

Fatty acids as gatekeepers of immune cell regulation

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Fatty acids have diverse roles in all cells. They are important as a source of energy, as structural components of cell membranes, as signalling molecules and as precursors for the synthesis of eicosanoids. Recent research has suggested that the organization of fatty acids into distinct cellular pools has a particularly important role in cells of the immune system and that forms of lipid trafficking exist, which are as yet poorly understood. This Review examines the nature and regulation of cellular lipid pools in the immune system, their delivery of fatty acids or fatty acid derivatives to specific locations and their potential role in health and disease.

Fatty acids are hydrocarbon chains, which can be saturated, monounsaturated or polyunsaturated. Unsaturated fatty acids contain double bonds between pairs of adjacent carbon atoms; monounsaturated fatty acids contain one double bond; and polyunsaturated fatty acids (PUFAs) contain more than one double bond. There are two essential fatty acids, linoleic and α -linolenic acid, which cannot be synthesized *de novo* in animal cells and must therefore be obtained from the diet. Linoleic acid is an n-6 PUFA, described by its shorthand notation of 18:2n-6, which refers to an 18-carbon fatty acid with two double bonds, the first of which is on carbon atom 6 from the methyl end. α -Linolenic acid is an n-3 PUFA with a shorthand notation of 18:3n-3, describing an 18-carbon fatty acid with three double bonds, the first being positioned at carbon atom 3 from the methyl end (Figure 1). Both essential fatty acids can be further elongated and desaturated in animal cells forming the n-6 and n-3 families of PUFAs (Figure 2). The metabolism of the n-6 and n-3 fatty acids is competitive because both pathways use the same set of enzymes. The major end-product of the n-6 pathway is arachidonic acid. This pathway is quantitatively the most important pathway of PUFA metabolism in humans because linoleic acid is abundant in vegetable oils and vegetable oil-based products, and therefore consumed in greater quantities than α -linolenic acid, which is present in green leafy vegetables and some seed and vegetable oils. The major end-products of the n-3 pathway are eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA); little α -linolenic acid proceeds along the entire metabolic pathway, giving rise to docosahexaenoic acid (DHA). However, oily fish contain lipids, which have a high proportion of the long chain n-3

PUFA, EPA and DHA, and are the chief sources of these fatty acids.

Fatty acids have diverse roles in all cells. They are important as a source of energy, as structural components of cell membranes and as signalling molecules. In addition, arachidonic acid and EPA can both serve as precursors for the synthesis of eicosanoids. In 1978, Meade and Merten [1] published the first, and somewhat speculative, review addressing the role of fatty acids in the immune system. In the 25 years that have elapsed since, there have been significant developments in our understanding of the organization of lipids within cells, some of which are particularly relevant to immune regulation. First, it is now recognized that 'lipid domains' in cellular membranes consist of lipid rafts and caveolae, which are highly organized microenvironments with several important functions. Second, the presence of intracellular lipid bodies, likely to contain precursors for the rapid production of eicosanoids within inflammatory cells, has been demonstrated. Third, new families of nuclear receptors, which can be activated by fatty acids, have been characterized. This has led to speculation about the mechanisms by which intracellular fatty acids might be channelled towards these receptors to influence target genes related to immunity and inflammation. The purpose of this Review is to relate these new data to the presence and composition of lipid domains

