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Review

Arachidonic acid and other unsaturated fatty acids and some of their metabolites function as endogenous antimicrobial molecules: A review

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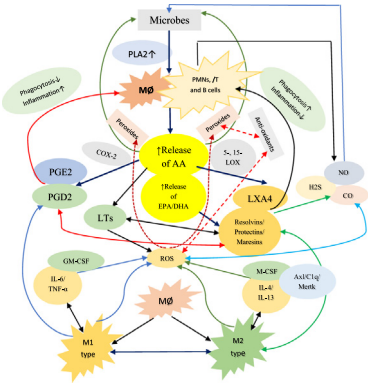
GRAPHICAL ABSTRACT



Scheme showing relationship among M1 and M2 macrophages, cytokines, bioactive lipids, eicosanoids and ROS.

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ABSTRACT

Our body is endowed with several endogenous anti-microbial compounds such as interferon, cytokines, free radicals, etc. However, little attention has been paid to the possibility that lipids could function as antimicrobial compounds. In this short review, the antimicrobial actions of various polyunsaturated fatty acids (PUFAs, mainly free acids) and their putative mechanisms of action are described. In general, PUFAs kill microbes by their direct action on microbial cell membranes, enhancing generation of free radicals, augmenting the formation of lipid peroxides that are cytotoxic, and by increasing the formation of their bioactive metabolites, such as prostaglandins, lipoxins, resolvins, protectins and maresins that enhance the phagocytic action of leukocytes and macrophages. Higher intakes of α-linolenic and cis-linoleic acids (ALA and LA respectively) and fish (a rich source of eicosapentaenoic acid and docosahexaenoic acid) might reduce the risk pneumonia. Previously, it was suggested that polyunsaturated fatty acids (PUFAs): linoleic, α-linolenic, γ-linolenic (GLA), dihomo-GLA (DGLA), arachidonic (AA), eicosapentaenoic (EPA), and docosahexaenoic acids (DHA) function as endogenous anti-bacterial, anti-fungal, anti-viral, anti-parasitic, and immunomodulating agents. A variety of bacteria are sensitive to the growth inhibitory actions of LA and ALA *in vitro*. Hydrolyzed linseed oil can kill methicillin-resistant *Staphylococcus aureus*. Both LA and AA have the ability to inactivate herpes, influenza, Sendai, and Sindbis virus within minutes of contact. AA, EPA, and DHA induce death of *Plasmodium falciparum* both *in vitro* and *in vivo*. Prostaglandin E1 (PGE1) and prostaglandin A (PGA), derived from DGLA, AA, and EPA inhibit viral

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replication and show anti-viral activity. Oral mucosa, epidermal cells, lymphocytes and macrophages contain and release significant amounts of PUFAs on stimulation. PUFAs stimulate NADPH-dependent superoxide production by macrophages, neutrophils and lymphocytes to kill the invading microorganisms. Cytokines induce the release of PUFAs from cell membrane lipid pool, a potential mechanism for their antimicrobial action. AA, EPA, and DHA give rise to lipoxins (LXs), resolvins, protectins, and maresins that limit and resolve inflammation and have antimicrobial actions. Thus, PUFAs and their metabolites have broad antimicrobial actions.

Introduction

It is evident that our body is constantly exposed to various pathogenic organisms and so our tissues need to be endowed with antimicrobial molecules to protect and ward off these exogenous potentially hazardous organisms. Some of these endogenous antimicrobial compounds include: interferon, cytokines, free radicals, etc., that are also yet times have harmful actions on various tissues. For instance, cytokines when produced in excess may cause tissue damage and sepsis. But relatively little attention is paid to the observation that certain lipids could have antimicrobial actions and thus, may serve as endogenous antibiotic-like actions. The importance of these antimicrobial lipids lies in the fact that they are present in all tissues of the body.

It is known that *Staphylococcus aureus* and coagulase-negative staphylococci, group A streptococci are present on normal human skin but do not cause any infection that could be attributed to the susceptibility of these bacteria to the action of skin surface lipids, especially unsaturated fatty acids. This is supported by the observation that group A streptococcus exposed to oleic acid (OA, 18:1n-9) showed decreased survival within 5 min of exposure showing condensation of the nucleoid and distortion of the streptococcal surface by numerous clumps and blebs indicating the ability of this fatty acid to alter the integrity of the cell membrane with loss of ribonucleic acid but not DNA [1]. M protein, located on the surface fimbriae of group A streptococci, is antiphagocytic in nature. Hence, the M− but not the M+ streptococci are not well phagocytized. On the other hand, oleic acid-killed and heat-killed streptococci (both M+ and M−) were readily phagocytized, while M+ streptococci killed by ultraviolet irradiation were inefficiently phagocytized. An extract of M protein reduced the bactericidal capacity of oleic acid, indicating that oleic acid may bind to and alter the M protein of group A streptococci and thus, enhance phagocytosis [2]. In addition, oleic acid enriched mouse peritoneal macrophages showed 3–4-fold greater erythrophagocytic capacity compared to palmitic acid-enriched macrophages [3].

