning domains (MSD 1, 2), two nucleotide (ATP) binding domains (NBD1, 2), and a unique regulatory domain (RD) with multiple phosphorylation sites (Riordan, 2008; Billet et al., 2015). The CFTR protein is a cAMP-activated chloride channel expressed at the apical membrane of most of the surface epithelial cells lining the airways and the gastrointestinal tract, exocrine pancreas, airway submucosal and sweat glands. It plays a key role in hydrating airway secretions and regulating other cellular functions, including Na^+ transport in airway epithelia (Welsh and Smith, 2001; Cutting, 2010). There are more than 2000 sequence variations in the CFTR gene, many of which have been associated with causing diseases (see the Cystic Fibrosis Mutation Database of the Cystic Fibrosis Gene Analysis Consortium, www.genet.sickkids.on.ca/cftr/). The

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most common CF mutation, a three base pair deletion resulting in the loss of phenylalanine at position 508 of the protein from the first NBD1, causes a folding defect in the protein and impaired localization of the CFTR channel on the apical surface of epithelial cells, leading to defective epithelial ion transport (Cheng et al., 1990; Du et al., 2005). This mutation occurs in approximately 70% of CF chromosomes worldwide, in at least one allele of 90% of CF patients, and it is associated with a severe clinical phenotype. The consequences of mutated CFTR are considerable in the respiratory tract (Wright et al., 2006). Here, mutations in CFTR impair the mucociliary clearance due to reduced periciliary fluid volume and increased viscosity of submucosal gland secretions, leading to chronic bacterial infections mostly caused by *Pseudomonas aeruginosa* (*P.aeruginosa*) (Mogayzel and Flume, 2010). The destruction of the airways in chronically colonized CF individuals is due to a massive influx of polymorphonuclear neutrophils (PMN) in the bronchial lumen. This is orchestrated by the bronchial epithelial cells secreting the neutrophilic chemokine interleukin 8 (IL-8) in response to continuous stimulation by bacteria or their products (Bezzerri et al., 2011; Cohen and Prince, 2012) which activate a series of kinases and transcription factors depending on Toll-like Receptor signalling (Bezzerri et al., 2011). Obstructive lung disease is currently the primary cause of morbidity and is responsible for about 80% of mortality (Cutting, 2015).

2. Overview of sphingolipid homeostasis

Sphingolipids (SLs) are minor cell components of all mammal cell membranes with the hydrophilic head group protruding toward the extracellular environment and the lipid moiety, the Ceramide (Cer), deeply inserted into the membrane bilayer (Feizi, 1985). In the plasma membrane (PM), they reside asymmetrically in the extracellular leaflet, where they are concentrated in restricted membrane areas known as “lipid rafts” or “sphingolipid and cholesterol enriched membrane domains” (Sonnino et al., 2006). It is believed that in lipid rafts, SLs modulate the functional features of several membrane proteins (Prinetti et al., 2009) by both direct lateral interactions between SLs and plasma membrane proteins (Kabayama et al., 2007), and by short-range alterations of the physico-chemical properties of the protein membrane microenvironment (Sonnino et al., 2009).

SLs are important in the regulation of cell functions, and cells employ different strategies to establish the proper pattern of SLs at the plasma membrane. SLs are synthesized through complex metabolic networks involving neo-biosynthesis, catabolism and complex intracellular trafficking, as well as exchanges with the extracellular environment. A general schematic of SL metabolism, as a well as of their intracellular transport, is depicted in Fig. 1.

Cer plays a key role in SL metabolism, since it is the common intermediary in both SL biosynthetic (sphingomyelin and glycosphingolipids biosynthesis) and catabolic pathways.

