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Review/Opinion/Hypothesis

Bioactive lipids in psychiatry, immunology, neurology, and endocrinology (PINE)

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Abstract

There is substantial evidence to suggest that several psychiatric conditions (including stress and depression), immunological disorders, neurological conditions, and endocrine abnormalities are low grade systemic inflammatory diseases in which pro-inflammatory mediators are substantially increased while anti-inflammatory molecules are deficient. This imbalance in the molecules involved in inflammation and immune response regulation results in the balance being shifted more towards pro-inflammatory events that can lead to the initiation, progression and continuation of the disease process(es). In such an event, methods designed to enhance the concentrations of anti-inflammatory molecules and suppressing inappropriate production and action of pro-inflammatory mediators may form a novel approach to many diseases. Cytokines, bioactive lipids and corresponding enzyme systems and their specific precursors and associated molecules seem to be at the centre of this imbalance between the pro- and anti-inflammatory events. Based on the current evidence, it is suggested that administration of appropriate amounts of bioactive lipids arachidonic, eicosapentaenoic and docosahexaenoic acids and anti-inflammatory cytokines IL-4 and IL-10 and anti-oxidants glutathione, vitamins C, B1, B6, B12 and other co-factors needed to restore the balance between pro- and anti-inflammatory events and restore homeostasis may form a new approach in the prevention and management of various diseases/disorders.

Keywords: inflammation, psychiatry, immunology, neurology, endocrinology, bioactive lipids, resolution, homeostasis.

Introduction

Inflammation is critical for human survival. Without inflammation there is no life. Inflammation-induced signs and symptoms are essential survival signals that are perceived and controlled by the vascular, neural, local and circulating cells and soluble mediators such that much needed cytoprotective and resolution of inflammation processes are initiated to resolve the inflammation, remove the debris of cells/tissues and regenerate and replace damaged cells/tissues and ultimately restore homeostasis (see Figure 1). All these processes occur simultaneously and take place in an orderly and logical fashion as the situation demands. Despite tremendous advances in our understanding of inflammation and its resolution process, we are yet to know the exact sequence of events both in the initiation of inflammation and its resolution. Such an understanding is needed to develop effective remedial measures to prevent and manage diseases associated with inflammation.