Macrophage AA has antimicrobial actions

Our lungs are constantly exposed to various viruses, bacteria and fungal elements through inhaled air. Hence, efficient mechanisms are needed to protect lungs from various infections. For this purpose, alveolar macrophages need to have efficient mechanism of inducing antimicrobial action. It is known that Staphylococci in the alveoli are killed predominantly by macrophages [4–7]. Paradoxically, alveolar macrophages have poor chemotactic and phagocytic ability compared with peritoneal macrophages [8–10] and have weak intracellular killing activity *in vitro* [11,12]. Studies evaluating intraalveolar killing of staphylococci by use of a bronchoalveolar lavage technique revealed that inhaled staphylococci are killed mainly outside alveolar macrophages. Further studies in search of these extracellular bactericidal factors for pneumococci revealed that the surfactant fraction (55,000-g pellet) of leukocyte-free lavage of rats and other animal species contain heat and trypsin resistant factors that are rapidly bactericidal and lytic for pneumococci *in vitro* [12] and complete characterization of these extracellular bactericidal activity was found to reside in the surfactant lipids that can be stored at −70 °C in chloroform and stable indefinitely. The most anti-pneumococcal activity was found to reside in the most highly unsaturated acid namely arachidonic acid (AA, 20:4n-6). Other unsaturated fatty acids: linoleic, oleic, and palmitoleic also showed anti-bacterial activity but were less potent compared to AA. AA was found to be active against gram-positive and gram-negative bacteria [13–17], fungi [18,19], and enveloped viruses, including influenza [20–22]. The ability of unsaturated fatty acids including AA is further supported by the observation that polyunsaturated free fatty acids and lysolecithin in the small intestine of pigs can prevent proliferation of *Clostridium welchii* [23]. Human fecal lipids contain a mixture of long chain free fatty acids such as C16:0, C I8:1, C18:2, and C 20 or more, which are bactericidal for gonococci [24]. The mechanism of the antimicrobial action of AA seems to be by inducing leakage and even lysis of bacterial cell membranes [25,26] as well as various cellular metabolic effects, including but not limited to inhibition of respiratory activity, effects on transportation of amino acids, and uncoupling of oxidative phosphorylation [27–30].

These results suggest that alveolar macrophages release AA and other unsaturated fatty acids into the alveolar fluid that, in turn, exert their antimicrobial action and thus, protect lungs from various infective organisms. There is no reason to believe that this is not so even with macrophages in other body cavities and organs. Extending this argument further, it is reasonable to propose that even leukocytes including macrophage-like cells in various organs, T and B lymphocytes (in addition to their adaptive immune response) under some well-defined conditions may release unsaturated fatty acids to bring about their antimicrobial actions to protect from various infections. This could be one of the fundamental mechanisms employed by human body to protect itself from the onslaught of various microbes. It is noteworthy that even HIV could be inactivated by unsaturated fatty acids especially, AA [31].

Fatty acids can damage plasma membranes and thus, bring about their lethal effects on phytoplankton: chlorophytes (*Chlorella vulgaris Beij* and *Monoraphidium contortum* (Thur.) Kom.-Legn.) and a cyanobacterium *(Anabaena* P-9). When these organisms were treated with fatty acids, an elevation of extracellular potassium (K+) was detected in the culture medium, indicating leakage of intracellular K+ because of damage to the plasma membranes [32].

Phospholipase A(2) is an endogenous antibiotic

Type-IIA secreted phospholipase A(2) (sPLA(2)-IIA) releases AA from the cell membrane phospholipids. This implies that sPLA (2)-IIA could serve as a potent bactericidal protein. This enzyme is present in animal and human biological fluids at concentrations sufficient to kill bacteria. In fact, human recombinant sPLA(2)-IIA-induced release of PUFAs can kill Gram-positive bacteria at concentrations as low as 1.1 ng/ml. This property is ascribed to the preference of sPLA(2)-IIA for anionic phospholipids such as

phosphatidylglycerol, one of the main phospholipid component of bacterial membranes on which it acts. On the other hand, much higher concentrations of sPLA(2)-IIA are required for its action on host cell membranes and surfactant both of which are predominantly composed of phosphatidylcholine, a poor substrate for sPLA(2)-IIA. This is supported by the observation that transgenic mice over-expressing human sPLA(2)-IIA are resistant to infection by *Staphylococcus aureus, Escherichia coli*, and *Bacillus anthracis*. It is noteworthy that *B. anthracis, E. coli* and *Bordetella pertussis* inhibit sPLA(2)-IIA expression by host cells, and thus, are capable of subverting the host immune system. Intranasal administration of recombinant sPLA(2)-IIA protects mice from mortality due to pulmonary anthrax even with *B. anthracis* strains that have the ability to down-regulate the expression of endogenous sPLA(2)-IIA. These results imply that instilled sPLA(2)-IIA can successfully overcome the subversive action of *B. anthracis* [33–36]. Based on these results, it can be suggested that sPLA(2)-IIA functions as an efficient endogenous antibiotic of the host and has a significant role in host defense against pathogenic bacteria by releasing AA from the host cell membrane and one mechanism by which majority of the antibiotic-resistant bacteria function is by inactivating/-downregulating the expression of sPLA(2)-IIA enzyme [34–37].