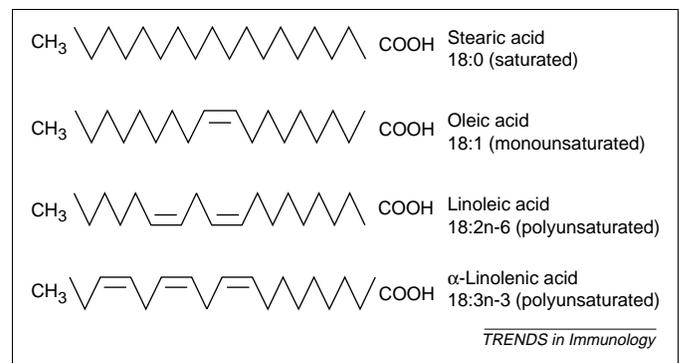
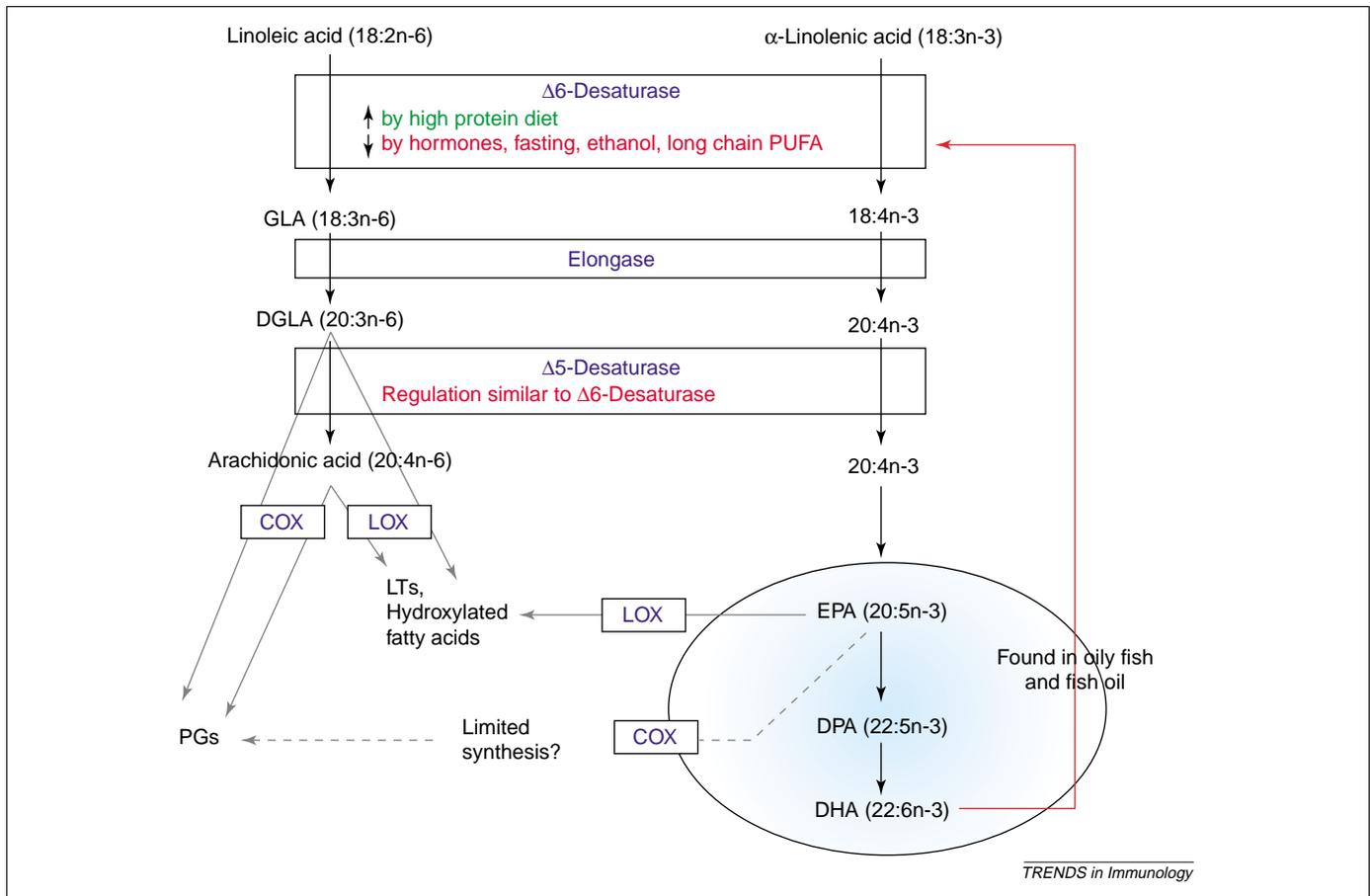


Figure 1. Examples of the structure and nomenclature of fatty acids. Unsaturated fatty acids contain double bonds between pairs of adjacent carbon atoms; monounsaturated fatty acids contain one double bond; and polyunsaturated fatty acids (PUFAs) contain more than one double bond. The two essential fatty acids, linoleic and α -linolenic acid, cannot be synthesized *de novo* in animal cells and must therefore be obtained from the diet. Linoleic acid is an n-6 PUFA, described by its shorthand notation of 18:2n-6, which refers to an 18-carbon fatty acid with two double bonds, the first of which is on carbon atom 6 from the methyl end. α -Linolenic acid is an n-3 PUFA with a shorthand notation of 18:3n-3, describing an 18-carbon fatty acid with three double bonds, the first being positioned at carbon atom 3 from the methyl end.