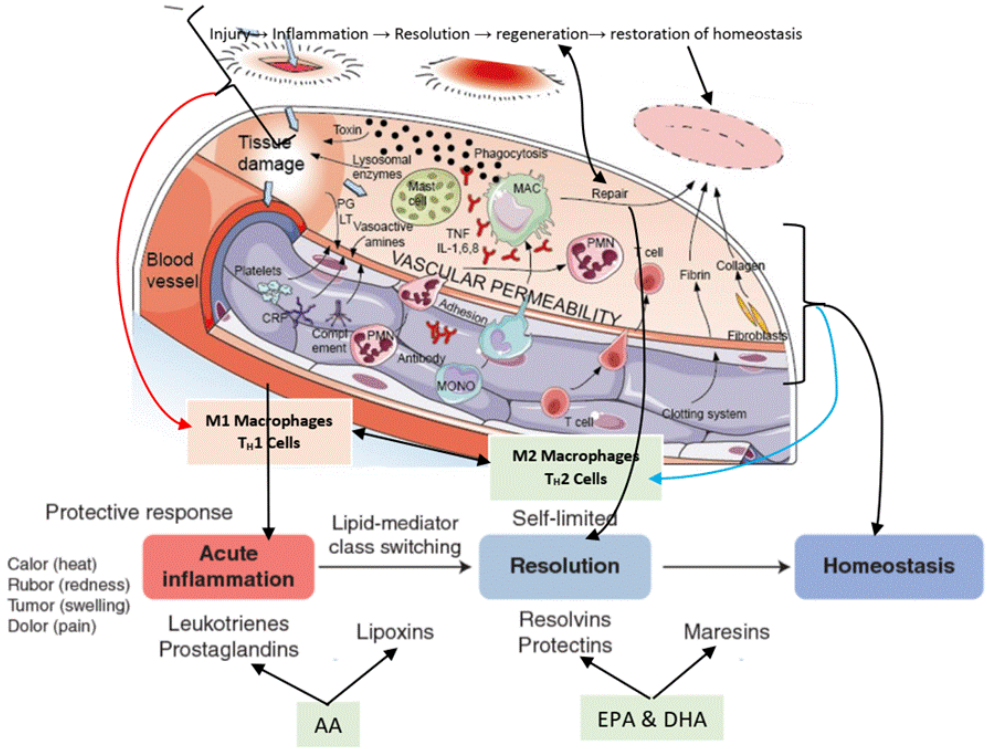

Figure N° 1. Scheme showing events that occur following injury (infection) that lead to subsequent set of events that under normal physiological conditions restore homeostasis. If this normal orderly sequence of events fails to occur, it will lead to chronic inflammation and/or autoimmunity. The role of bioactive lipids PGs and LTs in the initiation and perpetuation of inflammation, and the potential role of lipoxins, resolvins, protectins and maresins in the resolution of inflammation and reestablishment of homeostasis is also outlined.

Lupus, type 2 DM and schizophrenia are inflammatory conditions

It is now well established that many diseases that were once believed to be degenerative conditions are in fact low-grade inflammatory conditions. These diseases include obesity, type 2 diabetes mellitus (type 2 DM), hypertension (HTN), coronary heart disease (CHD), atherosclerosis, Alzheimer's disease, depression, schizophrenia, multiple sclerosis, cancer, NAFLD (non-alcoholic fatty liver disease), cirrhosis of the liver, chronic active hepatitis (CAH), osteoarthritis (OA) and peripheral vascular disease (PVD) (Antonopoulos, et. al., 2018; Arrese, et. al., 2016; Berenbaum, 2013; Berk, et. al., 2013; Calsolaro, et. al., 2016; Das, 2001; 2006; 2007; Dinh, et. al., 2014; Guo, et. al., 2015; Hameed, et. al., 2015; Li, et. al., 2018; Liu, et. al., 2015; Müller, 2018; Parola, et. al., 2019; Rincón-Arévalo, et. al., 2020; Zhu, et. al., 2018) The role of inflammation in the pathobiology of several other acute conditions such as nephritis, hepatitis, rheumatoid arthritis (RA), lupus (systemic lupus erythematosus, SLE), scleroderma, psoriasis, acute multiple sclerosis, and several other acute infectious diseases (such as malaria, etc.,) ischemia-reperfusion injury, burns, radiation injury including radiation treatment of cancer and peritonitis is well known. Thus, through the degree of inflammation is variable in all the above-mentioned conditions, it is evident that inflammation is at the centre in the pathobiology of these diseases. This implies that a deeper understanding of the molecules and cells involved in the onset and perpetuation and/or resolution of inflammatory process may lead to the development of newer therapeutic approaches in many diseases. It is suggested that the pathobiology of these diseases is similar at the molecular level but the clinical presentation of various diseases is different and appears apparently distinct simply because the cells/tissues/organs/system involved are different. Thus, RA is due to the involvement of synovial membrane of the affected joints; lupus is due to collagen vascular tissue of different organs (such as skin, blood vessels, renal tissue, etc.,); vascular endothelial and smooth muscles in PVD and CHD; hepatic cells in hepatitis and CAH and so on. This argument implies that once the pathobiology of inflammation and its resolution process are understood, the therapeutic approach might be the same or similar for all the conditions enumerated above though the mode of delivery of the molecules/drugs for these diseases may vary based on the cells/tissues/organs/systems involved/affected.

In this context, it is reasonable to suggest that understanding the pathophysiology of inflammation and its resolution is crucial to institute appropriate measures to suppress/cure/ manage these conditions. Both lupus and type 2 DM are not only systemic diseases but also have distinct local and systemic presentations based on the tissues involved in each phase of the respective diseases. For instance, skin involvement and vascular component (in the form of vasculitis) in lupus are very distinct features of the disease that resolve spontaneously and/or in response to treatment especially corticosteroids, immunosuppressive drugs and NSAIDs (non-steroidal anti-inflammatory drugs) implying that these drugs can regulate and control the inflammatory process. Furthermore, lupus can present itself as an acute inflammatory process and with or without treatment assumes a chronic, indolent, chronic inflammatory phase. It is interesting that in both acute and chronic phases