In this context, it is noteworthy that inhibition of cyclooxygenase (COX)-derived prostaglandins (PGs) by nonsteroidal anti-inflammatory drugs (NSAIDs) mediates leukocyte killing of bacteria that may, in part, be ascribed to accumulation of PG precursors namely PUFAs especially AA. COX1 is the predominant isoform active in PG synthesis during infection and its prophylactic or therapeutic inhibition primes leukocytes to kill bacteria by enhancing phagocytic uptake and reactive oxygen intermediate-mediated killing in a cyclic adenosine monophosphate (cAMP)-dependent manner. NSAIDs enhance bacterial killing, exerting an additive effect when used in combination with antibiotics. NSAIDs, through the inhibition of COX, prime the innate immune system to mediate bacterial clearance of penicillin-resistant *Streptococcus pneumoniae* [38]. It is likely that COX1 activity leads to an increase in intracellular concentration of AA and other unsaturated fatty acids and thus, bring about their anti-bacterial action emphasizing the significant actions of lipid mediators in host defense against infections.

PGs, LXA4/resolvins/protectins/maresins, and LTs modulate macrophage phenotype and function

Macrophages are important in defense against infectious agents. Macrophages kill microbes, and clear pathogens, dead cells, debris and play an important role in tissue repair. Macrophages adopt initially an inflammatory phenotype, which enables them to clear debris and bacteria. Subsequently, macrophages change their phenotype and produce anti-inflammatory cytokines and bioactive lipids to dampen inflammation [39]. In this process there is a close interaction among cytokines, bioactive lipids and M1 and M2 macrophages.

AA is acted upon by COX and LOX (lipoxygenase) enzymes to form various prostaglandins (PGs), leukotrienes (LTs) and thromboxanes (TXs) that are considered predominantly as pro-inflammatory molecules [40–43]. Since these metabolites of AA have many actions, it is reasonable to propose that they could also have a modulatory role in macrophage phagocytosis.

It was reported that bovine oviduct epithelial cells (BOECs) regulate phagocytic activity of PMNs (polymorphonuclear leukocytes) for sperm and that this action is modulated by PGE2. The BOEC supernatant showed significant suppressive action on sperm phagocytosis by PMNs, and the (luteinizing hormone) LH-stimulated BOEC supernatant further suppressed phagocytosis. It was noted that LH stimulated the secretion of PGE2 that, in turn, suppressed sperm phagocytosis by PMNs. These results support that PGE2 suppress the phagocytic activity of PMNs [44]. It was also reported that PGE2 alters the expression of scavenger receptor and miR-155 expression to account for alterations in the phagocytosis capacity of alveolar macrophages [45]. In addition, PGE2 inhibited H_2O_2 production and thus, inhibited bacterial killing by alveolar macrophages [46]. These actions of PGE2 on phagocytic capacity of PMNs and macrophages explains to a certain extent its (PGE2) immunosuppressive actions. In contrast to this, the anti-inflammatory metabolites of AA and EPA and DHA: lipoxins, resolvins, protectins, and maresins enhance human macrophage efferocytosis and bacterial phagocytosis, increased neutrophil bacterial phagocytosis and intracellular reactive oxygen species (ROS) generation, and reduced human platelet-PMN aggregation. These results imply that pro- and anti-inflammatory metabolites of AA/EPA/DHA have opposite actions on PMNs and macrophage functions and thus, modulate immunoresolvent actions in host defense, host protection and antimicrobial defense [47–49]. In this context, it is interesting to note that both IL-10 and PGE2 augment the production of anti-inflammatory resolvins and possibly, lipoxin A4 (LXA4), protectins and maresins [50–58]. These results indicate that there is a need for the presence of adequate amounts of PGE2 to trigger the production of LXA4, resolvins, protectins, and maresins to initiate and sustain resolution of inflammation. In other words, it implies that inflammation should reach sufficient degree of severity to trigger resolution process. Based on these evidences, it is tempting to propose that though PGE2 has been dubbed as a pro-inflammatory molecule, it has both pro- and anti-inflammatory actions. Initially, PGE2 probably triggers inflammatory process and once the concentrations of PGE2 reach sufficient degree and the inflammatory process is at its optimal levels, it initiates the anti-inflammatory process by augmenting the synthesis of anti-inflammatory bioactive lipids such as LXA4/resolvins/protectins/maresins. In this process, IL-10 seems to have a crucial role by itself triggering the synthesis of LXA4/resolvins/protectins/maresins. This positive and negative freed-back control between pro- and anti-inflammatory molecules and processes is needed to maintain normal tissue homeostasis (see Fig. 1). Based on these results [47–58], it is reasonable to assume that in critically ill patients such as those suffering from sepsis-recovery or succumbing to disease depends on the ability of tissues to produce adequate amounts of LXA4/resolvins/protectins/maresins at the right time to resolve inflammation and initiate tissue repair. It is also likely that inappropriate production of LXA4/resolvins/protec tins/maresins at inappropriate time such as in the beginning of sepsis process may suppress much needed inflammation and lead to worsening of the illness [59–62]. Thus, production of adequate amounts of PGE2/LTs and other pro-inflammatory molecules including ILs, TNF-α and anti-inflammatory molecules (lipoxins/resolvins/protectins/maresins/IL-4, IL-10/IL-13) at the most appropriate times of any illness are critical that ultimately determines recovery or death. Studies have demonstrated that both PGD2 and PGJ2 have actions like PGE2 [63–67]. In this interaction between cytokines and eicosanoids, there is a critical role for nitric oxide (NO, produced by vascular endothelial cells, monocytes, macrophages, and neutrophils and several other cells as well), carbon monoxide (CO, is an activator of guanylyl cyclase, is formed by the action of the enzyme heme oxygenase that is present throughout the brain and like NO is a physiologic regulator of cGMP and may function as a neurotransmitter.) and hydrogen sulfide (H2S, produced mainly by vascular endothelial cells, neurons and macrophages) as well [55,56,65–67] (see Fig. 1).