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Figure 2. Essential fatty-acid metabolism. Both essential fatty acids can be elongated and desaturated by several sequential steps in animal cells forming the n-6 and n-3 families of PUFAs. Competition favors metabolism of n-6 over n-3 fatty acids because both pathways use the same set of enzymes. Although DGLA, arachidonic acid and EPA can all potentially act as precursors for the synthesis of eicosanoids, the main precursor is arachidonic acid, chiefly because of its availability. Consumption of EPA can both reduce the amount of arachidonic acid available for the synthesis of eicosanoids (by replacing it in biological membranes) and can also act as a precursor for the synthesis of eicosanoids with potentially different activities and potencies. The $\Delta 6$ desaturase is regulated by hormones (adrenaline, glucagon, thyroxine, glucocorticoids), fasting, ethanol and long chain PUFAs (especially DHA and EPA). Abbreviations: COX, cyclooxygenase; DGLA, dihomo- γ -linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; GLA, γ -linolenic acid; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LT, leukotriene; LOX, lipoxygenase; PG, prostaglandin; PUFAs, polyunsaturated fatty acids.

within cells of the immune system and to examine what controls these lipids in health and disease.

Lipid rafts as platforms for cell activation in the immune system

Lipid rafts are dynamic microenvironments in the exoplasmic leaflets of the phospholipid bilayer of plasma membranes. They are rich in saturated fatty acids, sphingolipids, cholesterol and glycosylphosphatidylinositol-anchored (GPI) proteins [2–5]. Rafts serve as platforms to facilitate apical sorting, cell migration, the association of signalling molecules and interactions and crosstalk between cell types [6–9].

Activation of the proteins within rafts by an extracellular ligand can result in rapid clustering, which appears to be important for signal transduction in both T and B lymphocytes [4,7,8]. The T-cell receptor (TCR) clusters within lipid rafts on contact with an antigen-presenting cell, forming an ‘immunological synapse’, or contact zone, where intracellular signalling is thought to be initiated. For this reason, T-cell activation has become a model for studying lipid rafts [8]. A two-step model for T-cell activation has been suggested, whereby preformed rafts containing the TCR initiate the signalling process, and a

second, possibly intracellular, compartment translocates to the aggregated TCR and facilitates co-stimulation and amplification of the signal [10,11]. There is also evidence for dynamic lateral rearrangement of lipid microdomains and novel associations between proteins within the plasma membrane, visualized by fluorescence microscopy [12]. However, because rafts have been characterised biochemically and immunological synapses microscopically, the exact relationship between the two is not clear. Interestingly, the role of membrane rafts in Th1 and Th2 cells appears to be markedly different, with TCR activation in Th1 cells being dependent on rafts, whereas that in Th2 cells is not [13]. The reason is not clear but has been suggested to be due to differences in the composition, distribution or quantity of lipid rafts [8,14].

An increasing number of raft-associated proteins, many of them regulating TCR signalling, are being identified as negative regulators of T-cell activation. For example, the cytoplasmic adaptor protein, Cb-1b, inhibits TCR clustering, shown by the enhanced TCR clustering, hyperproliferation of T cells and spontaneous autoimmunity in knockout mice [15]. Another potential negative regulator of raft formation in T cells is cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), the negative regulator of

CD28 co-stimulation, which appears to inhibit the redistribution of intracellular raft compartments to the surface of activated T cells [16]. This highlights the fact that there could be 'trafficking' of lipid, as well as proteins, along specific routes within cells to target locations.