of lupus a variety of tissues can be involved (including but not limited to skin, blood vessels, synovium, kidney, central nervous system, liver, etc.). In contrast to this, in type 2 DM the inflammatory process is subtle, systemic, and of such a low grade that it is hardly realized by both the patient and the physician. Hence, type 2 DM is considered as a low-grade systemic inflammatory condition. But when the disease progresses and starts producing target organ(s) damage, it can lead to sudden onset of myocardial infarction, PVD leading to gangrene of toes, stroke, and in the long run renal failure and diabetic retinopathy. Thus, the clinical features and presentation of lupus is an example of how the acute inflammatory process can resolve with or without treatment, leading to the low grade systemic inflammatory condition seen in the chronic phase of the disease that may be resistant to treatment offered and present with acute flares at times suggesting how acute inflammation resolves or ends in chronic phase and how suddenly the dormant disease assumes acute inflammatory phase as seen as flares. In contrast, the life-long chronic inflammatory nature of type 2 DM is an example of a dormant and low-key but persistent inflammatory process. The acute, chronic, and sudden flares of lupus can be correlated to the acute, residual, and/or prodromal phases of schizophrenia or major depressive disorder, bipolar depressive and/or persistent depressive disorder phases. Thus, it is envisaged that lupus, type 2 DM and schizophrenia are all inflammatory conditions, but their clinical manifestations are different due to the involvement of different tissues/organs in each disease process. The differences in the inflammatory process may simply be attributed to differences in the type of cells/tissues affected but the underlying inflammatory process is similar, if not identical. Thus, it is opined that psychiatry (as exemplified by schizophrenia), immunology and neurology (Alzheimer's disease and lupus), and endocrinology (type 2 DM) -PINE-diseases are all inflammatory conditions. In this context, the author proposes that arachidonic acid (AA, 20:4 n-6), a precursor of both pro-inflammatory prostaglandin E2 (PGE2) and anti-inflammatory lipoxin A4 (LXA4) and other bioactive lipids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and their metabolites have a significant role in PINE diseases.

Essential fatty acids' (EFAs') metabolism

As depicted in Figure 2, dietary EFAs' *cis*-linoleic acid (LA, 18:2 n-6) and α-linolenic acid (ALA, 18:3 n-3) are widely distributed in our diet and form precursors to their long-chain metabolites that have important biological actions. Both LA and ALA seem to be metabolized by the same set of desaturases and elongases though there is a distinct possibility that their isoenzymes may exist. γ-linoleic acid (GLA, 18:3 n-6), dihomo-GLA (DGLA, 20:3 n-6), and arachidonic acid (AA, 20:4 n-6) formed from LA, and eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3) formed from ALA possess important biological actions and maresins (MaRs). Desaturases are the rate-limiting steps in the metabolism of LA and ALA. In addition, several co-factors are needed for adequate activity of desaturases. Some of these factors include magnesium; insulin; vitamins C, B1, B6,

and B12; and folic acid, whereas high glucose inhibits their activity. DGLA is the precursor of 1 series prostaglandins (PGs) such as PGE1, whereas AA is the precursor of 2 series of PGs, thromboxanes (TXs), and 4 series leukotrienes (LTs); while 3 series PGs, TXs, and 5 series LTs are derived from EPA. Most of these PGs, TXs, and LTs are pro-inflammatory in nature. In general, 2 series PGs, TXs, and 4 series LTs are more pro-inflammatory in nature compared to 3 series PGs, TXs, and 5 series LTs. Thus, PGE2 is more potent compared to PGE3 in inducing inflammatory events (Das, 2008; 2020; Poorani, et. al., 2016). PGE1 derived from DGLA has significant anti-inflammatory actions (Das, 2021; Poorani, et. al., 2016).

