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Review

# Orchestration of membrane receptor signaling by membrane lipids

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ABSTRACT

Receptors on cell membrane bind to their respective ligands and transduce intracellular signals resulting in variety of effector functions. Membrane lipid composition determines the receptor signaling behavior, as the receptors assume different conformation to suit the biochemical milieu in its immediate vicinity in the membrane. Accordingly, these accommodate different signaling intermediates that dictate the course of intracellular signaling and the resulting effectors functions. In this review we provide an overview of how membrane lipids modulate membrane-properties, membrane-receptor functions and their significance in the host–pathogen interaction.



## 1. Introduction

Membrane receptors, involved in downstream signal transduction are generally transmembrane proteins. Their assembly and arrangement in the membrane determine how they interact with their ligands through the extracellular domains and generate signaling cascades through the cytoplasmic domain [1]. The conformation of transmembrane domain of a receptor regulates the ligand binding properties of the extracellular domain as well as recruitment of adapter molecules [2–4]. The transmembrane domain is surrounded by various lipid molecules and the interaction of the lipids with transmembrane domain plays important role in the functioning of receptors [5–7]. Fluorescence probing of the membrane has become a key technique to study the role of lipids in governing the biophysical properties of the membrane [8]. Furthermore, fluorescence microscopy is being used to study the organization of lipid domains in a biological membrane and their interactions with membrane proteins [9–11]. In addition, different biophysical, computational and high resolution structural studies suggested that membrane lipids affect the physio-chemical properties of the membrane, that ultimately alter receptor–ligand interactions, receptor clustering in the membrane and recruitment of different signaling intermediates to the cytoplasmic domain of the receptor [12–16]. All these changes culminate in significant alteration in membrane-receptor signaling [17–19]. Due to involvement of lipids in modulation of majority of membrane receptor functions, recent studies showed that pathogens target membrane-lipids to alter the membrane-receptor signaling for their survival and spread of infection [2,20,21]. Till date only few reviews have addressed the regulation of different membrane receptors by different group of membrane lipids [22,23]. Lipidome analysis through different approaches such as Thin-layer Chromatography (TLC), High Performance Liquid Chromatography (HPLC), Electrospray Ionization

*Abbreviations:* AC, adenylyl cyclase; CaMK, $Ca^{2+}$–calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate; ChOx, cholesterol oxidase; CREB, cAMP response element-binding protein; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal regulated kinase; GCS, GlcCer synthase; GlcCer, glucosylceramide; GM3, monosialodihexosylganglioside; *M.tb*, *Mycobacterium tuberculosis*; M-β-CD, methyl-β-cyclodextrin; NGF, nerve growth factor; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PIP, phosphatidylinositol phosphate; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol trisphosphate; PI5P, phosphatidylinositol 5-phosphate; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PDMP, D-threo-1-phenyl-2-decannoylamino-3-morpholino-1-propanol; PS, phosphatidylserine; SM, sphingomyelin; TCR, T-cell antigen receptor; TH, tyrosine hydroxylase; TLR, toll like receptor; TNF, tumor necrosis factor; 5-$HT_{1A}$ receptor, serotonin$_{1A}$ receptor.

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(ESI), Nuclear Magnetic Resonance (NMR), etc, have broaden the knowledge of individual lipid composition in the biological systems [24].

There are three major classes of lipids; glycerophospholipid, sphingolipid and sterol which contribute extensively to the organization of the membrane (Fig. 1). The major glycerophospholipids present in the cell membrane are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (PI) [25]. These are asymmetrically distributed in exoplasmic and cytoplasmic face of plasma membrane and create a semi-impermeable barrier to maintain the integrity of the cells [26]. Sphingolipids are the second major group of lipids which are present exclusively in the outer leaflet of the membrane bilayer and play a significant role in the formation of microdomains in cell membranes and regulate their properties [27]. Sterols are the third important group of lipids that are present in membrane and regulate various properties of the membrane and biological processes of the cells [28]. Cholesterol is the major sterol in the mammalian cell membrane that regulates many biological processes such as signal transduction, cytoskeleton reorganization and manifestation of infectious diseases [29,30]. Effect of cholesterol metabolites such as 24(S)-hydroxycholesterol has also been shown to regulate neuronal signaling via downregulation of cholesterol synthesizing enzymes [31,32]. Most of these classes of lipids have their designated roles in maintaining the membrane properties and in the regulation of membrane receptor signaling [14,33]. In this review, we provide detailed regulation of membrane properties and biological functions of these membrane-lipids in the context of six most extensively studied receptors namely, Epidermal Growth Factor Receptor (EGFR), Serotonin Receptor, Acetyl Choline Receptor (AChR), Opioid Receptor, CD40 Receptor and T-Cell Receptor (TCR). We have also highlighted the importance of lipids in modulation of membrane receptor signaling during host–pathogen interactions.