Modulation of raft function by fatty-acid modification

The Src kinases have an important role in T-cell activation and their myristoylation or palmitoylation is regarded as essential for targeting them to rafts because proteins can be artificially targeted to rafts by acylation [17]. Lck and Fyn, which are members of the Src family of kinases, are concentrated on the cytoplasmic side of lipid rafts and become activated in response to stimulation of the TCR, triggering several downstream signalling events [18]. Lipid rafts from Jurkat cells treated with arachidonic acid *in vitro* have a reduced content of Lck and Fyn, a decline in calcium signalling and a decline in some other downstream events [19]. Of significant interest is the fact that PUFA treatment results in PUFA acylation of Fyn itself. The authors suggest that this is possible because palmitoyl acyltransferase is a relatively promiscuous enzyme, which is able to form covalent attachments between a wide range of fatty acids and proteins [18,20]. However, it is not clear whether this is a physiological phenomenon.

The transmembrane adaptor protein, LAT (linker for activation of T cells) is another signalling molecule constitutively present in rafts and when phosphorylated binds to several other molecules, including phospholipase C γ 1 (PLC γ 1), initiating key pathways in T-cell activation [21]. The functionality of LAT is dependent on its palmitoylation. Treatment of Jurkat cells with the n-3 PUFA EPA, but not stearic acid, diminished the phosphorylation of LAT and PLC γ 1 and it was suggested that this was as a result of selective displacement of LAT from lipid rafts [22]. Another example of an alteration of lymphocyte function as a result of modulation of raft fatty-acid composition is the displacement and subsequent activation of phospholipase D by the n-3 PUFA DHA in human T cells [23]. The authors suggest that this activation of phospholipase D might be responsible for the antiproliferative effects of DHA in lymphoid cells [23]. However, it will be important to determine whether there is a physiological threshold for these reported disruptive effects of PUFAs on lipid rafts and, indeed, whether all PUFAs exert the same effect. It is interesting to note that n-3 PUFAs promote activation-induced cell death in Th1, but not Th2, cells [24]. Because Th1 activation is suggested to be dependent on lipid rafts, whereas that of Th2 cells is not, Fan *et al.* [25] speculate that modulation of lipid raft composition could have a role in the downregulation of Th1 responses and therefore in the anti-inflammatory properties of n-3 PUFAs.

Caveolae

Caveolae are a subset of lipid rafts that are flask-shaped invaginations of plasma membrane observed by electron microscopy in many cell types but notably not in most lymphocytes (reviewed in Ref. [26]). As with lipid rafts, palmitoylated proteins are responsible for the structural organization of the caveolae, forming hairpin-like

structures, which tightly bind cholesterol [26]. In this case, the proteins are termed caveolins and their absence from most lymphocytes suggests that they are essential for the formation of caveolae [27]. Indeed, forced expression of caveolins in lymphocytes results in the formation of caveolae [28]. An exception is human CD21⁺ and CD26⁺ lymphocytes isolated from peripheral blood, which stain positive for caveolin-1 [26].

Stimulation of murine macrophage cell lines with lipopolysaccharide (LPS) increases expression of caveolin-1 mRNA [29] and it has been suggested that specific lipid microdomains destined to form caveolae originate in the Golgi apparatus and are transported to the plasma membrane as vesicular organelles [27]. Thus, it would appear that the presence of caveolae at the cell surface might be a transient phenomenon, although this could depend on the cell type and/or its state of activation [26]. It is interesting to note that this trafficking system operates in both directions because caveolin can bind free cholesterol, which, if oxidized, results in the displacement of caveolin from the plasma membrane to intracellular vesicles [30].

Local generation of fatty acid-derived mediators by lipid bodies in inflammatory cells

Eicosanoids have numerous roles in the regulation of immune and inflammatory responses, the true extent of which have probably not yet been realized. It is becoming clear that the regulation of eicosanoid formation involves activation of enzymes at specific intracellular sites and that this local generation of eicosanoids might be facilitated by the presence of lipid bodies present within many (if not all) cell types. Lipid bodies within eosinophils increase in number following an inflammatory stimulus and appear to contain all of the enzymes necessary for eicosanoid synthesis [31]. Unlike lipid rafts, these distinct intracellular domains are not resistant to detergent solubilization and there are consequently some methodological limitations to their study. Because it is not possible to prepare lipid bodies, their structure and composition have not yet been elucidated. Bandeira-Melo *et al.* [32] describe them as inducible structures lacking a membrane but containing a 'honeycomb membranous matrix' underlying their lipid.

