HHS Public Access

Author manuscript

Int Immunopharmacol. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Int Immunopharmacol. 2018 December ; 65: 580–592. doi:10.1016/j.intimp.2018.10.026.

Immune regulation and anti-cancer activity by lipid inflammatory mediators

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Abstract

Rodent and clinical studies have documented that myeloid cell infiltration of tumors is associated with poor outcomes, neutrophilia and lymphocytopenia. This contrasts with increased lymphocyte infiltration of tumors, which is correlated with improved outcomes. Lifestyle parameters, such as obesity and diets with high levels of saturated fat and/or omega (ω)-6 polyunsaturated fatty acids (PUFAs), can influence these inflammatory parameters, including an increase in extramedullary myelopoiesis (EMM). While tumor secretion of growth factors (GFs) and chemokines regulate tumor-immune-cell crosstalk, lifestyle choices also contribute to inflammation, abnormal pathology and leukocyte infiltration of tumors. A relationship between obesity and high-fat diets (notably saturated fats in Western diets) and inflammation, tumor incidence, metastasis and poor outcomes is generally accepted. However, the mechanisms of dietary promotion of an inflammatory microenvironment and targeted drugs to inhibit the clinical sequelae are poorly understood. Thus, modifications of obesity and dietary fat may provide preventative or therapeutic approaches to control tumor-associated inflammation and disease progression. Currently, the majority of basic and clinical research does not differentiate between obesity and fatty acid consumption as mediators of inflammatory and neoplastic processes. In this review, we discuss the relationships between dietary PUFAs, inflammation and neoplasia and experimental strategies to improve our understanding of these relationships. We conclude that dietary composition, notably the ratio of ω−3 vs ω−6 PUFA regulates tumor growth and the frequency and sites of metastasis that together, impact overall survival (OS) in mice.

Keywords

Inflammation; Immune escape; Tumor induction; Tumor progression; TAM; Infiltration; MDSC; PUFA; High fat diet

Introduction

Diet composition affects the onset and progression of chronic degenerative diseases, including cancer, that are controlled in part by inflammatory processes.[1, 2] Growing evidence indicates that diet and its composition critically influence human health and immunity via secretion of adipokines, and their regulation of metabolic pathways. Dietary ω−3 PUFA has been a focus due to its anti-inflammatory, immunomodulatory and potential anticancer activity.[1, 3, 4] In this review, we discuss the systemic expansion, as well as, local/regional infiltration of immune and myeloid cells, which can support or inhibit tumor initiation and progression in a phenotypic dependent manner. As an example, tumor-associated macrophages (TAMs) have direct tumoricidal activity and can induce antitumor T-cell responses; but can also suppress cytotoxic T-lymphocyte (CTL) numbers and functions; thereby, facilitating tumor growth and progression (Figure 1). Tumor infiltration by myeloid cells is regulated, in part, by tumor-secreted GFs and chemokines, and as discussed herein, PUFAs, all of which control the migration, expansion and tissue infiltration of myeloid progenitors[5, 6]. Growing epidemiological, experimental, and clinical evidence suggests that ω−3 PUFAs have a role in the control of neoplastic cell growth and relapse and, by improving the efficacy of radiation and chemotherapy, reduce therapy-associated secondary complications.[7, 8] These bioactivities may be related to the immunomodulatory

and anti-inflammatory activities of ω−3 PUFA, as this can influence inflammatory processes, notably those induced by ω−6 PUFA bioactivity.[1, 3, 4]