Leukotrienes (LTs) are released during inflammation and play a role in innate immunity. Cys-LTs (Cysteinyl leukotrienes) enhance FcgammaR-mediated phagocytosis by alveolar macrophages.

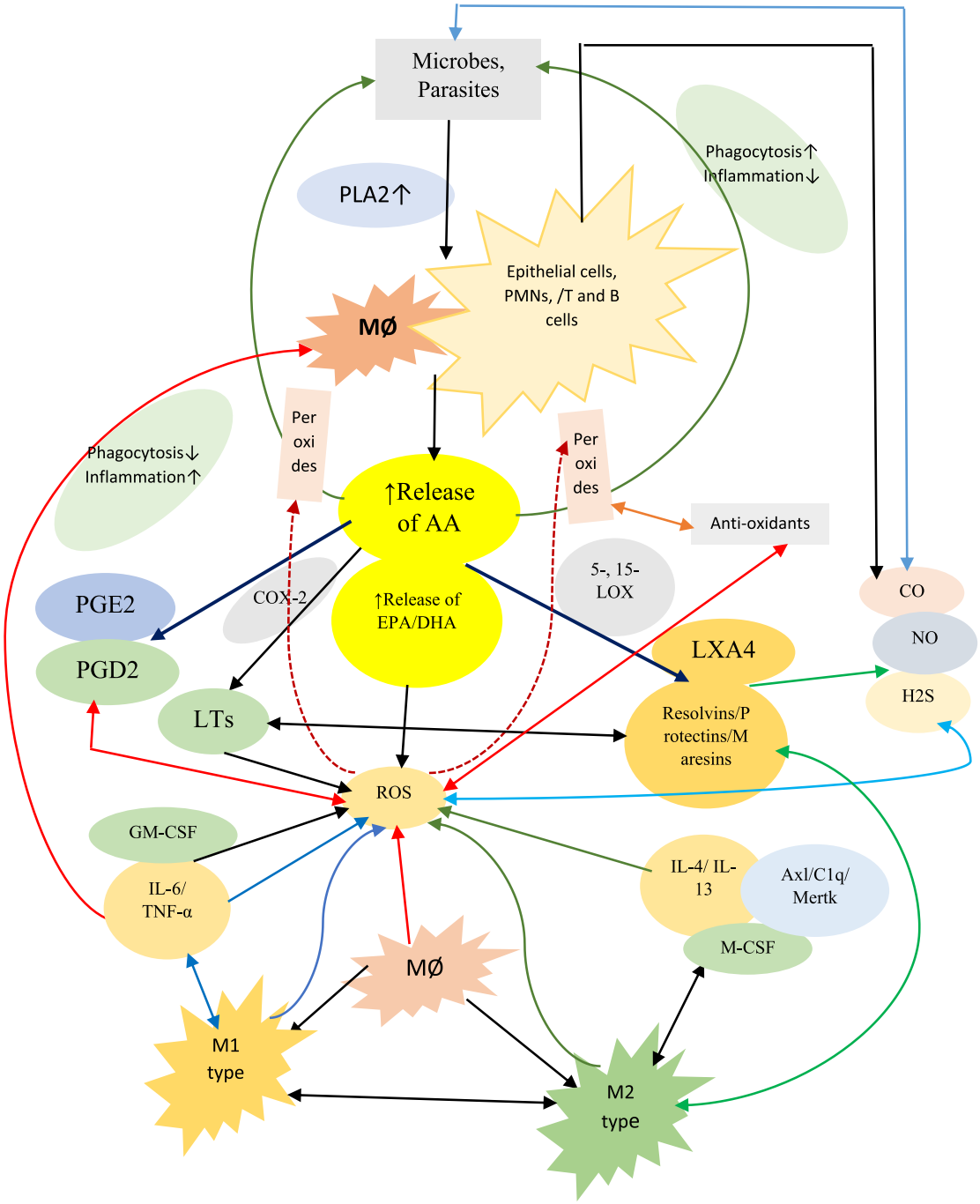

Fig. 1. Scheme showing possible relationship among M1 and M2 macrophages, cytokines, bioactive lipids, eicosanoids and ROS. Microbes = Bacteria, viruses, fungi, parasites (such as malaria, schistosomiasis), etc. —— Black lines indicate normal physiological process. —— Red lines indicate inflammatory events or molecules involved in inflammation or inflammation related events such as formation of lipid peroxides that have antimicrobial action. —— Green lines indicate anti-inflammatory events or molecules. —— Indicates interaction among ROS and NO, CO and H2S. —— Blue lines indicate interaction among pro-inflammatory cytokines, ROS and M1 macrophages. PGD2 is known to have both pro- and anti-inflammatory actions (though predominantly anti-inflammatory actions). Since both PGE2 and PGD2 are derived from the precursor PGH2, suggesting that, perhaps, there is a balance maintained between PGE2 and PGD2. PGI2 (not shown in the figure) is also derived from PGH2 that also has anti-inflammatory actions. When microorganisms invade the tissues, they are first encountered by PMNs and macrophages that leads to activation of PLA2 of the cell membrane. Consequently, PUFAs, especially AA/EPA/DHA; are released that are utilized for the formation of PGs, LTs, TXs (that have pro-inflammatory actions) and lipoxins/resolvins/protectins/maresins that have anti-inflammatory actions. In the initial stages, macrophages (M1 type) release IL-6 and TNF-α and PGE2 and LTs to initiate inflammation and eliminate the invading organisms by a mechanism that is dependent on generation of reactive oxygen species (ROS). Once inflammation reaches an optimal level, PGE2/PGD2/PGJ2 activate PLA2 for the release of second wave of AA/EPA/DHA that leads to the formation of anti-inflammatory lipoxins/resolvins/protectins/maresins and convert M1 to M2 macrophages by the release of IL-4, IL-10, IL-12 and IL-13. Macrophages when ingest dead PMNs (efferocytosis) they are triggered to become M2 macrophages due to the release of IL-4/IL-13 and exposure to Axl, C1q and Mertk and formation of lipoxins/resolvins/protectins/maresins that further enhances phagocytosis of M2 macrophages and kills ingested microorganisms and initiates resolution of inflammation and enhances wound healing. The exact initial source of these anti-inflammatory cytokines and bioactive lipids is not clear but may include local tissues involved in inflammation, PMNs and macrophages. It is known that ROS generated by PMNs and macrophages act on AA/EPA/DHA and lead to the formation of respective lipid peroxides that show antimicrobial action. These results also emphasize the close interaction among PMNs, macrophages, T cells, local tissues/cells and invading organisms. This delicate balance between pro- *vs* anti-inflammatory cytokines and lipids and M1 *vs* M2 macrophages and ROS *vs* anti-oxidants is essential to maintain tissue homeostasis and restore physiology to normal. For more details see text.

