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Terpenoids and membrane dynamics evolution

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Cellular membranes define the physical boundary of life and provide scaffolds for various fundamental metabolic activities, including ATP synthesis, respiration, phototrophy, endocytosis and ion transport. Terpenoids, also known as isoprenoids, are known to play important roles in membrane organization and regulation across the three domains of life through unique interactions with other membrane lipids and membrane proteins. Terpenoids are present in not only the membranes of the three domains, but also viral membranes and extracellular vesicles. The large structural diversity of terpenoids and their ubiquitous distribution in modern organisms make terpenoids distinct from other membrane lipids, such as fatty acyls that are nearly absent in archaea. Addressing the biochemical and biophysical properties that allow terpenoids to play critical roles in membrane organization is important to understand the driving forces that shaped cellular life as we know it. This review summarizes the major classes of terpenoids that are involved in membrane organization and discuss the impact of terpenoid-membrane interactions on the evolutionary trajectory of membrane dynamics and the fitness of host organisms.

KEYWORDS

membrane evolution, membrane dynamics, terpenoids, Archaea, LUCA (the last universal common ancestor), membrane organization

1 Introduction

Cellular membrane was among critical factors for the emergence of life. Compartmentalization of small molecules in a cellular structure would have been a prerequisite for the onset of pre-biotic chemistry and subsequent biochemistry during the formative period of life (Deamer et al., 2002). In modern biology, cellular membranes are mixtures of a variety of lipid molecules that have a distinct evolutionary origin and history. Among those lipids, terpenoids, also known as isoprenoids, are known for their large structural and functional diversity (Bloch, 1991; Hartmann, 1998; Xu et al., 2004). Terpenoids are present in the cellular membrane of all three domains of life – Archaea, Bacteria and Eukarya – but are utilized distinctly from one another. Archaea use terpenoids as structural components of their membranes (Jain et al., 2014), while bacteria and eukaryotes use terpenoids as membrane regulators (Sezgin et al., 2017; Belin et al., 2018). The establishment of the archaeal and eukaryotic domains is in fact built upon

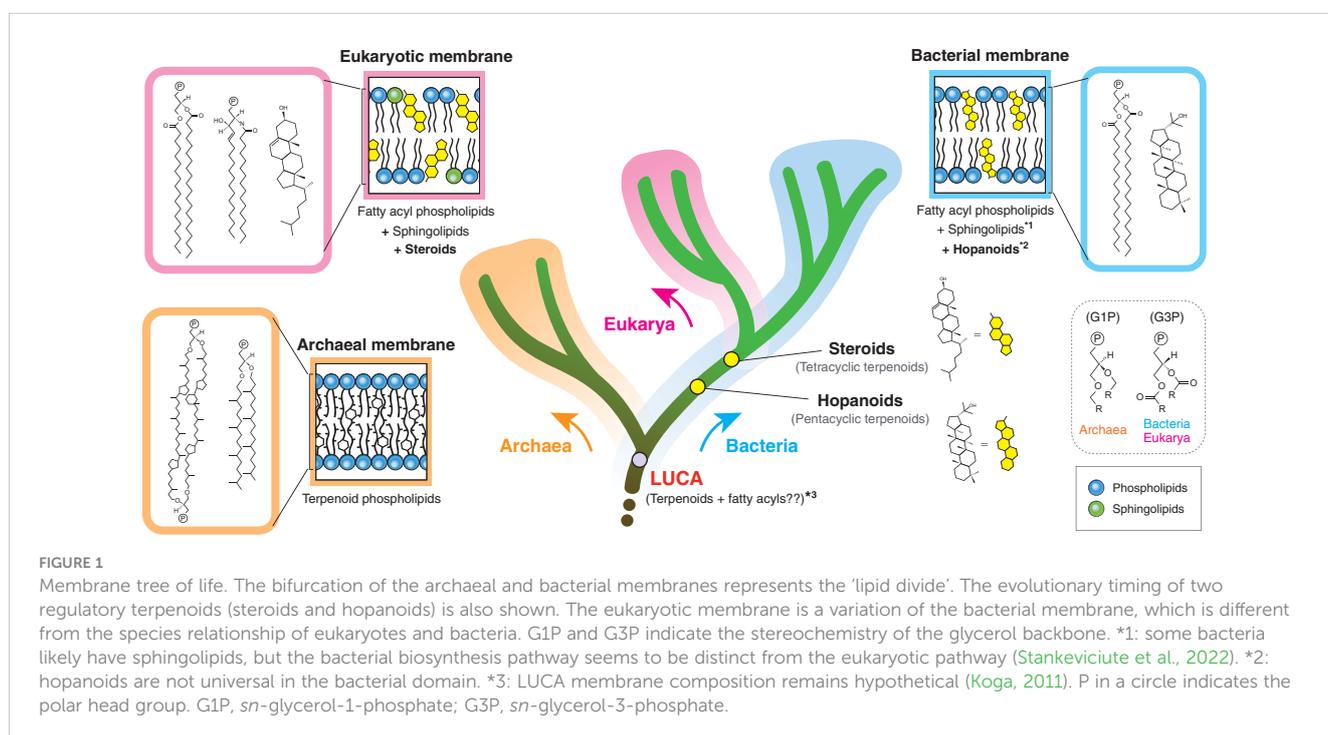
the presence of certain terpenoids. Hence, the structural and functional divergence of terpenoids was an important driving force for some major evolutionary events of life. This review focuses on the role of terpenoids in the diversification of membrane organization and associated dynamics in cellular life, thereby providing an integrated perspective for the co-evolutionary relationship between terpenoids and biological membranes.