Novel techniques have been used to cross-link newly synthesized leukotriene C₄ (LTC₄) at sites of synthesis within eosinophils and to follow its fate on stimulation [31]. This approach demonstrated that LTC₄ formation does indeed occur in lipid bodies and that, depending on the nature of the stimulus, LTC₄ can be either targeted towards the perinuclear membrane or released into the extracellular milieu [31,32]. Like lipid rafts, the distribution of lipid bodies can be polarized, but it is not clear whether those producing eicosanoids destined to be secreted are located close to the plasma membrane and those that are perinuclear produce eicosanoids solely for autotropic effects [31]. A potential role for lipid bodies in sepsis has recently been described, which could apply to other disease situations. Pacheco *et al.* [33] showed that lipid body numbers were higher in leukocytes from septic patients compared with healthy patients and that lipid bodies were inducible by LPS in murine macrophages.

Interactions between fatty acids and nuclear transcription factors in immune cells

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors present in a variety of cell types, with diverse actions, mainly in lipid metabolism. They bind DNA as obligate heterodimers with one of the retinoid X receptors but they are also able to influence gene expression by interacting with other transcription factors and either enhancing or inhibiting their binding to DNA (transactivation and transrepression, respectively). A range of synthetic PPAR γ and PPAR α ligands have been demonstrated to inhibit phorbol ester-stimulated cytokine production by monocytic cells [34] and studies using PPAR α knockout mice have demonstrated prolonged inflammatory responses [35], suggesting that PPARs could be anti-inflammatory. PPAR α is the predominant isoform expressed in murine T and B lymphocytes, whereas PPAR γ dominates in myeloid cells [36]. Following activation of T cells, PPAR α expression is decreased, whereas PPAR γ expression is increased [36]. PPAR γ ligands have been reported to decrease the production of interferon- γ (IFN- γ and interleukin-2 (IL-2) by mitogen-activated splenocytes [37], inhibit proliferation of human T cells [38,39] and promote apoptosis in murine helper T-cell clones [38].

There has been increasing interest in the role of PPARs in atherogenesis because synthetic PPAR α and PPAR γ agonists appear to downregulate inflammatory responses in endothelial cells and leukocytes (reviewed in Ref. [40]). PPAR γ agonists also induce the expression of the scavenger receptor, CD36, on monocyte-derived macrophages, promoting lipid uptake [41,42]. This was initially interpreted as a pro-atherogenic effect and it was proposed that the natural ligand for PPAR γ was a lipid component of oxidized low-density lipoprotein (oxLDL). However, more recent work suggests that PPAR γ agonists simultaneously induce the expression of proteins involved in cholesterol efflux, with the net effect that cholesterol does not accumulate in macrophages and foam cells are thus not formed [43]. It is now suggested, therefore, that PPAR γ is atheroprotective because it promotes reverse cholesterol transport as a result of its effects in macrophages [40,44,45]. Interestingly, a recent study demonstrates that phospholipid components of oxLDL promote lipid body formation in macrophages and indirect evidence suggests that the induction of lipid body formation by these components could involve activation of PPAR γ [46].

To date, most of the research examining the biological effects of PPARs has used synthetic agonists at concentrations significantly higher than their Kds for binding to PPARs. The reliance on synthetic activators of PPARs has meant that there is still little information about the physiological roles of the natural ligands of these transcription factors. It is often assumed that because some fatty acids and their metabolites (which include eicosanoids and lipid peroxides) have been demonstrated to act as PPAR ligands in competitive binding and/or reporter assays, they must act as natural ligands. This has led to considerable speculation regarding the potential for specific classes of fatty acids (particularly the n-3 PUFAs) and their derivatives (eicosanoids and lipid peroxides) to

mediate effects on cell function through PPARs. However, there appears to be no distinction in the binding affinity and/or activating capacity between the n-3 and the n-6 PUFAs and no relationship with chain length or the number of double bonds [47–52]. Thus, there is a lack of plausible evidence to support the idea that any particular class of fatty acids has a superior capacity to act as ligands for PPARs in the immune system *in vivo*. However, it has been suggested that fatty acid-binding proteins are able to interact physically with both PPAR α and PPAR γ to direct ligands to their responsive genes, in what has been described as a ‘cytosolic gateway’ [52,53]. If this were the case, it would represent an elegant mechanism by which cellular fatty acids could be directed to interact with a target gene. The potential roles of fatty acids as gatekeepers of immune cell regulation are summarized in Figure 3.