Although, myeloid cell infiltration of tumors is predominantly pro-tumorigenic[9], myeloid cells can also inhibit tumor growth including activated macrophage tumor cytotoxicity as measured *in vitro*[10]. Despite the lack of a correlation between immunogenicity, metastatic propensity and the frequency of TAMs[11–13], TAM infiltration is associated with poor outcomes[14] and rapid disease progression[15, 16]. Myeloid-derived suppressor cells (MDSCs) are increased in the circulation of tumor bearing (TB) hosts and within tumors, and are associated with an immunosuppressive tumor microenvironment[17–21]. This immunosuppressive activity occurs via multiple mechanisms, including reactive oxygen species (ROS), nitric oxide (NO) synthetase (NOS-2) and arginase, as well as the secretion of immunosuppressive cytokines[22]. Preclinical and clinical studies have shown that macrophages and MDSCs can stimulate tumor growth[11, 23], while immune augmenting M1 macrophages and/or dendritic cells (DC) −1 cells contribute to antitumor T-cell responses, although, often insufficient for tumor rejection[24]. A low frequency of M1 macrophages, or an increase in infiltrating M2 macrophages, DC2s, and MDSCs are associated with a poor prognosis and an increase in tumor relapse following primary tumor resection[25, 26]. In contrast to tumor infiltration by myeloid cells, numerous clinical studies have demonstrated a correlation between tumor-infiltrating lymphocytes (TILs) and disease free survival (DFS) and OS in cancer patients[27, 28]. However, the relationship is dependent on the infiltrating lymphocyte phenotype, density and location. For example, infiltration by $CD4^+$ T-regulatory (T-reg) cells is associated with poor outcomes, while infiltration by $CD8^+$ cytotoxic effector cells is associated with positive outcomes[29]. In this review, we focus on the potential role of ω−3 PUFAs as a therapeutic adjuvant agent, highlighting their immunomodulatory effects and potential for beneficial effects, as well as the pro-tumorigenic activity of the inflammatory ω−6 PUFAs.

Tumor Infiltrating Inflammatory Cells and Patient Outcomes.

Human health and disease are controlled by both genetic and environmental factors. Numerous studies have examined the relationship between dietary habits and the types and amounts of essential fatty acids, particularly PUFA and resultant tumor development[30]. The ω−3 PUFAs have anti-cancer effects based on *in vitro* and *in vivo* studies[31–33]. Thus, the addition of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) to tumor cell cultures, but not normal cells, is cytotoxic[34]. This bioactivity is predominantly associated with long-chain (LC) ω−3 PUFA as compared to the shorter chain plant ω−3, α-linolenic acid (ALA)[35]. Perhaps of greater import is the finding that co-culture or pre-exposure of tumor cells with LC ω−3 PUFA enhances the cytotoxicity of antimitotic and other chemotherapeutic drugs against tumor cells[36]. Several additional anticancer mechanisms have been proposed including an alteration in the growth of tumor cells, interference with the cell cycle, increasing cell death via necrosis or apoptosis[37, 38], inhibition of angiogenesis and metastasis[39] and down regulation of inflammation and inflammatory cell infiltration of tumors[40, 41]. Based on these and other studies LC ω−3 PUFAs are being examined in a therapeutic context in combination with traditional adjuvant therapy in patients with cancer[42]. Similar to inflammatory cells, tumor specific CTLs can also infiltrate tumors, and

their frequency is predictive of improved outcomes[43]. However, a subset of $CD4^+$ infiltrating lymphocytes can suppress antitumor T-cell functions and are identified as suppressive T-cells (*i.e.*, T-regulatory cells (T-regs)). In contrast, infiltrating $CD8^+$ CTLs have anti-tumor activity but generally occur at low frequencies and with low avidities[44] such that, they have minimal ability to control tumor growth[45]. Nonetheless, a high frequency of tumor infiltrating T-cells (primarily $CD8^+$ T-cells) is associated with improved outcomes[46–53].