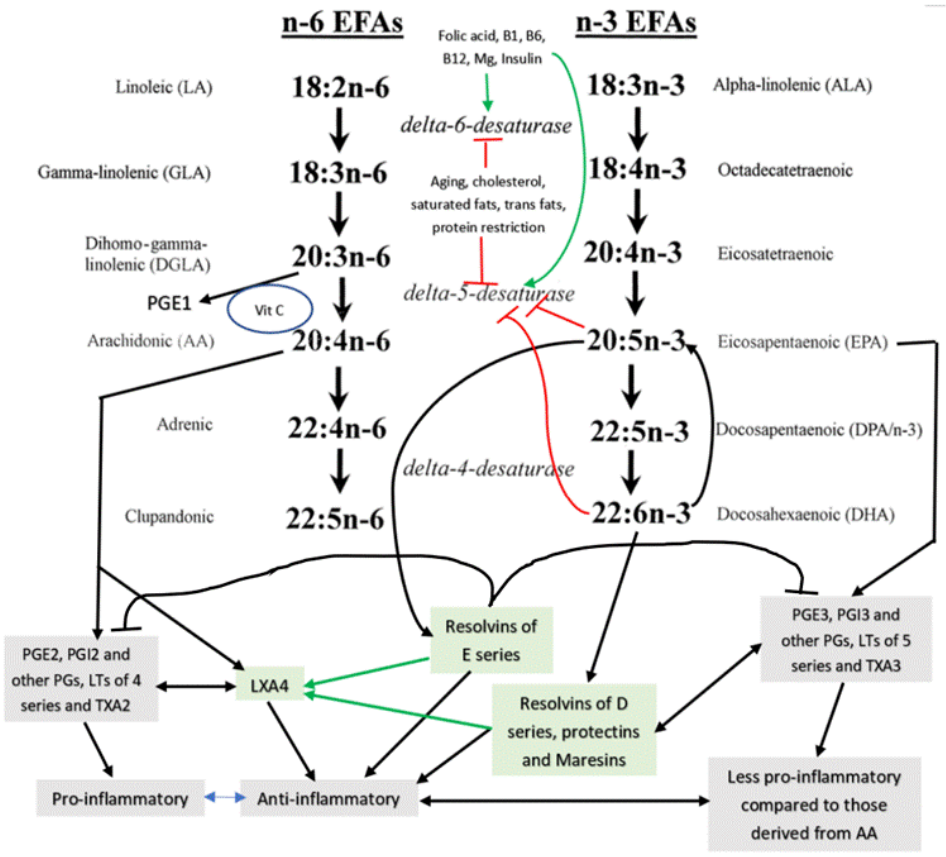

Figure N° 2. Metabolism of EFAs and various co-factors involved in their metabolism. This figure is taken from reference no. 21 (Das, 2021).

In addition to the formation of PGs, TXs and LTs from DGLA, AA and EPA; there are some specific anti-inflammatory products are formed from these fatty acids. AA is the precursor of lipoxin A4 (LXA4) whereas EPA is the precursor of E series resolvins while DHA gives rise to D series resolvins, protectins and maresins that are all potent anti-inflammatory (Das, 2020; 2021; Chatterjee, et. al., 2014; Fang, et. al., 2021; Kohli, 2009; Poorani, et. al., 2016; Ramon, et. al., 2016; Serhan, 2005;

2010; 2014). These facts imply that under normal physiological conditions a balance is maintained between pro- and anti-inflammatory metabolites of GLA, DGLA, AA, EPA and DHA and this balance is tilted more towards pro-inflammatory events in inflammatory diseases especially in low-grade systemic inflammatory conditions.

Essential fatty acids and their metabolites in the pathobiology of inflammation and its resolution

Induction of inflammation and its resolution in a timely fashion is essential for health and disease, especially to recover from injury, surgery, microbial infections and age-associated diseases such as type 2 diabetes mellitus, hypertension, metabolic syndrome, coronary heart disease, Alzheimer's disease, which are all inflammatory conditions. Thus, both acute and chronic inflammatory conditions need to be resolved in an orderly and appropriate way so that normal homeostasis is maintained under normal conditions and homeostasis is restored in diseases states. In serious illnesses such as sepsis, ischemia/reperfusion injury, ARDS (acute respiratory distress syndrome), post-surgical sepsis/shock, malaria, urinary tract infections cytokine production may be inappropriately high. These patients may become severely sick and recovery from which depends on how best these excess cytokines are suppressed without interfering with the body's defenses nd at the same time instituting appropriate inflammation resolution evens. When this switch over from acute inflammation to its orderly resolution fails to occur, it could lead to chronic and even low-grade systemic inflammation as seen in those with type 2 diabetes mellitus, hypertension, Alzheimer's disease. In diseases such as type 2 diabetes mellitus, hypertension, Alzheimer's disease even to start with there is only low-grade systemic inflammation that fails to resolve due to the failure of the inflammation resolution process. In both acute and chronic inflammatory states the balance between pro- and anti-inflammatory mediators and the respective cells that produce them are tilted more towards pro-inflammatory status. Macrophages, leukocytes, T cells, dendritic cells and their soluble mediators such as essential fatty acids and their metabolites including but not limited to prostaglandins, leukotrienes, thromboxanes, HETE, HPETE, lipoxins, resolvins, protectins, maresins, various cytokines, ROS, nitric oxide, carbon monoxide, hydrogen sulfide, growth factors, pro- and anti-angiogenic factors, adhesion molecules, etc., are all involved in inflammation and its resolution. Maintaining the delicate balance among these factors and cells is critical to prevent continuation of inflammation (whatever may be the reason for initial inflammation) and restore homeostasis.