## 2. Membrane lipids and their significance in the regulation of membrane properties

Effect of lipids on the properties of membrane has been extensively studied and it has been found that lipids affect the biophysical properties of membrane such as rigidity, permeability, surface tension, fluidity and membrane curvature [34–37]. Alteration in the bio-physical properties of membrane leads to the modulation of cellular functioning like vesicle fusion, solute permeability, carrier mediated transport, etc. [38–40]. In general, membranes properties are affected by the presence or absence of constitutive lipids or secondary messenger lipids. Constitutive lipids such as cholesterols, phospholipids, sphingomyelin etc. are the sole component of membrane and play significant role in determining the biophysical properties of membrane. Ceramide, sphingosine, phosphatidic acid, arachidonic acid etc. are categorized under secondary messenger lipids that are not only key players in intracellular signaling but also regulate several aspects of membrane properties. In this section we summarize the role of constitutive and secondary messenger lipids in regulating the membrane properties.

### 2.1. Role of constitutive lipids

PS is an anionic phospholipid which is non-uniformly distributed between the leaflets of the membrane bilayer. This non-uniformity is maintained due to the activity of ATP-dependent aminophospholipid flippases that flips PS from exoplamic side to the cytoplasmic side [41]. The tendency of flipping of PS during vesicular transport increases the membrane curvature and thus adds extra negative charge to the cyto-facial side of the membrane [42]. Changes in the PS distribution modulate cell membrane activities such as $Ca^{2+}$ and $Na^{+}$ uptake [43]. Membrane PS also regulates surface charge of the membrane and localization of

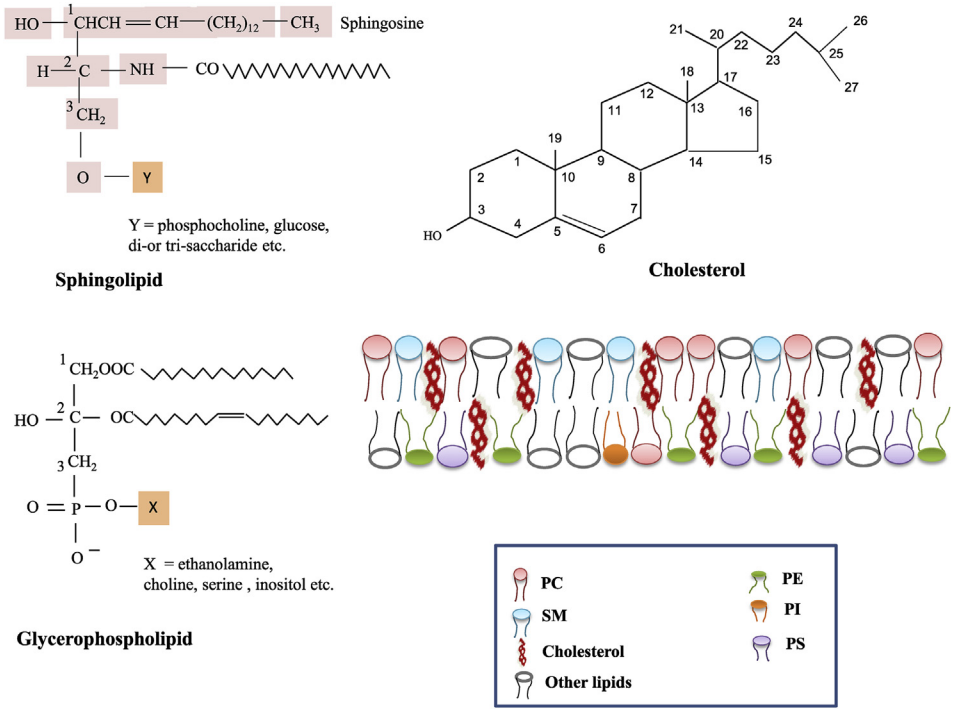


**Fig. 1. Lipids involved in the structural organization of the cell membrane.** Membrane bilayer is composed of glycerophospholipids, sphingolipids and sterols. The major glycerophospholipids that are present in the cell membrane are PS, PE, PI and PC. PC is preferentially present in the outer leaflet of the membrane whereas PE, PI and PS are preferentially present in the inner leaflet of the membrane. SM is the main sphingolipids that is more commonly present in outer leaflet. Cholesterol is the major sterol present in animal cell membrane and is commonly distributed in both the leaflets but more in the outer side.