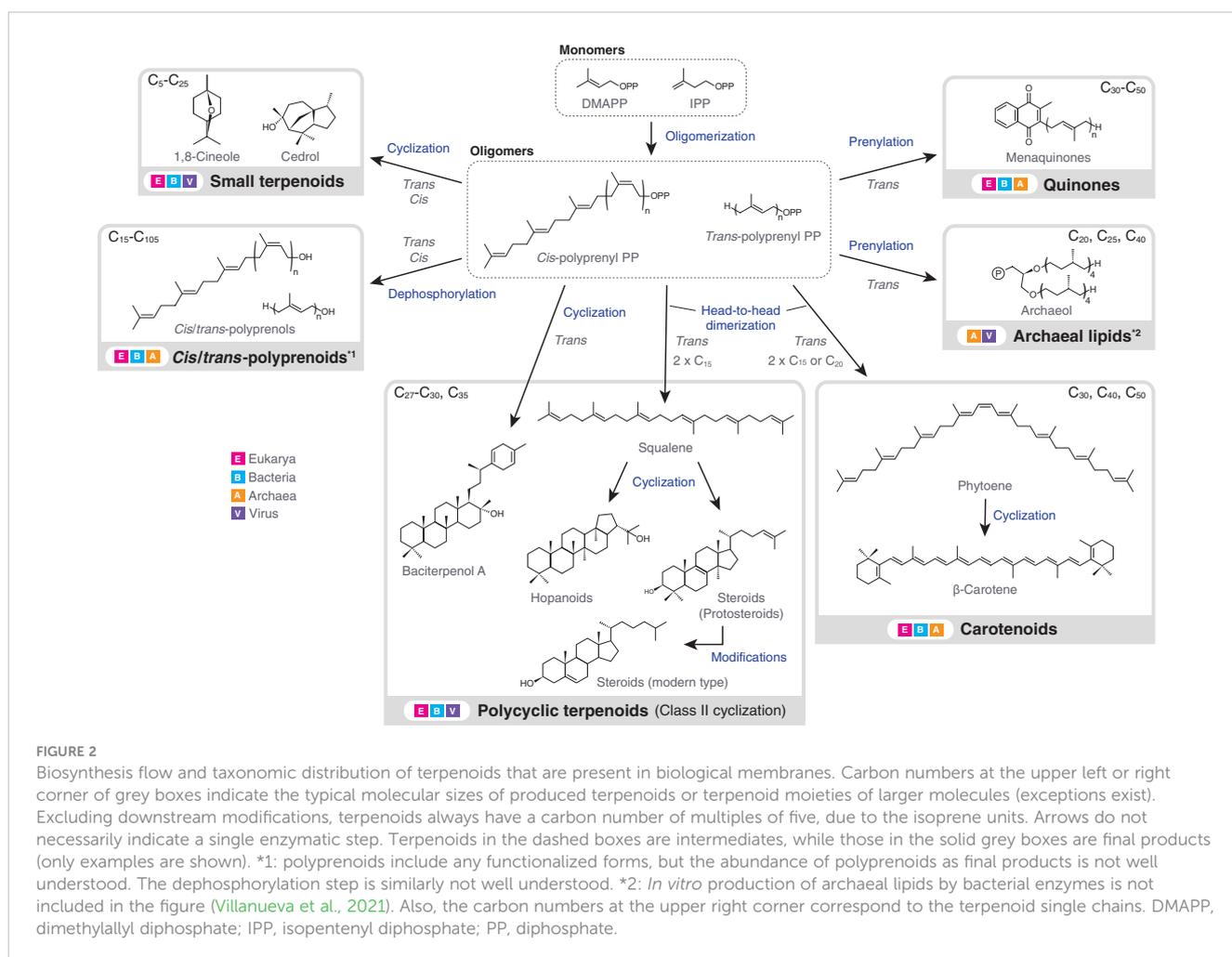
2 Terpenoids in biological membranes

Biological membranes encompass not only cellular membranes, but also ‘non-cellular’ membranes, including endomembranes (intracellular membranes), extracellular vesicles and viral envelopes. These non-cellular membranes are derived from host cells, but not necessarily directly from cellular membranes. Hence, the actual composition may be divergent, depending on individual membranes. In principle, there are only two cellular membrane systems in biology: archaeal-type and bacterial-type membranes (Koga, 2011) (Figure 1). The archaeal membrane lipids have *sn*-glycerol-1-phosphate (G1P) as the lipid backbone that is linked to linear terpenoid chains via ether bonds, while the bacterial lipids have *sn*-glycerol-3-phosphate (G3P) that is linked to fatty acyl chains via ester bonds. This structural difference is known as the ‘lipid divide’ and represents one of fundamental differences between Archaea and Bacteria, despite that both domains evolved from LUCA (Koga, 2011; Jain et al., 2014). Eukarya has a bacterial-type membrane, even though the domain is inferred to have evolved from within Archaea (Eme et al., 2017). Some bacteria are known to possess genes to biosynthesize archaeal-type membrane lipids, but the *in vivo* production of those archaeal-type lipids is yet to be confirmed (Villanueva et al., 2021).

Terpenoids are present in all types of biological membranes and also in all forms of cellular life on Earth (Figure 1). The involvement of terpenoids in membrane organization seems to have a deep root and the possible presence of terpenoids in the hypothetical membrane of the last universal common ancestor (LUCA) has been debated (Coleman et al., 2019; Villanueva et al., 2021; Hoshino and Villanueva, 2023). Terpenoid biosynthesis starts from the oligomerization of C₅ isoprene units, but subsequent modifications, including cyclization and prenylation, produce the large structural diversity of terpenoids (Figure 2).

