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REVIEWS: CURRENT TOPICS

Biophysical and biochemical mechanisms by which dietary N-3 polyunsaturated fatty acids from fish oil disrupt membrane lipid rafts☆,☆☆

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Abstract

N-3 polyunsaturated fatty acids (PUFAs) from fish oil exert their functional effects by targeting multiple mechanisms. One mechanism to emerge in the past decade is the ability of n-3 PUFA acyl chains to perturb the molecular organization of plasma membrane sphingolipid/cholesterol-enriched lipid raft domains. These domains are nanometer-scale assemblies that coalesce to compartmentalize select proteins for optimal function. Here we review recent evidence on how n-3 PUFAs modify lipid rafts from biophysical and biochemical experiments from several different model systems. A central theme emerges from these studies. N-3 PUFA acyl chains display tremendous conformational flexibility and a low affinity for cholesterol and saturated acyl chains. This unique flexibility of n-3 PUFA acyl chains impacts the organization of inner and outer leaflet lipid rafts by disrupting acyl chain packing and molecular order within rafts. Ultimately, the disruption in raft organization has consequences for protein clustering and thereby signaling. Overall, elucidating the complex mechanisms by which n-3 PUFA acyl chains reorganize membrane architecture will enhance the translation of these fatty acids into the clinic for treating several diseases.

Keywords: Lipid rafts; n-3 PUFA

1. Consumption of fish oil has health benefits

Dietary consumption of fish oil is increasingly recognized to have beneficial health effects, especially for the prevention or treatment of specific diseases. As examples, fish oil intake is associated with decreased risk for coronary heart disease, and prescription fish oil supplements lower serum triglycerides [1,2]. There is also emerging evidence that fish oil has immunosuppressive properties, which may have clinical applications for the treatment of symptoms associated with autoimmune and inflammatory diseases [3]. Finally, there is some suggestion that fish oil may lower the risk of cognitive disorders, prevent the progression of specific cancers and improve insulin sensitivity [4,5].

One major obstacle in effectively translating fish oil into the clinic for the treatment of some of the aforementioned afflictions is a limited understanding of its molecular mechanisms. The bioactive components of fish oil are the n-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic (EPA, 20:5) and docosahexaenoic (DHA, 22:6) acids. Mechanistically, these fatty acids modify gene expression, give rise to bioactive oxygenated metabolites known as resolvins and protectins, disrupt cellular signaling and protein trafficking, and modify plasma membrane domains [6,7]. This review focuses on recent advances in n-3 PUFA and plasma membrane lipid raft domain research.

2. Lipid rafts are a molecular target of N-3 PUFAs

Lipid rafts are operationally defined as sphingolipid/cholesterol-enriched domains that under specific circumstances serve to compartmentalize signaling [8]. Since the inception of the lipid raft model, there has been considerable debate on their existence, composition, size and lifetime. Much of the controversy arose from the use of indirect methods to study rafts, predominately, the use of biochemical detergent extraction, which has utility as a predictive tool but can also introduce artifacts [9]. Recent advances in lipidomics and high-resolution imaging, which resolves domain sizes below the diffraction limit of a microscope, have provided stronger evidence for the existence of lipid rafts [10].

The current model proposes that lipid rafts are fluctuating assemblies that exist as nanometer-sized domains [10]. In response to stimuli such as a ligand binding to its receptor, the nanometer-scale domains coalesce. The coalesced domains are larger in size, up to the micrometer-size scale, and display high molecular order relative to the surrounding nonrafts [10]. The formation of these ordered domains is driven by favorable molecular interactions between sphingolipids and cholesterol and is regulated by the underlying actin cytoskeleton. Lipid raft domains are not limited to the plasma membrane; for instance, they exist in intracellular organelles such as

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the Golgi where they regulate protein trafficking [10]. Their existence is questionable in other endomembranes; for instance, mitochondrial membranes, which have low levels of cholesterol, are unlikely to form rafts [11].

