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1 Review

Q1 Functional competition within a membrane: Lipid recognition *vs.* transmembrane helix oligomerization ☆

Q2 Michael Stangl, Dirk Schneider *

5 *Department of Pharmacy and Biochemistry, Johannes-Gutenberg-University Mainz, Johann-Joachim-Becher-Weg 30, 55128 Mainz, Germany*

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ABSTRACT

Binding of specific lipids to large, polytopic membrane proteins is well described, and it is clear that such lipids 19 are crucial for protein stability and activity. In contrast, binding of defined lipid species to individual transmem- 20 brane helices and regulation of transmembrane helix monomer–oligomer equilibria by binding of distinct lipids 21 is a concept, which has emerged only lately. Lipids bind to single-span membrane proteins, both in the juxta- 22 membrane region as well as in the hydrophobic membrane core. While some interactions counteract transmem- 23 brane helix oligomerization, in other cases lipid binding appears to enhance oligomerization. As reversible 24 oligomerization is involved in activation of many membrane proteins, binding of defined lipids to single-span 25 transmembrane proteins might be a mechanism to regulate and/or fine-tune the protein activity. But how 26 could lipid binding trigger the activity of a protein? How can binding of a single lipid molecule to a transmem- 27 brane helix affect the structure of a transmembrane helix oligomer, and consequently its signaling state? These 28 questions are discussed in the present article based on recent results obtained with simple, single-span trans- 29 membrane proteins. This article is part of a Special Issue entitled: Lipid–protein interactions. 30

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33
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37 **Contents**
36

38 1. Dimerization of TM helices regulates cellular functions . . . 0
39 2. Lipids interact with membrane proteins . . . 0
40 2.1. Binding to negatively charged lipid head groups can control TM peptide oligomerization and clustering . . . 0
41 2.2. Sphingomyelin binding to the transmembrane helix triggers oligomerization of the COP I machinery protein p24 . . . 0
42 2.3. C99, the β-secretase cleavage product of the amyloid precursor protein APP specifically binds cholesterol . . . 0
43 3. Summary: how could lipids control oligomerization of TM helices? . . . 0
44 Transparency document . . . 0
45 Acknowledgments . . . 0
46 References . . . 0

47

1. Dimerization of TM helices regulates cellular functions 48

Folding of large, polytopic transmembrane (TM) proteins in- 49 volves interactions of multiple TM helices, and thus individual TM 50 helix–helix interactions can affect or even dictate the assembly of 51 large protein complexes [1–4]. In fact, altered interaction propensi- 52 ties of individual TM helices might be linked to various diseases, 53 due to destabilization or misfolding of polytopic TM proteins [4–6]. 54 However, almost half of the whole human TM proteome consists of 55 single-span TM proteins [7,8]. Single-spanning membrane proteins 56 (MPs) mediate a wide range of cellular processes, including cell–cell 57 adhesion (integrins) [9,10], immune recognition (major histocompati- 58 bility complex, MHC) [11] and signal transduction (*e.g.*, receptor 59

Abbreviations: TM, transmembrane; MP, membrane protein; GpA, glycophorin A; PIP, phosphatidylinositol phosphate; PI, phosphatidylinositide; RTK, receptor tyrosine kinase; MHC, major histocompatibility complex; PG, phosphatidyl glycerol; PS, phosphatidyl serine; PLC, phospholipase C; PH, pleckstrin homology; NMR, nuclear magnetic resonance; COP, coat protein complex; APP, amyloid precursor protein; ErbB, epidermal growth factor receptor; CRAC, cholesterol recognition amino acid consensus; CARC, inversed cholesterol recognition amino acid consensus; Kir, inwardly rectifying potassium channel; ER, endoplasmic reticulum; GOLD, Golgi dynamic; HIV, human immunodeficiency virus; SBD, sphingolipid-binding domain; SM, sphingomyelin; GPCR, G-protein coupled receptor; SNARE, soluble *N-ethylmaleimide sensitive factor* attachment protein receptor; CCM, cholesterol consensus motif

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* Corresponding author. Tel.: +49 6131 39 25833; fax: +49 6131 39 25348.
E-mail address: Dirk.Schneider@uni-mainz.de (D. Schneider).