Terpenoids are directly or indirectly involved in membrane organization. The ability of terpenoids to modulate membrane properties is based on their hydrophobic structure. C_{<25} linear terpenoids either constitute membrane lipids (e.g. archaeol) (Jain et al., 2014), or are used as membrane anchors for certain biomolecules such as chlorophylls, hemes and proteins (Hederstedt, 2012; Jiang et al., 2018; Proctor et al., 2022). Other C_{<25} small terpenoids, such as 1,8-cineole and cedrol, may function as transient membrane modulators in bacteria and eukaryotes, through permeating membranes due to their size and hydrophobic nature (Pham et al., 2015) (Figure 2). In contrast, C_{>25} polycyclic terpenoids – most notably hopanoids and steroids – are permanent membrane regulators in bacteria and eukaryotes (Sezgin et al., 2017; Belin et al., 2018). These terpenoids are produced by the so-called class II terpene cyclase (TC) family (Christianson, 2017). In turn, carotenoids, quinones and polyprenoids primarily engage in photosynthesis, respiration and cell envelope biogenesis, respectively (Jones et al., 2009; Hashimoto et al., 2016; Franza and Gaudu, 2022), but can also alter the property of surrounding membrane environments. While carotenoids are mainly found in phototrophic bacteria and eukaryotes, quinones





and polyprenoids (particularly polyprenyl diphosphates) are universally distributed in the three domains.

2.1 Terpenoids in cellular membranes

Bacterial and eukaryotic membranes contain terpenoids mainly as regulatory components. While hopanoids and steroids are the two major membrane terpenoids, several specific lineages, including anaerobic protists and ciliates, alternatively produce a unique structural homolog called tetrahymanol (Takishita et al., 2012; Banta et al., 2015). In some species, the abundance of regulatory terpenoids is comparable to that of fatty acyl phospholipids (van Meer et al., 2008; Belin et al., 2018).