A key component of the lipid raft model is that coalescence of nanometer-scale assemblies, driven by both lipid–lipid and lipid–protein interactions, serves to enhance or optimize the function of specific plasma membrane proteins [10]. Compartmentalization of signaling is central to the lipid raft concept and is a target of n-3 PUFAs [12].

3. Biophysical studies on an atomic scale show N-3 PUFAs adopt unique molecular orientations that do not pack efficiently with raft molecules

Some of our understanding of how n-3 PUFAs from fish oil impact the physical organization of membranes comes from biophysical experiments using model membranes (e.g., lipid vesicles, supported bilayers, monolayers) and molecular dynamic (MD) simulations [13]. The advantage of model membrane and MD simulation studies is they provide a highly controlled environment for investigating the dynamic nature of n-3 PUFA acyl chains in the presence of sphingolipids and/or cholesterol. Of course, this approach has a major limitation, that is, they are not an accurate depiction of the plasma membrane that contains hundreds of different lipid species and proteins. Nevertheless, these studies provide mechanistic details on an atomic scale that are not readily discerned from cellular studies.

The majority of work on n-3 PUFAs in model membranes has focused on DHA [14]. The molecular structure of DHA is unique. It is somewhat polar due to the presence of six double bonds and is highly flexible with rapid reorientations through multiple conformational states [15]. A combination of nuclear magnetic resonance (NMR), neutron diffraction and MD simulations shows that the DHA acyl chain can be displaced toward the head-group region, with the terminal methyl at times approaching the water interface (Fig. 1) [16–19]. Addition of cholesterol can partially redistribute the DHA acyl chain toward the bilayer center, but the ordering effect of cholesterol is still more pronounced when cholesterol interacts with saturated acyl chains [20].

The flexible and therefore disordered structure of DHA renders it incompatible with surrounding ordered saturated acyl chains and cholesterol. Rosetti and Pastorino very recently reported with MD simulations that DHA acyl chains do not pack efficiently with saturated acyl chains [21]. Similarly, we reported, in collaboration with others, that DHA-containing phospholipids did not mix ideally with sphingolipids with predominately saturated acyl chains in the absence of cholesterol [22].

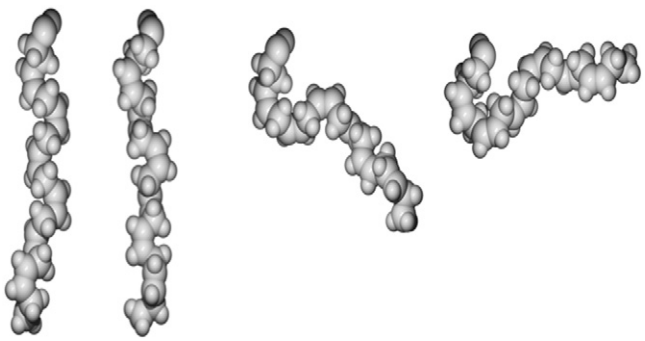

Fig. 1. DHA acyl chains adopt unique conformations. The different conformational states of DHA were obtained with molecular dynamic simulations. The images show that the DHA acyl chain is highly flexible and that the terminal methyl can even approach the head-group region. This degree of flexibility likely contributes to its ability to disrupt lipid raft molecular organization. The figure was obtained with permission from the Feller lab.

The Stillwell and Wassall labs over the past decade have demonstrated a packing inability between saturated acyl chains and DHA, which was further enhanced in the presence of cholesterol [14]. Spectroscopic and calorimetric studies from their labs established that DHA-containing phosphatidylcholines and phosphatidylethanolamines have a low affinity for cholesterol in the presence of sphingomyelin [23,24].Their NMR data suggest that DHA-containing phospholipids are forming their own organizationally distinct domains (<20 nm in size) in the presence of sphingolipids and cholesterol as a mechanism to avoid saturated acyl chains and cholesterol [23]. Lately, novel data from the Katsaras and Wassall labs imply that the presence of select PUFAs in the membrane can force cholesterol to adopt unusual orientations in the membrane, for instance, forcing the polar hydroxyl group of cholesterol to be buried into the interior of the bilayer [25,26].