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tyrosine kinases, RTKs) [12], and contacts between individual bitopic MPs are common [13,14]. Importantly, the TM helices that anchor MPs in the membrane are often critically involved in oligomerization of the full-length MPs. While strongly associating single-span TM helices are thought to form stable membrane-inserted protein–protein complexes, modestly strong interacting TM helices exist in a dynamic equilibrium of the free monomers and the associated oligomers. Reversible oligomerization of individual TM helices can trigger and regulate signaling processes at and across cellular membranes. *E.g.,* while dimerization of the various integrin α- and β-subunits is not completely understood, the respective TM domains are most likely crucially involved in integrin dimerization, and it has been shown that integrin TM domain interactions trigger integrin functions [15–19]. The immune active MHC class II complex is formed by an α/β-heterodimer and invariant chain proteins. Recent results also indicate that here TM helix–helix contacts are crucial for formation of the MHC II complex [20]. RTKs form dimers or even higher-ordered multimeric complexes, and a plethora of data has demonstrated in recent years that dimerization and activation of RTK-family members are mediated by the single TM helix [21–26]. In line with this, the isolated single-span TM domains of all human RTKs have been shown to have an intrinsic propensity to interact, and thus oligomerization of RTK TM helices appears to be common [27]. In the case of ErbB (HER) proteins, probably the best characterized RTK family members, defined adjustments of the TM helix dimer structure appear to be involved in signaling [21,28]. A recent analysis of the human single-span TM proteome has revealed that the isolated TM helices of many single-span TM proteins have an intrinsic propensity to form higher ordered oligomeric structures [14], and thus oligomerization of single-span TM proteins appears to be the rule rather than the exception.

Molecular forces driving interactions of single- and multi-span TM proteins within the membrane include Van der Waals interactions, resulting from close packing of interacting helices, hydrogen bonding, as well as ionic and aromatic interactions [5,29–31]. That formation of tightly packed, homo-oligomeric helix bundles driven by sequence-specific interaction of TM helices was demonstrated more than 25 years ago for the TM domain of the human glycophorin A (GpA) protein [32], a membrane integral protein located in the red blood cell plasma membrane. Later, seven amino acids of the LIxxGVxxGVxxT-motif were identified in a mutational study to be involved in dimerization [33–35]. The GxxxG-core of the GpA interaction motif turned out to be highly overrepresented in TM proteins and still represents the most significant motif in interacting TM helices identified thus far [36,37]. Besides this, several motifs mediating oligomerization of TM domains have been identified, including Ser and/or Thr-containing motifs [38,39], motifs containing aromatic residues [40,41] or residues with carboxamide side chains [42–47], as well as the QxxS-motif [48,49]. More than one dozen high-resolution structures of simple TM helix oligomers have been published in recent years, revealing defined helix–helix contact interfaces. However, often no defined interaction motifs have been identified, and two TM helices interact by forming complementary surfaces, which allow close helix packing, as summarized recently in Cymer et al. [30]. However, since reversible interactions of TM helices might be involved in inhibition or activation of the full-length proteins, TM helix oligomerization has to be regulated to avoid constitutive activation or inhibition of the proteins. Formation and stability of TM helix bundles are not only defined by the specific amino acid context, but also by the composition of the intimate lipid environment, as well as by the overall physico-chemical properties of the membrane. MPs communicate with the lipid environment and thereby the association and activity of MPs might be manipulated and/or triggered.