Steroids in eukaryotes are the most extensively studied terpenoids for their roles in membrane organization. Eukaryotic-specific membrane dynamics is based on the triad of distinct lipid components – fatty acyl phospholipids, sphingolipids and steroids (van Meer et al., 2008; Sezgin et al., 2017). The planar polycyclic structure of steroids, particularly cholesterol, has an ability to decrease the fluidity and the permeability of host membranes and laterally compress membranes, forming a liquid-ordered microdomains (Cheng and Smith, 2019). Further, it has

increasingly been suggested that eukaryotic membranes are kept near the critical state (Shaw et al., 2020), which enables eukaryotic cells to respond to external stimuli in a highly dynamic way (Hammond et al., 2005; Levental et al., 2010). Individual steroids have varying effects, due to their subtle structural differences. For instance, C-24 alkylated steroids have elevated interactions with other lipid components, relative to cholesterol, enabling host membranes to have a wider resilience against temperature fluctuations and thus providing a selective advantage for host algae and plants (Beck et al., 2007). Hopanoids have a similar membrane packing ability (Sáenz et al., 2012; Sáenz et al., 2015), but to a lesser degree than cholesterol, because of the presence of additional methyl groups in the rings.

Bacterial membranes have also been suggested to have a eukaryotic-like heterogeneous membranes (functional membrane microdomains; FMMS) (Bramkamp and Lopez, 2015; Lopez and Koch, 2017), although the critical status of FMMS is currently unclear. It is suggested that FMMS are induced by terpenoids, including hopanoids, carotenoids and farnesol (Feng et al., 2014; Bramkamp and Lopez, 2015; García-Fernández et al., 2017; Cheng and Smith, 2019). Also, sphingolipids are distributed in some bacteria (Stankeviciute et al., 2022) and hence those bacteria might have eukaryotic-like membrane regulations based on the

combination of sphingolipids and hopanoids. The presence of membrane heterogeneity has also been suggested in the archaeal membrane that is entirely composed of linear terpenoids, but its dynamics remains underexplored (Bagatolli et al., 2000; Salvador-Castell et al., 2020; Tourte et al., 2020).

Other terpenoids may also engage in membrane organization and protein-lipid interactions locally and/or temporarily. Quinones, polyprenoids and C_{<25} small terpenoids can alter the membrane fluidity and/or permeability, although their physiological significance is not fully understood (Hartley and Imperiali, 2012; Camargos et al., 2014; Sévin and Sauer, 2014; Pham et al., 2015; Mishra et al., 2021). Also, C₁₅ or C₂₀ prenylation of eukaryotic Ras proteins not only anchors the proteins in membranes, but also mediates protein-protein and protein-lipid interactions (Sinensky, 2000).

2.2 Terpenoids in endomembranes

Endomembrane systems are observed in all three domains of life and often have divergent lipid compositions from outer cellular membranes. In archaea, the hyperthermophilic anaerobe *Ignicoccus hospitalis* contains two cytoplasmic regions enclosed by outer and inner membranes. These two membranes have different terpenoid profiles and are utilized for different metabolic activities (Flechsler et al., 2021; van Wolferen et al., 2022). The presence of such a double membrane is suggested for several additional archaea, but the overall distribution remains punctate in the domain (Klingl, 2014). In contrast, bacteria are well known to have several unique endomembrane systems, including thylakoids and chromatophores in photosynthetic bacteria (Jürgens et al., 1992; Simonin et al., 1996; Orf and Blankenship, 2013; Mullineaux and Liu, 2020), anammoxosomes in anammox bacteria (van Niftrik et al., 2004) and magnetosomes in magnetotactic bacteria (Barber-Zucker and Zarivach, 2017). Also, eukaryotes are well known to universally possess a variety of membrane-bound organelles, including mitochondria, endoplasmic reticulum, Golgi apparatus and plastids.

However, terpenoids are not necessarily present in those endomembranes, even if terpenoids are present in cellular membranes. This heterogeneity presumably reflects the physiological requirements of individual endomembranes and/or their evolutionary origins. For instance, hopanoids are found in thylakoids in cyanobacteria, but are mostly absent in other bacterial endomembranes (Ratray et al., 2008; Schüler, 2008). Also, steroids are only minor components in mitochondria and endoplasmic reticulum in animals and fungi (van Meer et al., 2008). Mitochondria also lack sphingolipids and this might reflect the membrane composition of ancestral symbiotic alphaproteobacteria. Steroids are similarly absent in eukaryotic thylakoids, possibly reflecting their cyanobacterial origin (Hözl and Dörmann, 2019).