Studies showed that challenged alveolar macrophages have a markedly increased phagocytic capacity and enhanced killing of *Klebsiella pneumoniae* compared to controls [68,69]. There is evidence to suggest that LTs and LXA4/resolvins/protectins/maresins interact with each other and regulate inflammation, phagocytosis and macrophage function [55–57]. For instance, LXA4 can suppress the production of LTs and thus, antagonize its pro-inflammatory action [70,71]. It is likely that resolvins, protectins and maresins may have similar action on LTs [55–57]. This is supported by the observation that human monocytes that can be induced to differentiate toward M1 or M2 phenotype by granulocyte Mϕ colony-stimulating factor (GM-CSF) or Mϕ colony-stimulating factor (M-CSF) respectively produced under resting conditions (both Mϕ phenotypes) released PGE2, LXA4, and 18-hydroxyeicosapentaenoic acid. However, GM-CSF and M-CSF Mϕs displayed different eicosanoids upon bacterial stimuli with M2 Mϕs producing predominantly LTC4 [72]. In a similar fashion, rat alveolar macrophages treated with GM-CSF for 24 h significantly increased the synthesis of immunoreactive LTB4 upon subsequent stimulation with calcium ionophore accompanied by increased phospholipase A2 (PLA2) activity. GM-CSF primed alveolar macrophages for enhanced generation of LTB4, as well as the 5-lipoxygenase products LTC, and 5-HETE [73]. These results emphasize the possibility that the balance between pro-inflammatory LTs and PGs and anti-inflammatory lipoxins/resolvins/protectins/maresins [74–76] and this shift in eicosanoid metabolism seems to influence NO/CO/H2S generation that aids in the acceleration of resolution of inflammation, tissue regeneration and reduction in pain [77–79].

Though it is not clear how exactly this shift in the balance between M1 and M2 macrophages is triggered and what factors influence this shift, there is evidence to suggest that when activated by IL-4/IL-13, macrophages produce collagen type 1, alpha 1 (Colta1), and resistin-like molecule alpha (RELMα/FIZZ), which form the extracellular matrix and cross-link collagen with fibrils respectively to provide strength or stiffness to the tissues. IL-4 macrophages also produce arginase-1, which metabolizes arginine to urea and ornithine, a pathway that generates L-proline that is needed for collagen synthesis, and polyamines, which enhance cellular proliferation during wound healing [80]. Thus, IL-4/IL-13 signaling through the type 1 receptor {IL-4 receptor alpha (IL-4Rα) and IL-13Rα1 and/or common gamma chain} seem to represent a common mechanism by which macrophages balance inflammation resolution and tissue repair. It is noteworthy that in instances such as helminth infection IL-4/IL-13-stimulated macrophages cannot initiate tissue-repair process unless they (macrophages) first sense the presence of apoptotic neutrophils. The recognition and apoptosis of neutrophils by macrophages-a process called as efferocytosis-triggers macrophages to produce anti-inflammatory cytokines: IL-4/IL-13 and synthesis and release of lipoxins/resolvins/protectins/maresins [74,75]. These efferocytosis receptors, AXL receptor tyrosine kinase (Axl) and c-mer protooncogene tyrosine kinase (Mertk) promote IL-4/IL-13-triggered tissue repair. Lung surfactant protein A (SP-A) can trigger efferocytosis and C1q, a component of the complement pathway, showed a unique ability to activate macrophages and increases the expression of Mertk [39,81,82]. Based on these evidences, it is tempting to propose that Axl, C1q and Mertk can enhance synthesis, release and actions of lipoxins/resolvins/protectins/maresins and thus, initiate the conversion of M1 to M2 macrophages and enhance repair process (see Fig. 1). This unique protein-lipid interaction is interesting but needs further evaluation. Since lipoxins/resolvins/protectins/maresins not only enhance M2 macrophage formation, macrophage phagocytosis, efferocytosis but also kill intracellular pathogens [53], it is likely that these bioactive lipids function as anti-microbial molecules.

