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Models of plasma membrane organization can be applied to mitochondrial membranes to target human health and disease with polyunsaturated fatty acids

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ABSTRACT

Bioactive n-3 polyunsaturated fatty acids (PUFA), abundant in fish oil, have potential for treating symptoms associated with inflammatory and metabolic disorders; therefore, it is essential to determine their fundamental molecular mechanisms. Recently, several labs have demonstrated the n-3 PUFA docosahexaenoic acid (DHA) exerts anti-inflammatory effects by targeting the molecular organization of plasma membrane microdomains. Here we briefly review the evidence that DHA reorganizes the spatial distribution of microdomains in several model systems. We then emphasize how models on DHA and plasma membrane microdomains can be applied to mitochondrial membranes. We discuss the role of DHA acyl chains in regulating mitochondrial lipid–protein clustering, and how these changes alter several aspects of mitochondrial function. In particular, we summarize effects of DHA on mitochondrial respiration, electron leak, permeability transition, and mitochondrial calcium handling. Finally, we conclude by postulating future experiments that will augment our understanding of DHA-dependent membrane organization in health and disease.

1. Introduction

Fish oil is highly enriched in n-3 polyunsaturated fatty acids (PUFA). The major bioactive n-3 PUFAs of fish oil are eicosapentaenoic (EPA) and docosahexaenoic acids (DHA). Consumption of n-3 PUFAs is known to provide benefits for a number of diseases and disorders, although the cellular mechanisms underlying PUFA-mediated improvements are still a matter of investigation and debate [1]. To translate n-3 PUFAs for treating a wide variety of afflictions, an understanding of their fundamental molecular mechanisms is essential.

Several pathways, which work in concert, have been proposed by which n-3 PUFAs target cellular function in inflammatory and metabolic diseases. These include manipulation of eicosanoid metabolism, production of neuroprotectins/resolvins, alterations in signaling pathways and gene expression, and spatial redistribution of lipids and proteins in the plasma membrane [1]. Very recently, several studies ranging from the atomic level to animals have emerged to show that DHA, in particular, targets the physical organization of plasma membrane microdomains [2]. Here we briefly review this evidence and then apply models developed with these studies toward understanding how DHA acyl chains could manipulate mitochondrial membrane organization and thereby impact disease endpoints.

1.1. DHA and models of plasma membrane molecular organization

Studies over the past decade have shown that DHA can manipulate the molecular organization of plasma membrane microdomains known as lipid rafts [2]. Lipid rafts are operationally defined as nanoscale fluctuations composed of sphingolipids and cholesterol that coalesce into larger signaling assemblies in response to stimulation (i.e. antigen bindings its receptor) [3,4]. Although lipid rafts have remained controversial for various reasons, recent lipidomic and high-resolution imaging approaches have provided more compelling evidence for their existence [4].

Studies on DHA and lipid microdomains have relied on three types of model systems, each with its own weaknesses and strengths (Table 1). The first model system has investigated how DHA impacts the molecular organization of liquid ordered raft-like domains using lipid vesicles of defined composition [5]. These studies have revealed several novel findings. One, DHA acyl chains, due to their high degree of conformational flexibility [6],

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Table 1
Model systems used to study the effects of n-3 PUFAs on lipid microdomain organization. Extensive explanation of the results from these model systems is described in a recent review [2].

	Lipid vesicles	Cell culture	Animals
Description of model system	Vesicles of defined size and composition relying on DHA-containing phospholipids	Lymphocytes, hepatocytes, splenocytes, cardiomyocytes	C57BL/6 mice
		Macrophages	Fat-1 transgenic mice, rats
		Cancer cells	–
Recent results	Cholesterol avoids DHA acyl chains; however, when cholesterol is forced to interact with DHA, there is an ordering effect on the phospholipid	EPA/DHA infiltrate raft-like membranes	Fish oil increases B and T lymphocyte microdomain size on a micron scale and molecular order
		EPA/DHA differentially modify cholesterol distribution	
		EPA/DHA differentially modify lipid microdomain size	EPA/DHA infiltrate raft-like membranes in differing cell types
Advantages	Atomic to nanoscale measurements	Determine bioactivity of EPA vs. DHA	Physiological relevance
	Address mechanisms	Address mechanisms	–
Disadvantages	Physiological relevance	EPA/DHA membrane incorporation does not completely model the diet	Difficult to address membrane-based mechanisms in vivo

can impart unique effects on numerous membrane properties to regulate lipid microdomain formation [5,7]. Second, phosphatidylethanolamines containing DHA prefer to avoid interactions with cholesterol and sphingolipid acyl chains [5]. However, when heteroacid phosphatidylcholines containing DHA are forced to interact with cholesterol, molecular order of the phospholipid containing DHA increases [5,8].

