



Review

Pore-forming toxins: Properties, diversity, and uses as tools to image sphingomyelin and ceramide phosphoethanolamine[☆]



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ABSTRACT

Pore-forming toxins (PFTs) represent a unique class of highly specific lipid-binding proteins. The cytotoxicity of these compounds has been overcome through crystallographic structure and mutation studies, facilitating the development of non-toxic lipid probes. As a consequence, non-toxic PFTs have been utilized as highly specific probes to visualize the diversity and dynamics of lipid nanostructures in living and fixed cells. This review is focused on the application of PFTs and their non-toxic analogs as tools to visualize sphingomyelin and ceramide phosphoethanolamine, two major phosphosphingolipids in mammalian and insect cells, respectively. This article is part of a Special Issue entitled: Pore-Forming Toxins edited by Mauro Dalla Serra and Franco Gambale.

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Abbreviations: AFM, atomic force microscopy; Chol, cholesterol; CPE, ceramide phosphoethanolamine; CTxB, cholera toxin B subunit; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; EM, electron microscopy; EqII, equinatoxin II; EryA, erylysin A; ER, endoplasmic reticulum; IPC, inositol phosphoceramide; M β CD, methyl- β -cyclodextrin; MDCK, Madin–Darby canine kidney; NPA, Niemann Pick disease type A; NT-lysenin, non-toxic lysenin; Oly, ostreolysin; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PFT, pore-forming toxin; PI(4,5)P₂, phosphatidylinositol 4,5-bisphosphate; PlyA2, pleurotolysin A2; PS, phosphatidylserine; SDS-FRL, SDS-digested freeze-fracture replica labeling; SL, sphingolipid; SM, sphingomyelin; SMase, sphingomyelinase; SMS, sphingomyelin synthase; SMSr, sphingomyelin synthase-related protein; StI, sticholysin I; StII, sticholysin II.

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1. Introduction

Sphingolipids (SLs) constitute a group of essential lipid components that affect membrane structures and participate in a wide range of biological functions, such as cell growth, endocytosis, and secretion [1]. In recent decades, knowledge of the sphingolipidome has improved considerably, reflecting progress in the mass spectrometry techniques that are used to reveal the structural diversity of these molecules. Additionally, state-of-the-art microscopy approaches not only reveal the assembly but the incredible dynamics of these compounds. SLs have

attracted extensive interest because of their ability to form distinctive domains or lipid rafts in the presence of cholesterol (Chol), exhibiting a considerable degree of lateral mobility [2,3]. In this review, we will focus on the visualization of two phosphosphingolipids, namely sphingomyelin (SM), a major SL in the mammalian plasma membrane, and its analog, ceramide phosphoethanolamine (CPE), detected in trace amounts in mammalian cells and in bulk amounts in insect cells and certain parasitic forms of *Trypanosoma*.

As the majority of lipids, including phosphosphingolipids, are not intrinsically fluorescent, a variety of lipid probes have been identified and

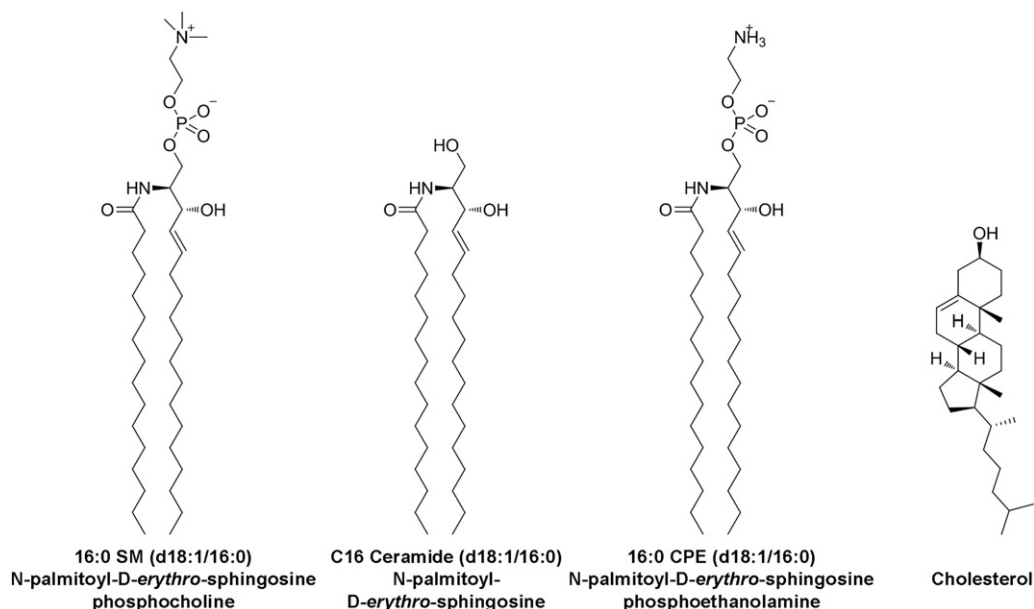


Fig. 1. Structure of the main lipids described in this review.

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