Modification of cellular lipid domains by dietary fatty acids

Ingestion of arachidonic acid in the diet is low and most tissue arachidonic acid is in fact derived from dietary linoleic acid. Several factors favour the partitioning of arachidonic acid to tissue phospholipids, ensuring selective retention of arachidonic acid in cellular phospholipids [54]. However, it is important to realize that the n-3 series of PUFAs, particularly DHA, are also preferentially incorporated into certain phospholipid species and, potentially, into specific cellular lipid pools. Because the n-6 and n-3 PUFAs compete for the same metabolic, transport and acylation pathways, the composition of phospholipid species and cellular lipid pools reflects alterations in dietary intakes of these fatty acids to some degree. Moderate fluctuations in dietary arachidonic acid or its precursor, linoleic acid, have little impact on immune function [55–57]. However, consumption of the long chain n-3 PUFA, EPA and DHA has been demonstrated to alter the composition of phospholipid species [58,59], the composition of lipid rafts [25], eicosanoid production [58,59] and leukocyte function [56–60], although the doses required to achieve this are rather higher than would be considered acceptable in a western diet. These observations have given rise to the suggestion that n-3 PUFAs have anti-inflammatory actions and could be useful in inflammatory conditions, such as rheumatoid arthritis (reviewed in Ref. [61]). The effects of n-3 PUFAs on eicosanoid production are perhaps the most potent because EPA both inhibits the production of arachidonic acid-derived eicosanoids and acts as a precursor for the synthesis of distinct eicosanoids, whose potency and/or actions might be different [58–60]. However, this is not always the case because prostaglandins E1, E2 and E3 (derived from dihomog- γ -linolenic acid, arachidonic acid and EPA, respectively) are equipotent in their inhibition of production of Th1 cytokines by human lymphocytes [62].

Lipids and host defense

If some classes of fatty acid possess immunosuppressive properties, it is reasonable to suggest that they might impair host resistance to infection and therefore have undesirable effects. This issue has been subject to controversy. Studies conducted in animals, investigating the