There could be several reasons for low-grade systemic inflammation to occur in psychiatric diseases such as schizophrenia, immunological and neurological conditions like Alzheimer's disease and lupus, and endocrinological disorder type 2 DM -PINE-diseases-could be attributed to alterations (i) in the cell membrane lipid composition especially that of EFAs and their metabolites; (ii) imbalance in the pro- and anti-inflammatory cytokines; (iii) impaired interactions between EFAs

and their metabolites and the cytokine network with the balance tilted more towards pro-inflammatory milieu. It is envisaged that the interaction between EFAs and their metabolites and the cytokines is crucial in the prevention and management of these diseases (see Figure 3). In addition, there seems to be a critical role for EFAs, and their metabolites in the regulation of immune response as shown in Figure 4.

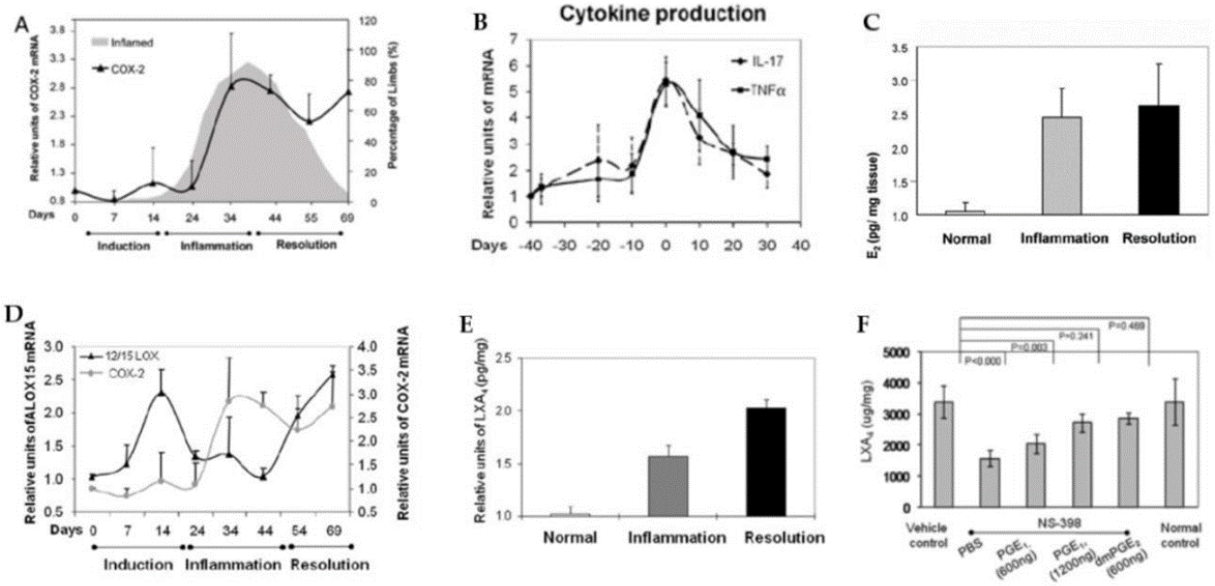

Figure N° 3. Changes in the expression of COX-2 and cytokines that occurs in low-grade systemic inflammatory conditions.