The second model system has relied on treating various cell types, often lymphocytes, with fatty acids to assess changes in "raft" composition (Table 1). These studies have revealed EPA and DHA incorporate directly into raft-like membranes and thereby influence protein lateral organization and activity [9–12]. Very recent studies from cell culture experiments have provided novel mechanistic insight into how DHA could manipulate raft organization; that is, n-3 PUFA acyl chains could be altering the distribution of cholesterol between rafts and non-rafts. This would be highly consistent with model membrane studies [5]. However, more studies are needed in this area since the results are discrepant. One lab showed DHA treatment of SH-SY5Y cells promoted cholesterol to move from rafts to non-rafts while another lab showed EPA treatment of hepatocytes promoted cholesterol to move from nonrafts to rafts [13,14]. Perhaps these differences are due to the unique bioactivity of EPA versus DHA.

The third model system is animals fed diets enriched in n-3 PUFAs or the fat-1 transgenic mouse (Table 1). These studies suggest that n-3 PUFAs increase the size and molecular order of lipid rafts on a micron scale. For example, the Shaikh lab showed that cholera toxin induced raft clustering of $B220^+$ B cells was diminished in different n-3 PUFA diet models accompanied by suppression of B cell mediated antigen presentation [15,16]. Furthermore, DHA, but not EPA, increased membrane order upon cross-linking rafts relative to no cross-linking [16]. Similarly, Chapkin and co-workers have established n-3 PUFAs promoted the formation of ordered immunological synapses to suppress $CD4^+$ T cell activation [17]. Overall, changes in raft size and order impact protein activity and thereby downstream signaling and gene expression [2].

1.2. Integrating models on DHA and lipid microdomains

The differing model systems must be effectively integrated to generate complete mechanisms by which n-3 PUFAs manipulate microdomain molecular organization (Table 1). While lipid vesicles and cells allow very direct mechanistic studies, physiological application towards animals and humans is limited. Similarly, although studies at the animal level are highly physiologically relevant, dissecting the effects of fatty acids from the diet on membrane organization is difficult. Irrespective of the model system used to study n-3 PUFAs and membrane domains, more studies are needed at the nanoscale, which is the relevant size scale.

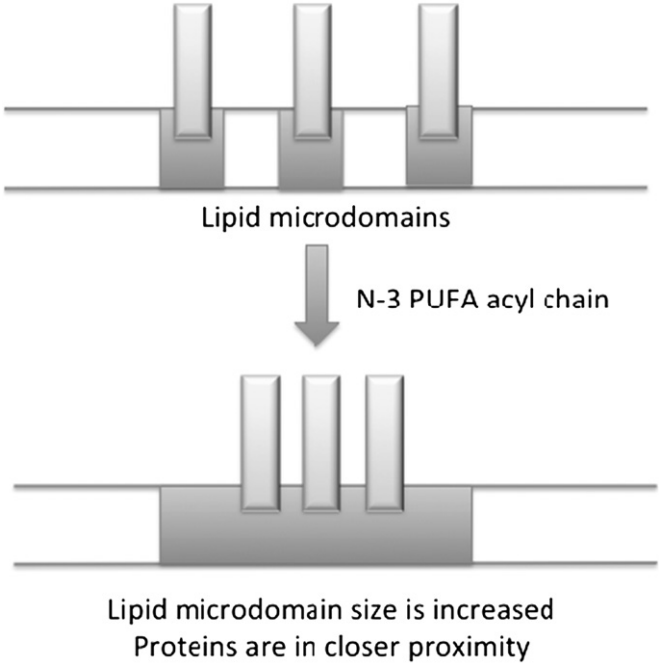

Fig. 1. Generalized model on how the underlying lipid environment in a membrane can regulate protein clustering and thereby downstream function. Studies on the plasma membrane suggest that incorporation of n-3 PUFA acyl chains, DHA in particular, modify the composition and size of lipid microdomains. As a consequence of this change, the ability of proteins to cluster, communicate and signal is modified. For simplicity, this model shows n-3 PUFA acyl chains increasing protein clustering but could also do the opposite; that is, de-cluster proteins. This model is applicable to endomembranes such as the mitochondrial membrane.

Taken together, the model that emerges from the differing experimental systems is that DHA, more than EPA, acyl chains incorporate directly into ordered lipid microdomains to manipulate protein organization (Fig. 1). These effects appear to be driven biophysically and biochemically by DHA [2]. Changes in