Pufas have anti-bacterial action

The anti-bacterial activity of PUFAs against Staphylococci, streptococci, Mycobacteria, Helicobacter, Bacilli, enveloped viruses and fungi is well known [83,84]. Unsaturated fatty acids function as the key ingredients of antimicrobial food additives which inhibit the growth of unwanted microorganisms [85]. Both linoleic and oleic acids form an important antibacterial component in the herbs (*Helichrysum pedunculatum* and *Schotia brachypetala*) used for dressing wounds in South Africa [86,87]. Even fatty acid derivatives also showed potent antimicrobial activities that are found in microorganisms, algae, or plants, which may mediate chemical defense against microorganisms [88–92]. Thus, linolenic acid can rapidly kill *Staphylococcus aureus* which implies that naturally occurring free fatty acids may have a therapeutic role. McDonald and colleagues [92] showed that hydrolysed linseed oil, which contains 52% linolenic acid, and pure linolenic acid can inactivate methicillin-resistant *S. aureus*. Accumulation of antimicrobial stress metabolites in potato tubers due to mycelial extracts from *Phytophthora infestans* contains EPA and AA. These fatty acids are present in either free or esterified form in all the active fractions of these mycelial extracts. The wound hormone traumatin found in these plants is an oxidation product of linoleic or linolenic acid [93,94]. These findings suggest that, in potato tubers, animals and humans, fungitoxic compounds could be EPA and AA [83]. Kohn and coworkers showed that LA and AA can inactivate animal herpes, influenza, Sendai and Sindbis viruses within minutes of contact [95]. Human lymphocytes contain large amounts of esterified AA (and possibly, EPA and DHA and other PUFAs) that can be released with appropriate stimulation, one of which could be cell membrane perturbation due to invading microorganisms. These released PUFAs may be used in the body to inactivate viruses and to stimulate PMNs, macrophages and T cells to produce other antimicrobial substances such as lipid peroxides, PGs, LTs, lipoxins, resolvins, protectins and maresins production (see Fig. 1). Thus, it is likely that PUFAs such as LA, GLA, DGLA, AA, ALA, EPA, DHA and their metabolites have antibacterial, antifungal, antiviral and immunomodulatory actions [53,54,59,60,83,84,96,97].

In the year 1940, it was reported by Stok and Francis [98] that an unsaturated fatty acid oleic acid, 18:1, n-9 can inactivate influenza type A virions. Subsequently, it was shown that unsaturated long-chain alcohols and monoglycerides exhibit high potent virucidal effects against HSV, HCV and bacteriophages ϕp6 and PM2 [95,99–101,31,102]. In this context, it is interesting to note that Schlager and associates demonstrated that mice peritoneal macrophages can be activated by linolenic acid (possibly, GLA) and that linolenic-acid-enriched macrophages are highly tumoricidal [103,104]. They also proved that lymphokine activation of macrophages is due to an increase in their linolenic acid content compared to control values.

AA and other PUFAs are cytotoxic to malaria and schistosomiasis parasites

PUFAs have been shown to have antimalarial effect. C18 fatty acids, such as oleic, elaidic, linoleic, and linoleic acids inhibited proliferation of malarial parasites in mice infected with *Plasmodium vinckei petteri* or with *Plasmodium yoelii nigeriensis*. *In vitro* studies revealed that C18 fatty acids can inhibit the growth of *Plasmodium falciparum*. The cytotoxic effect of the fatty acids is rather rapid and completely inhibited nucleic acids and protein syntheses in less than 30 min. Treatment of malarial parasite with fatty acids did not show any effect on the lipid peroxidation, ATP levels, transport through the parasite-induced permeability pathways, or on

the phagocytosis of the infected cells and do not act at the mitochondrial level of pyrimidine synthesis [105].