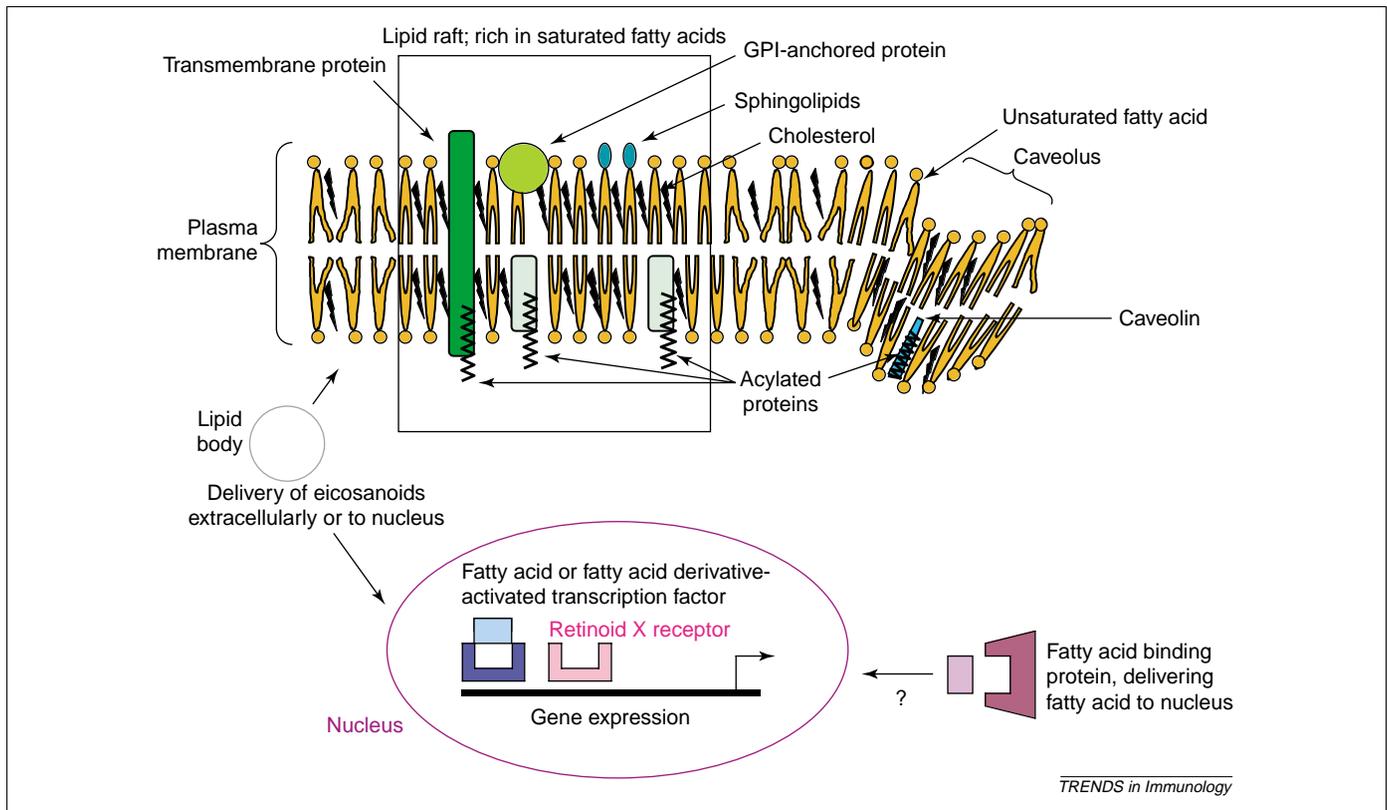


Figure 3. Fatty acids as gatekeepers in cell regulation. Fatty acids have important roles in the stability of lipid rafts and caveolae, in the acylation of key membrane proteins involved in cell regulation and in the delivery of fatty acid-derived signals to target locations within cells. Some of the postulated pathways of fatty acid trafficking within cells, which are discussed in this review, are illustrated. The structure and composition of lipid bodies are as yet undefined and although they are suggested to be associated with cyclooxygenase and lipoxygenase, the location of these proteins in relation to lipid bodies is not clear. Abbreviation: GPI, glycosylphosphatidylinositol-anchored.

influence of dietary fatty acids on host survival and/or pathogen clearance in animals challenged with a live infectious agent are inconclusive, some showing that n-3 PUFAs improve host defense and others showing impairment [63]. A recent study has provided a novel perspective on the mechanisms by which fatty acids could influence host defense. Anes *et al.* [64] demonstrated that several lipids normally present in cells (including arachidonic acid, ceramide and sphingosine) stimulate actin nucleation around phagosomes and subsequent fusion of the phagosomes with late endocytic organelles in macrophages infected with pathogenic mycobacteria. This would suggest that the lipids tested could potentially enhance pathogen killing, a prediction that was verified by *in vitro* experiments [64]. However, the n-3 PUFAs, EPA and DHA inhibited actin assembly in an *in vitro* latex bead phagosome assay, which the authors suggest would be detrimental to host defense. Because lipid rafts are thought to represent favoured regions for actin nucleation [64], the mechanism might once again involve an influence of n-3 PUFAs on raft composition. However, the physiological importance of the data needs to be addressed and a direct examination of the influence of n-3 PUFAs on human infectious disease resistance is warranted.

Conclusion

This Review presents fatty acids as gatekeepers of immune cell regulation in the sense that their location and organization within cellular lipids have a direct influence on

the behaviour of several proteins involved in immune cell activation. It does not attempt to be exhaustive but to provide specific examples of fatty acids acting as facilitators of immune responses in several cell types. It is proposed that modification of the fatty acid composition of lipid domains, and in particular, replacement of n-6 PUFA by n-3 PUFA, could alter immune cell activation. Although the composition of lipid domains within cells of the immune system can be modified through diet, the functional implications of such modifications are unclear (Box 1).

Box 1. Outstanding questions

- Is modulation of lipid raft composition and displacement of raft proteins by polyunsaturated fatty acids (PUFAs) a physiological phenomenon?
- What controls intracellular trafficking of lipids in lipid bodies?
- To what extent can cellular pools of fatty acids be modified by dietary intake of PUFAs and can this impact on immune function?
- Can different classes of diet-derived fatty acids alter an immune response through differential modulation of peroxisome proliferator-activated receptors (PPARs)?
- If n-3 PUFAs inhibit immune responses, could they impair host defense?

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