Overall, model membrane and MD simulation data suggest that when disordered DHA acyl chains incorporate into the plasma membrane of cells, they do not pack efficiently with saturated acyl chains or cholesterol, both of which are essential for the formation of lipid rafts.

4. Biochemical studies *in vitro* and *ex vivo* demonstrate that N-3 PUFAs disrupt detergent resistant "rafts" and associated protein distribution

The initial observation of how n-3 PUFAs disrupted lipid domain organization in cells came from studies using biochemical detergent extraction [27–29]. For instance, the Stulnig lab showed that treatment of T-cells with n-3 PUFAs modified detergent resistant membranes (DRMs), which are a crude cellular fraction that supposedly represents cellular "lipid rafts" (we use quotes to remind the reader that DRMs are not the same as lipid rafts) [27]. A significant proportion of n-3 PUFA was localized into DRMs, with the remaining portion in "nonraft" detergent soluble membranes (DSMs). The intriguing aspect of this work was that proteins localized in DRMs were displaced in response to n-3 PUFA treatment.

More recent *in vitro* and *ex vivo* measurements in several cell types have verified the basic hypothesis that n-3 PUFAs incorporate directly into DRMs to displace proteins either into or out of these "raft"-like fractions [30–36]. In some cell types, n-3 PUFAs lower the levels of cholesterol and sphingolipids in the DRMs [31]. Grimm et al. recently demonstrated that treatment of SH-SY5Y cells with DHA displaced cholesterol from DRMs to DSMs [37]. We and others have also observed a trend for cholesterol to move from DRMs to DSMs with DHA treatment [29,38,39]. Thus, DHA and perhaps EPA may be promoting the displacement of cholesterol from DRMs to DSMs, which is consistent with NMR and X-ray diffraction data that show DHA has a low affinity for cholesterol [14,40]. Once the cholesterol is displaced toward nonrafts, it is likely to associate with saturated acyl chains.

Several questions arise from the biochemical detergent extraction experiments: (a) How does one effectively connect findings from different model systems: i.e., model membranes, *in vitro*, *ex vivo* data? (b) Are n-3 PUFAs exerting their effects by directly incorporating into lipid rafts? Alternatively, are n-3 PUFAs exerting their effects indirectly on rafts (e.g., by targeting the cytoskeleton, nonraft domains, etc.)? (c) What is the molecular nature of lipid rafts upon incorporation of n-3 PUFAs into the raft? In other words, are these domains still ordered rafts or are they simply disrupted rafts? (d) Where are n-3 PUFA acyl chains localizing to (e.g., what lipid species, which membrane leaflet, etc.)? To address these questions, sophisticated imaging and lipidomic methods are starting to provide some insights.

5. Quantitative imaging and lipidomics reveal that N-3 PUFAs disrupt raft composition and molecular order to alter protein distribution

Recently, several labs, including our own, have corroborated biochemical methods with quantitative imaging methods to address some of the aforementioned questions on how n-3 PUFAs disrupt lipid rafts. We very recently reported using a combination of confocal and FRET (Förster resonance energy transfer) imaging to show that, *in vitro* and *ex vivo*, n-3 PUFAs selectively disrupted the clustering of lipid rafts of EL4 and B cells [38,41]. However, n-3 PUFAs had no impact on nonraft organization under physiologically relevant conditions [41]. Our model system addressed raft formation in the outer leaflet of the plasma membrane since we measured cholera toxin binding to GM1 molecules. Our data were in agreement with an electron microscopy study *in vitro* with HeLa cells, which showed that DHA treatment selectively disrupted lipid raft, but not nonraft, domains of the inner leaflet [42]. Thus, recent data suggest that n-3 PUFAs are selectively disrupting lipid rafts of both the outer and inner leaflets with little impact on nonraft organization.