In another study, Taylor et al. [106] showed that n-3 fatty acids (rich in EPA and DHA) but deficient in vitamin E when fed to mice (*nu/nu* mice that do not develop anti-malarial antibody) developed controlled parasitemia whereas those fed vitamin E containing diets quickly died. These and other studies (including studies done with *scid/scid.bg/bg* mice that lack B cells and *ab* and *gd* T cells and have reduced NK cell activity) suggest that under pro-oxidant dietary conditions mice and possibly, humans can control and even survive malaria even in the absence of malaria-primed T cells and anti-malarial antibody [107–114]. These studies [105–114] indicate the importance of cellular oxidative processes against parasite infections. These results are supported by other studies which showed that infections due to Leishmania, Trypanosoma and Schistosoma parasites can be treated successfully with PUFAs including AA both in experimental animals and humans [115–124]. AA seem to have the ability to stimulate the parasite tegument-bound neutral sphingomyelinase that renders hydrolysis of the apical lipid bilayer sphingomyelin molecules, allowing access of specific antibody molecules, and eventual worm attrition [116]. This concept can be extended to the tumoricidal action of AA and other PUFAs.

Neutral sphingomyelinase (SMase) is a hydrolase enzyme that has an important role in sphingolipid metabolism reactions. SMase is a member of the DNase I superfamily of enzymes and has the ability to break sphingomyelin (SM) down into phosphocholine and ceramide. The activation of SMase is a major route to control ceramide in response to cellular stresses. Robinson et al. [125] showed that AA stimulates SMase activity of leukocytes in a dose dependent fashion. In addition, they also showed that other PUFAs such as DHA, EPA, OA (oleic acid) and LA can also activate SMase. However, methyl ester of AA, 15-HPETE and 15-HETE and saturated fatty acids did not show any effect on SMase activity. By its action on SMase, AA enhanced ceramide formation in cells, which is known to have tumoricidal action [126,127]. In this context, it is interesting to note that altered SMase activity drives immune evasion and facilitates tumor growth and thus, PUFAs by virtue of their ability to enhance SMase activity can induce significant enhancement of Th1-mediated and cytotoxic T-cell-mediated antitumor immunity, possibly by influencing synthesis and action of TNF-α and other cytokines and COX-2 expression [128–131]. Similar opinion was expressed by El-Ridi et al. [116] who showed that AA-mediated attrition of Schistosoma organisms is associated with high titers of serum antibodies to tegumental antigens and serum antibodies from AA administered hamsters readily bound to the surface membrane of AA-treated, but not untreated, adult worms [119]. Thus, there is a close and complex relationship among the anti-parasitic action of AA, neutral sphingomyelinase activity, ceramide formation, generation of pro-inflammatory cytokines, COX-2 activity and cell and humoral immune responses against