2. Lipids interact with membrane proteins

Eukaryotic membranes are composed of diverse phospholipids with different head groups and acyl chain lengths as well as cholesterol [50]. It is not finally resolved yet why membrane lipids have different acyl chain lengths. Possibly, it is important for grouping proteins and lipids with similar hydrophobic thicknesses, as hydrophobic regions of TM domains also differ in their length in membrane proteins. In fact, based on the OMP database [51], the hydrophobic thickness of dimeric single-span human TM proteins found in the human plasma membrane varies between 30 and 36 Å, which strongly indicates that the thickness of the lipid bilayer locally adjusts to completely mask the hydrophobic region. Hydrophobic mismatch conditions can result in protein aggregation within lipid bilayer environments [52–56].

Besides the hydrophobic thickness of the membrane, the lateral pressure profile within the acyl chain region as well as the distribution of lipid head group charges at a protein–lipid interface control interactions of MPs with lipids [30,57–59]. In general, lipid binding to a MP can be stabilized by electrostatic and hydrophobic interactions between the lipid head groups and amino acid residues and additionally by a large number of hydrophobic interactions between the hydrophobic lipid tails and TM moieties of the protein (Fig. 1).

Based on the residence time of a particular lipid at the lipid–MP interface, three types of interactions of lipids with MPs might be distinguished (Fig. 2) [60]. Lipids, which diffuse rapidly within the bilayer plane and show a low residence time at the protein–lipid interface, so-called bulk lipids, do not directly affect the structure and/or function of MPs. The bulk lipid phase represents the total lipid volume of the membrane and determines its global characteristics, such as the membrane fluidity, the lateral pressure, the bilayer thickness or the membrane surface charge. When the polar lipid head group interacts with a MP or when hydrophobic matching between the lipids and the TM domain of the MP is crucial, the residence time of the lipids might significantly increase and a shell of annular lipids is formed around the MP. The composition of this annular lipid shell is determined by the local architecture of the protein. In the annular lipid shell, which is composed of around 50–100 lipids and which is not necessarily homogeneous [61], the specific characteristics of the lipids can strongly affect the structure and function of a MP [62,63].

If the interaction of lipids and MPs is even stronger, the so-called non-annular surface lipids will bind specifically and tightly to MPs, typically in cavities and clefts of hydrophobic binding pockets [64]. Non-annular lipids often remain bound to MPs, even if the MPs were purified and crystallized in detergent [65,66]. Especially in larger protein complexes, non-annular lipids fill the crevices between adjacent monomers or subunits and thereby mediate protein complex formation. These lipids seem to play an important role in the structural stability of MPs, and tightly bound lipids can be essential for the activity of MPs [67].

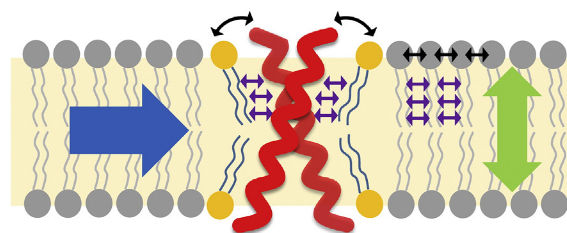

Fig. 1. How the lipid environment can affect transmembrane protein structures. Non-annular lipids (orange) bind specifically at the surface of TM proteins *via* salt bridges between charged lipid head groups and charged residues at the membrane water interface (black arrows). Hydrophobic, Van der Waals and weak dipolar interactions might additionally be involved in lipid binding. Van der Waals interactions between the acyl chain and hydrophobic amino acids further contribute to tight lipid binding (purple arrows). Annular lipids define the global membrane environment of TM proteins and affect membrane protein folding *via* membrane properties, such as the hydrophobic thickness (green arrow) and the lateral membrane pressure profile (blue arrow). The geometry of the lipids (bilayer-forming *vs.* non-bilayer-forming) as well as electrostatic interactions between the lipid head groups (black arrows) and packing of the lipid acyl chains determine the global membrane properties.

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