If n-3 PUFAs directly incorporate into lipid rafts, then what is the nature of the lipid raft domains? Given the steric incompatibility between DHA acyl chains and lipid raft molecules, one would predict that incorporation of n-3 PUFA acyl chains into rafts would disrupt their molecular order. Two different labs have attempted to address this issue, which have yielded opposite results.

The Chapkin lab showed that incorporation of n-3 PUFAs into the immunological synapse of $CD4^+$ T-cells from the fat-1 transgenic mouse increased the molecular order of lipid rafts, as measured with fluorescence polarization microscopy [43]. In contrast, the Harder lab demonstrated, also with fluorescence polarization imaging, that EPA treatment of Jurkat T-cells *in vitro* decreased the molecular order of lipid rafts in the synapse [44]. Lipidomics in the same study revealed significant incorporation of EPA into differing phospholipids with an increase in a select sphingolipid species [44]. One reason for the discrepancy was differential uptake of fatty acids between *in vitro* and *ex vivo* studies [45]. Furthermore, *in vitro* studies only provided a single fatty acid, whereas both EPA and DHA accumulated in T-cells from the fat-1 transgenic mouse. Clearly, more studies are needed to resolve how n-3 PUFAs are modifying the lipidome and molecular order of rafts.

The consequences of disrupting lipid rafts on protein lateral organization are also emerging. Recent imaging studies are overall confirming the biochemical observations that n-3 PUFAs displace proteins into or out of rafts. For instance, we discovered that DHA, upon disrupting lipid raft clustering, forced the nonraft immunological protein, MHC (major histocompatibility complex) class I, into lipid rafts [38]. We also recently observed with FRET imaging that DHA and EPA could modify MHC I spatial organization on a nanometer scale, which was driven by changes in plasma membrane size [41]. Similarly, several other labs have shown with imaging or biochemical approaches that protein–protein interactions, which are