Photosynthetic endomembranes (thylakoids and chromatophores) contain carotenoids either as part of the photosynthetic machinery, or as non-bound components. Carotenoids span both leaflets of a bilayer and have an ability to

vertically compress membranes (Cheng and Smith, 2019). The fluidity of thylakoid membranes is in fact controlled by carotenoids, rather than hopanoids. The imbalance between carotenoids, other lipids and proteins, hampers the proper conformation of thylakoid structures (Bykowski et al., 2021). Carotenoids are also directly involved in photosystem assembly in cyanobacteria (Tóth et al., 2015). Hence, thylakoid membranes seem to be regulated differently from other (endo)membranes of non-photosynthetic organisms.

2.3 Terpenoids in viral membranes

The presence of lipid membranes is not limited to cellular organisms. Many viruses have lipid membranes either as outer envelopes or as capsid-enclosed inner membranes. Membrane-containing viruses are unevenly distributed among eukaryotic, bacterial and archaeal viruses and viral membranes likely do not share a common ancestry (Poranen et al., 2015; Mäntynen et al., 2019). Viral membranes are thought to have evolved to overcome the surface barriers of host organisms (Poranen et al., 2015; Omasta and Tomaskova, 2022) and/or cope with environmental stress (Baquero et al., 2021). The presence of terpenoids in membranes is known for archaeal and eukaryotic viruses thus far. Archaeal viruses have archaeal-type membrane terpenoids, while eukaryotic viruses have steroids. Viral membranes are commonly acquired by budding of host cellular membranes and this causes a similar lipid composition of viral membranes to that of host membranes (Waheed and Freed, 2010). However, viral membrane formation within host cells is also known (Baquero et al., 2021). In this case, the lipid composition of the viral membrane is highly divergent from that of the host membrane. For instance, positive-strand RNA viruses manipulate the host lipid biosynthesis to optimize the lipid microenvironment for the viral replication (Nagy, 2022). It is currently unknown if viral membrane terpenoids are directly involved in viral entry and replication processes. In contrast, some structural homologs of steroids (e.g. oleanic acid and betulinic acid) in host membranes are known to interact with viral membrane proteins as antiviral agents and prevent viral-host membrane fusion (Si et al., 2018).

2.4 Terpenoids in extracellular vesicles

Various forms of membrane-bound extracellular vesicles (EVs) are secreted by cellular organisms, utilizing host membrane lipids (Deatherage and Cookson, 2012; Gill et al., 2019). EVs include plasmid vesicles to virus-like particles and eukaryotic exosomes. EVs facilitate the transfer of genetic materials and other metabolites between cells. EVs share some similarity with enveloped viruses and in fact a shared origin for certain types of archaeal EVs and viruses has been suggested (Nolte-'t Hoen et al., 2016). Further, infectious virus-like plasmids that are surrounded by membrane vesicles were recently discovered from haloarchaea (Erdmann et al., 2017).

Terpenoids are present in EVs from all three domains, reflecting host cellular membrane compositions (Berry et al., 1993; Skotland et al., 2020; Liu et al., 2021). However, the role of terpenoids in EVs remains unexplored.

2.5 Terpenoids in prokaryotic resting cells

Resting cells differentiate from vegetative cells to preserve genetic materials and other important metabolites under adverse environmental conditions. Resting cells are observed in multiple lineages of bacteria, including endospores in the phylum Bacillota, exospores in actinobacteria and akinetes in cyanobacteria. Endospores in Bacillota are coated with lipid membranes that contain a unique terpenoid called baciterpenol A that is a structural homolog of hopanoids and steroids (Sato, 2013; Willdigg and Helmann, 2021) (Figure 2). In fact, baciterpenol A is produced by class II TC in aerobic members of the phylum. Baciterpenol A increases the rigidity of the host membrane and thus the resistance against oxidative stress (Bosak et al., 2008). In contrast, polycyclic terpenoids have not been found in exospores, even though they are widespread in hopanoid-producing actinobacteria (e.g. *Streptomyces*). In turn, hopanoids are widespread in akinetes and even a correlation between a certain type of hopanoids and akinete formation is suggested (Doughty et al., 2009). Exospore formation was recently reported even for haloarchaea (Tang et al., 2023). Haloarchaea are unique because they horizontally acquired a large number of bacterial genes (Gophna and Altman-Price, 2022), including those for carotenoids and even fatty acids that are otherwise bacterial signatures (Dibrova et al., 2014). Hence, the membrane dynamics of haloarchaea may be divergent from that of other archaea.