In low-grade systemic inflammatory conditions, PGE2 levels (and other pro-inflammatory bioactive lipids) will be increased, whereas those of LXA4 (and other anti-inflammatory bioactive lipids) are decreased coinciding with enhanced COX-2 and decreased 12- and 15-LOX expressions and increased production of IL-17 and TNF-α. Under normal physiological conditions, optimum production of PGE2 occurs to induce appropriate degree of inflammation that triggers an increase in the conversion of AA to LXA4 to kick start resolution of inflammation as a result of induction of 12- and 15-LOX enzymes. When the production of PGE2 is not optimum due to AA deficiency, such an orderly transition from pro-inflammatory state to resolution phase would not occur. This results in continuation of the inflammatory process leading to low-grade systemic inflammatory diseases. In such a scenario, administration of AA (EPA and DHA as well) results in stimulation of 12- and 15-LOX and suppression of COX-2 and PGE2 resulting in resolution of inflammation and recovery from disease. AA, EPA and DHA are needed in appropriate amounts in view of their interaction as shown in Figure 2.

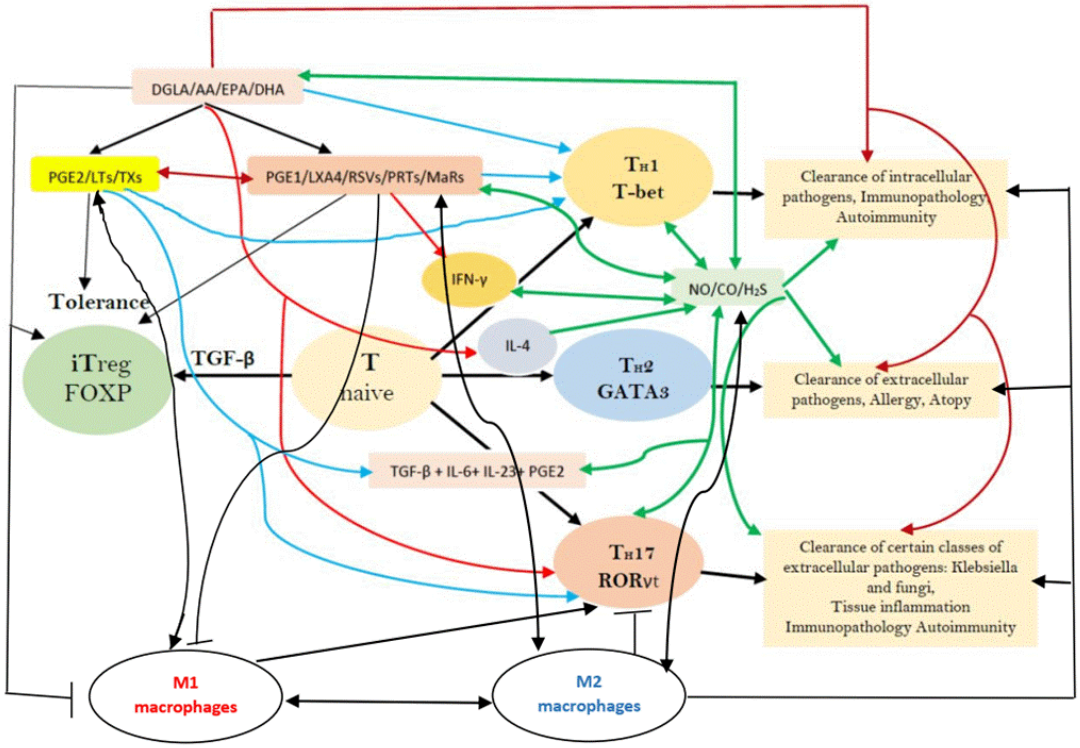

Figure N° 4. Factors that regulate in the formation of different subsets of T helper cells in the inflammatory process.

RSVs = Resolvins; PRTs = Protectins; MaRs = Maresins; LXA4 = Lipoxin A4; LTs = Leukotrienes; TXs = Thromboxanes; NO = Nitric oxide; CO = Carbon monoxide; H2S = Hydrogen peroxide; TGF-β = Transforming growth factor β; IFN-γ = Interferon-γ. Naïve CD41 T cells differentiate into T helper cells: TH1, TH2, and TH17. TGF-β converts naive T cells into FOXP3-expressing induced Treg (iTreg) cells. T helper cell differentiation needs T-bet, GATA3, and ROR-γt. Terminally differentiated T helper cells produce a specific combination of effector cytokines needed for the adaptive immune system. TGF-β, retinoic acid, or cytokines: IL-6, IL-1, IL-23, or IL-27 secreted by the innate immune system cells (immature or activated dendritic cells (DCs), respectively) dictate whether a naive T cell develops into a FOXP31 Treg cell, a TH17 cell, or otherwise. PGE2 through its receptor EP4 on T cells and dendritic cells facilitates TH1 cell differentiation and amplifies IL-23-mediated TH17 cell expansion. Bioactive lipids modulate the generation, proliferation, and function of several immunocytes, and their secretion of soluble mediators and nitric oxide (NO)/carbon monoxide (CO)/hydrogen sulfide (H2S) has a modulatory action on various immunocytes and their actions. The role of M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages is also regulated by various EFAs and their metabolites as shown in the figure. For more details see references (Das, 2008; 2020; 2021; Poorani, et. al., 2016).