The *de novo* biosynthesis of Cer occurs at the cytosolic face of the endoplasmic reticulum and starts with the condensation of L-serine to a fatty acyl-coenzyme A, usually palmitoyl-CoA. This reaction is catalysed by vitamin B6-dependent serine palmitoyltransferase and produces 3-ketosphinganine (Mandon et al., 1991; Nagiec et al., 1994; Weiss and Stoffel, 1997), which is then reduced to D-*erythro*-sphinganine by 3-ketosphinganine reductase, a NADPH-dependent reaction (Stoffel et al., 1970). Sphinganine is subsequently acylated to dihydroCer by a family of six Cer synthases, integral membrane proteins, each of which displays a different specificity to Acyl-CoAs (Merrill and Wang, 1986; Rother et al., 1992; Shimeno et al., 1998). Most of the dihydroCer pool is then desaturated to Cer *via* the dihydroCer desaturase reaction (Geeraert and van Veldhoven, 1997; Michel et al., 1997; Mikami et al., 1998). Once synthesized, Cer is directly routed to the membrane or used as a precursor for glycosphingolipids (GSL) or sphingomyelin (SM) biosynthesis. In particular, SM can be formed at the Golgi apparatus or at the plasma membrane by SM synthase 1 and SM synthase 2, respectively. Both isoforms transfer

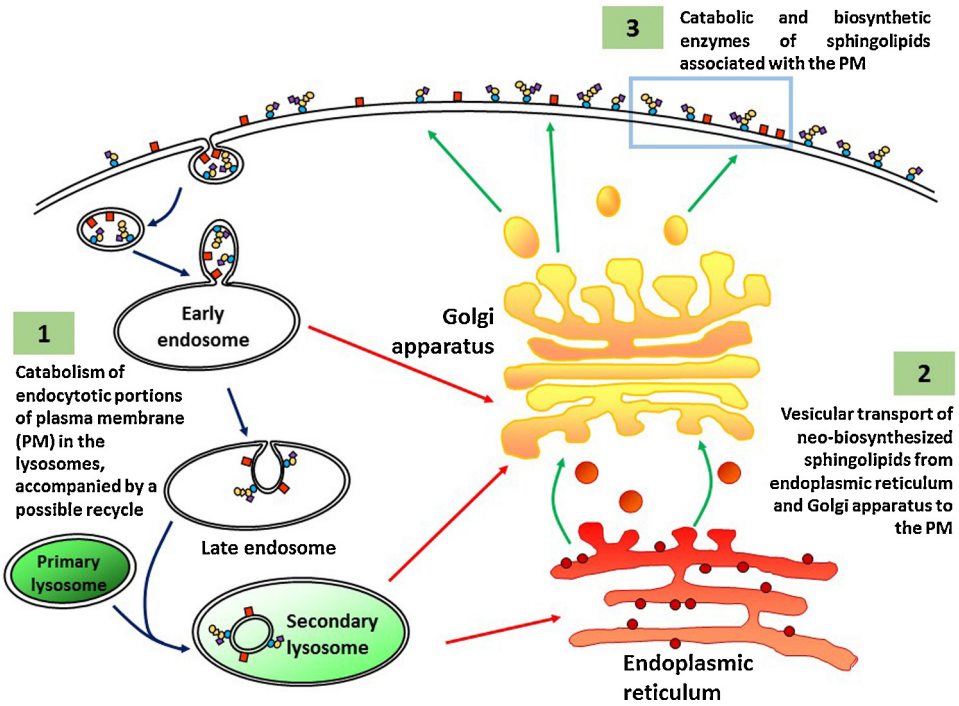

Fig. 1. Schematic representation of the major routes and the subcellular sites of sphingolipid metabolism.
The pathways of sphingolipid metabolism include their catabolism in the endolysosomal compartments (1) and their biosynthesis in the endoplasmic reticulum and Golgi apparatus (2). A fine-tuning of SL composition can also occur at the cell surface through the action of plasma membrane glycosyltransferases and glycosidases (3). -Glucose (light blue circle); galactose (yellow circle); *N*-acetyl-galactosamine (yellow square); sialic acid (purple diamond); methyl-choline (red rectangle).