3 Terpenoids as key players in membrane evolution

The diverse chemical structures of terpenoids enable them to involve in membrane organization in various different ways. In fact, the structural diversification of terpenoids is linked to the evolutionary trajectory of biological membranes. A prime example is the evolutionary history of class II TC that produces hopanoids and steroids (Hoshino and Villanueva, 2023). The emergence and the stepwise evolution of class II TC seem to reflect the molecular adaptation of host cellular membranes towards changes in Earth's environment. The distribution of class II TC is confined to bacteria and eukaryotes, hence to the bacterial-type membrane. Its ultimate origin is likely in bacteria, producing hopanoids (Santana-Molina et al., 2020). Class II TC acts on a special type of terpenoid oligomers that are formed via the so-called head-to-head condensation of isoprene units (Figure 2). This condensation reaction produces highly hydrophobic squalene and phytoene that are embedded in membranes. The influence of these

terpenoids on membrane property is well documented (Hauß et al., 2002; LoRiccio et al., 2023). Thus, these precursor terpenoids possibly evolved already as membrane regulators before the evolution of class II TC, while the cyclase contributed to the structural diversification of terpenoid regulators.

The modern diversity of class II TC products reflect their adaptation towards the oxygenated Earth. While hopanoids are formed by direct cyclization of squalene, steroids are formed by cyclization of 'oxygenated' squalene (oxidosqualene). Accordingly, steroid biosynthesis is performed only by aerobic organisms. Hence, the membrane dynamics of steroid-producing organisms – most notably eukaryotes – owes its emergence to the aerobic adaptation of terpenoids, which possibly occurred shortly after the Great Oxidation Event 2.4 billion years ago (Gold et al., 2017). Further, modern steroids undergo substantial modifications from original cyclization products (protosteroids) (Figure 2). These modifications enhance the membrane modulation ability of steroids and may reflect the evolutionary trajectory of eukaryotes themselves (Hoshino and Gaucher, 2021; Brocks et al., 2023). However, the onset of terpenoid-associated membrane dynamics likely predates the emergence of class II TC and the head-to-head condensation, as one of the simplest and oldest terpenoids, farnesol, already has the ability to induce microdomain formation in the bacterial membrane (Feng et al., 2014).

In contrast, the effects of terpenoids on archaeal-type membranes is largely unknown. In fact, regulatory terpenoids, such as hopanoids, steroids, carotenoids and squalene, are nearly absent in archaea, even though the archaeal membrane itself is made up of terpenoids (Figure 1). Quinones and polyprenoids that are universally distributed in all three domains may function as membrane regulators (Salvador-Castell et al., 2019), but the underlying molecular mechanisms that drive the membrane dynamics in archaea are generally not well understood. Hence, systematic and comprehensive studies about the impact of individual terpenoids on different membrane systems would be critical to elucidate the origin and the evolutionary history of life through the perspective of membrane evolution (King and Wang, 2023). Terpenoids were involved in the evolution of at least two domains – Archaea and Eukarya. The evolution of Archaea from LUCA entailed a fundamental shift in the lipid composition of the cellular membrane: either a terpenoid membrane was newly acquired, or alternatively a hypothetical mixed membrane converged to a terpenoid membrane (Koga, 2011) (Figure 1). Similarly, the evolution of Eukarya from Archaea was achieved by the transformation from a terpenoid membrane to a fatty acyl membrane, followed by the acquisition of a different class of terpenoids – i.e. steroids (Eme et al., 2017; Hoshino and Gaucher, 2021). In parallel, viruses also adapted to these membrane transformations in host cellular organisms. The interaction of viruses with host membranes is a critical factor for viruses' entry and propagation strategy (Omasta and Tomaskova, 2022). Hence, understanding the evolutionary relationship between host membranes and associated viruses may shed additional light on

the driving force behind the evolution of both cellular organisms and viruses.

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YH: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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