Conclusions and therapeutic implications

Based on the preceding discussion, it is evident that there is a critical role for EFAs and their metabolites and various cytokines and respective cells/tissues in the pathobiology of various low-grade systemic inflammatory conditions. Since AA, EPA and DHA form an important constituent of all cell membranes, it is likely that changes in the concentrations of AA/EPA/DHA results in dramatic alterations in the cell membrane fluidity and the expression of various receptors, ion channels and the actions of several growth factors, proteins due to decrease/increase in their affinity to their respective receptors. Such an alteration in the cell membrane

composition is likely to alter the expression of several genes due to the mechanotransduction role attributed to AA/EPA/DHA (see Figure 5, (Das, 2022). Thus, it is proposed that alterations in the cell membrane composition due to changes in the concentrations of AA/EPA/DHA will lead to an increase or decrease in the expression of various genes. This may account for alterations in the expression of genes observed in various diseases that are also characterized by alterations in the concentrations of various bioactive lipids, cytokines, receptors, growth factors, neurotransmitters, adhesion molecules, etc. If this proposal is true, it implies that administration of adequate concentrations of AA/EPA/DHA in right proportions will result in resolution of various diseases in which there is a fundamental role for inflammation and immune responses.

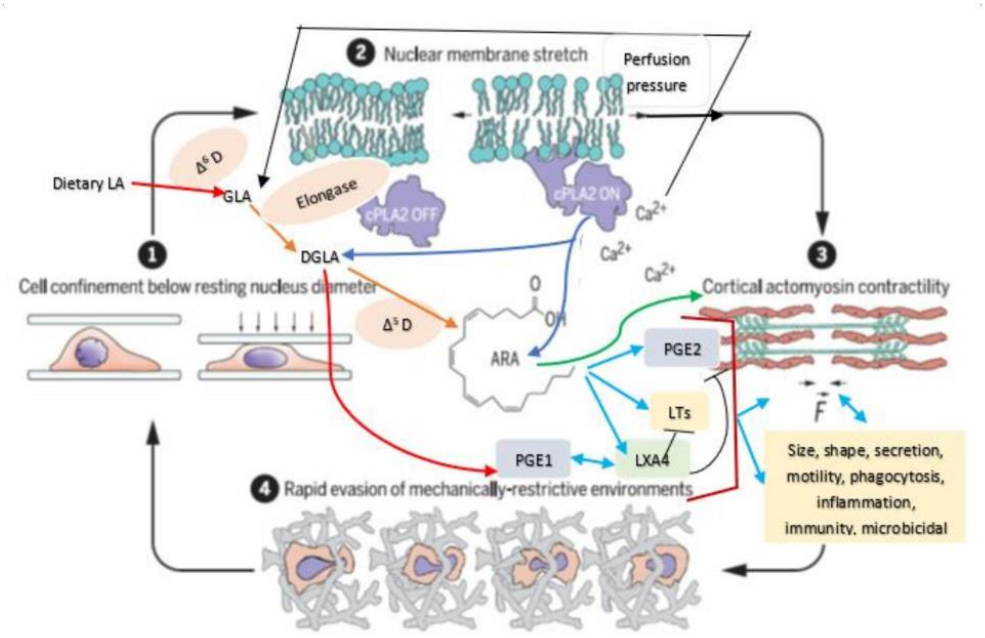

Figure 5. Scheme showing potential mechanotransducer function of nucleus in response to changes in pressure and stretch. Changes in pressure and stretch exerted on cell results in change sin nuclear membrane tension leading to calcium release, cPLA2 activation and release of AA/EPA/DHA that, in turn, alter actomyosin and other cytoskeletal structures that are known to induce change sin the expression of various genes. This figure is taken from reference: (Das, 2022).

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