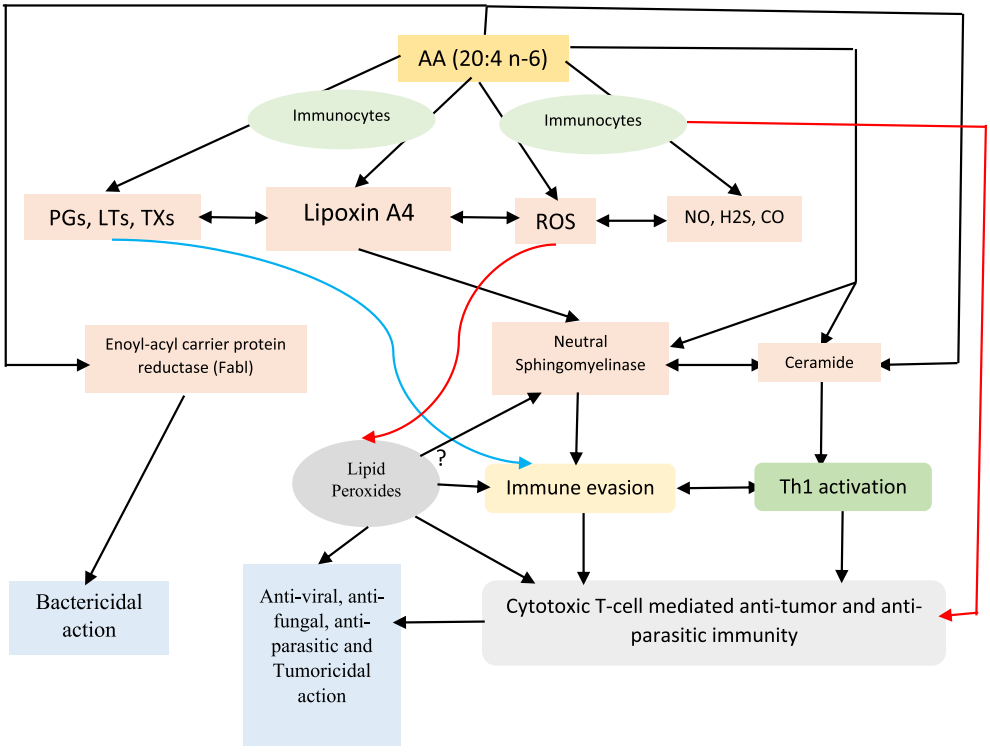

Fig. 2. Scheme showing possible mechanisms of anti-microbial and anti-cancer actions of AA. —— Black lines indicate normal physiological events. —— Red lines indicate pro-inflammatory events/molecules —— Indicate molecules involved in immune evasion/immunosuppression AA released from the cell membrane lipid pool by the action of phospholipase A2 (PLA2) can be acted upon by COX-2 to get converted into pro-inflammatory eicosanoids to produce inflammation seen in many microbial infections and also suppress immune response and aid in the growth of tumor cells. AA can induce generation of ROS in immunocytes (leukocytes, macrophages and T and B cells) that, in turn, act on AA to enhance formation of lipid peroxides that are toxic to microbes including viruses and fungi and intracellular parasites. AA can inhibit bacterial Enoyl-acyl carrier protein reductase (FabI) and thus, produce its bactericidal action. AA can enhance neutral sphingomyelinase activity that enhances ceramide formation, a tumoricidal molecule. It is likely that decreased neutral sphingomyelinase activity drives immune evasion and facilitates tumor growth and thus, PUFAs by virtue of their ability to enhance SMase activity can induce significant enhancement of Th1-mediated and cytotoxic T-cell-mediated antitumor immunity, and by virtue of their ability to enhance synthesis and action of TNF-α and other cytokines and COX-2 expression. In addition, AA can be converted to lipoxin A4, a potent anti-inflammatory and inflammation resolution molecule that can suppress COX-2 activity and inhibit production of pro-inflammatory prostaglandins, thromboxanes and leukotrienes; ROS and alter nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H2S) generation and thus, aid in the resolution of inflammation and enhance wound healing. Furthermore, LXA4 augments macrophage and PMNs phagocytic activity and thus, scavenge debris at the site of inflammation. It is not yet clear whether LXA4 and lipid peroxides can alter neutral sphingomyelinase activity. It is likely that activated macrophages release AA and corresponding lipid peroxides that, in turn may induce apoptosis of tumor cells. For further details see the text.

parasitic infections and cancer cells. Furthermore, PUFAs seem to inhibit bacterial enoyl-acyl carrier protein reductase (FabI), an essential component of bacterial fatty acid synthesis and thus, bring about their antibacterial action [132]. Thus, there are multiple mechanisms by which AA and other PUFAs bring about their anti-microbial and tumoricidal actions.

Conclusions and future perspectives

It is evident from the preceding discussion that AA and other PUFAs have significant anti-microbial actions on a variety of organisms including bacteria, viruses, fungi, and a variety of parasites. AA seems to possess the ability to enhance immune response (both cellular and humoral), modulate macrophage function (from M1 to M2), directly inhibit fatty acid synthesis that is critical for bacteria to survive, inactivate enveloped viruses (including HIV and HCV), and aid in inflammation resolution process by forming precursor to LXA4, an anti-inflammatory and proresolution molecule. It is also noteworthy that AA can activate macrophages and enhance their ability to generate free radicals that are critical to their anti-microbial or tumoricidal action [133–138]. It is possible that macrophages, T cells and other immunocytes deliver AA and other PUFAs to the target tissue to eliminate infections, disrupt cancer cell growth and aid in the healing of wounds by suppressing inflammation (see Fig. 2). Since AA can be given orally and has no significant side effects, it remains to be seen whether AA can be exploited as a potential therapeutic strategy in a variety of infections, prevention of cancer and to suppress inflammation in diseases such as lupus.

Despite the fact that AA and other unsaturated fatty acids possess antimicrobial action, it is not clear whether these effects are selective and have any actions on commensal bacteria and their supplementation with the diet may cause any deleterious shifts in the composition of intestinal microflora. Previous studies suggested that PUFAs in general are growth inhibitory to harmful bacteria but not to commensals [139–142]. These results emphasize that PUFAs are able to selectively enhance the growth of useful bacteria and, possibly, prevent the proliferation of harmful microbiota and imply that dietary supplementation of these fatty acids does not cause any deleterious effect on gut microflora. In this context, it is also important to note that certain short chain fatty acids such as lauric acid (C 12:0) and sapienic acid (C16:1Δ6) derived from sebaceous triglycerides have antimicrobial action and are found on the human skin. Long-chain bases (sphingosine, dihydrosphingosine and 6-hydroxysphingosine) are also potent antimicrobials normally present at the skin surface and may be part of the innate immune system of the skin [143]. Similarly, oral mucosal and salivary lipids (that are essentially sphingoid bases: sphingosine, dihydrosphingosine and phytosphingosine, and fatty acids: sapienic acid and lauric acid) exhibit potent antimicrobial activity against a variety of Gram-positive and Gram-negative bacteria [143–147]. Studies revealed that these oral and salivary compounds to bring about their antimicrobial action need the lipid structure and they produce ultrastructural damage to the bacterial plasma membrane. Further studies revealed that sapienic acid induces upregulation of a set of proteins unique to *P. gingivalis* stress response, including proteins important in fatty acid biosynthesis, metabolism and energy production, protein processing, cell adhesion and virulence. Thus, a variety of endogenous lipids present on mucosal surfaces function as mediators of innate immune response during the first encounter of our body to environmental microbes with skin and mucosal surfaces.

Based on the evidences presented above, it remains to be seen whether AA and other PUFAs and their metabolites such as lipoxins/resolvins/protectins/maresins and/or their stable synthetic analogues could be exploited as potential anti-microbial agents. It is possible that PUFAs and their metabolites may be used in combination with currently available traditional antibiotics to prevent and manage various infections. It is also likely that these bioactive lipids could be used to reverse/overcome antibiotic resistance that is assuming a major issue in fighting many infections. It is also possible that bioactive lipids may beneficial to overcome drug resistance shown by malaria and other parasitic infections as well. Such studies are the need of the hour.

Conflict of interest

The author has declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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