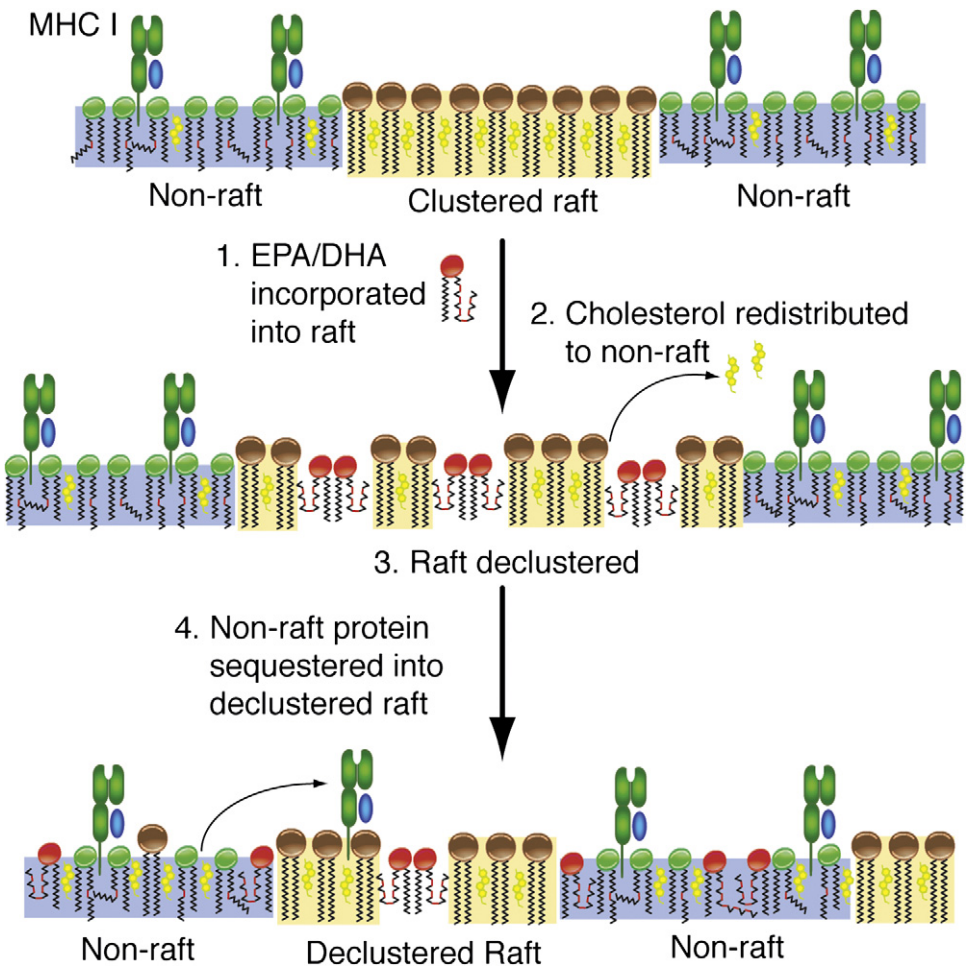

Fig. 2. Proposed model on how n-3 PUFA acyl chains disrupt the molecular organization of membrane lipid rafts and proteins. The model shows n-3 PUFAs declustering rafts by directly incorporating into the raft and then redistributing cholesterol toward nonrafts. As a consequence, a nonraft protein such as MHC class I is forced into the lipid raft. Similarly, raft proteins are likely declustered and forced into nonrafts. The order of events is shown for simplicity and may occur simultaneously.

central to generate intracellular signaling, are modified with dietary n-3 PUFAs. For instance, proteins essential for the activation of immune cells or growth of differing cell types are modified by n-3 PUFAs, which leads to changes in downstream signaling, gene expression and ultimately function [31,33–36,43,46].

6. Integrated model

In Fig. 2, we present a model on how n-3 PUFAs could disrupt lipid raft organization and thereby protein lateral distribution. The model is based on data from our lab and others from several model systems. The model shows, as an example, that MHC class I proteins localized to nonrafts. When n-3 PUFA acyl chains incorporate into the raft (possibly as nanodomains as suggested by recent NMR data in model membranes), the raft becomes declustered. The poor affinity between n-3 PUFAs and cholesterol forces some of the cholesterol molecules to move out of the raft into nonrafts, which contributes to the declustering. The declustering event allows a protein such as MHC class I to now move into the disrupted raft. The model is also applicable to proteins localized within the lipid rafts. In this case, incorporation of n-3 PUFA acyl chains into lipid rafts and subsequent declustering will force raft-localized proteins from rafts into nonrafts.

7. Future directions

Determining the mechanism by which n-3 PUFA acyl chains disrupt lipid raft spatial and temporal organization is in its infancy. As listed above, there are several questions that arise from the biochemical studies that are currently being addressed. Furthermore, there are many other questions that require attention that are central to developing a complete mechanism by which n-3 PUFAs disrupt raft molecular organization. For instance, do EPA and DHA exert differential effects on membrane raft organization? Our quantitative studies *in vitro* with EL4 cells showed that DHA, but not EPA, disrupted the clustering of lipid rafts [38]. However, our data are not in agreement with another lab that showed that both EPA and DHA disrupted lipid raft spatial distribution [30]. More studies are needed to understand what the molecular differences are, especially at an atomic scale, between EPA and DHA. As another example, how do EPA and DHA modify the plasma membrane lipidome? Recent advances have been with cell culture experiments [44], but studies at the animal and human level are needed. Finally, it is essential to determine how changes in lipid raft organization with n-3 PUFAs impact not just downstream signaling and gene expression but the impact on function at the tissue and whole animal level.

8. Conclusion

The goal of this review was to highlight recent mechanistic advances in biophysical and biochemical studies with n-3 PUFAs and lipid rafts. As the field is rapidly evolving, some central themes are emerging. DHA, and perhaps EPA, acyl chains are highly disordered, which renders them incompatible with packed lipid raft molecules. As a consequence, when lipid rafts are exposed to n-3 PUFAs, their molecular composition and order are changed, which has consequences for protein clustering and ultimately cellular function.

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