A better understanding of the regulatory events and pharmacophores, such as the PUFAs that can regulate tumor infiltration with antitumor T-cells, is needed to predict outcomes and develop novel therapeutic modalities[54]. In addition to immunoregulatory activity by infiltrating immune cells, some tumor and myeloid cells, including macrophages, polymorphonuclear neutrophils (PMN) and MDSCs, express immunosuppressive checkpoint mediators, such as PD-L1[55], resulting in cellular interactions that inhibit T-cell proliferation and functions. An effective antitumor immune response can occur, following a coordinated response, by innate and adaptive immune cells. Critical components include DC and macrophage presentation of tumor associated antigens (TAAs) and neoantigens, upregulation of costimulatory ligands, and increased cytokine and chemokine secretion, resulting in the induction of CTL responses, migration of activated T-cells to the tumor microenvironment, and T-cell tumoricidal activity. Tumor-specific T-cell responses also contribute to the recruitment of innate effector cells to the tumor microenvironment, including macrophages, DCs, gamma/delta (γ/δ) T-cells, natural killer (NK) cells and natural killer T-cells (NKT) cells, which are capable of tumor cell cytotoxicity, independent of T-cell receptor (TCR)-mediated T-cell recognition. Nonetheless, the immune system has developed potent mechanisms to maintain homeostasis and limit potentially dangerous complications due to an exuberant immune response. These negative regulatory feedback loops, are usurped by tumors, allowing them to evade immune surveillance, inhibit CTL responses, resulting in obstacles to the initiation and propagation of successful antitumor adaptive immune responses. The cellular mediators, mechanisms of action and molecular mediators of both pro- and anti-tumorigenic infiltrating cells are summarized in Table 1 and 2.

Innate and Adaptive Antitumor Cellular Mechanisms

Dietary supplementation with PUFAs, especially LC ω−3 PUFAs, has pro-resolving effects on both innate and adaptive immunity via multiple mechanisms. This includes effects on numerous cell phenotypes that coordinate the host response against tumors. Thus, resolvins, metabolites from LC ω−3 PUFAs have endogenous pro-resolution activity that protects against aberrant / uncontrolled innate inflammatory responses[56]. The present paradigm suggests that the activation of DCs, an innate immune cell, initiates the development of adaptive immune responses against tumors. Classically activated macrophages (M1s) are part of the tumor microenvironment, with a functional role limiting tumor progression. In early tumors, macrophages have an inflammatory, tumoricidal phenotype. Important features of M1 macrophages include the expression of iNOS, ROS and the secretion of the NK and type 1 T-cell stimulating cytokine IL-12. Further, M1 macrophages phagocytose and kill bacteria, viruses and tumor cells, and secrete proinflammatory cytokines[57]. M1s also promote indirect cytotoxicity by activating adaptive immune responses[58].

Granulocytes, specifically neutrophils, may also have a role in tumor regression, including cytotoxicity via Fas/Fas Ligand interactions, as well as, ROS. Eosinophils can also infiltrate tumors, with potential antitumor activity via their secretion of cytotoxic factors including major basic protein, cationic protein and peroxidase; however, it is unclear whether granulocytes exert direct anti-tumor activities[59].

NK cells are also highly cytotoxic, innate immune effectors with cytotoxicity, via perforin and granzyme-dependent mechanisms. NK cells have an array of different activating and inhibitory receptors facilitating recognition of stress ligands on tumor cells, which can regulate the levels of major histocompatibility complex (MHC) expression[60, 61]. It is noted that the anti-tumor activity of NK cells is largely limited to single tumor cells or micro-metastases.

Classical ($\alpha\beta^+$) CD8 T-cells recognize peptides presented by class I MHC on the membranes of Ag-presenting cells (APCs)[62, 63] and tumor cell, intracellular antigens (Ags), following phagocytosis, are subjected to proteolysis with antigenic (Agic) epitopes bound within the peptide-binding groove of the MHC molecule, and the peptide-MHC complexes transported to and inserted into the plasma membrane of APCs for T-cell recognition. In addition, $CD4^+$ T-cells recognize Ags in the context of MHC class II molecules, primarily expressed by APCs. T helper cell differentiation occurs via the secretion of cytokines that 'help' activate B cells, NK cells, and $CD8^+$ CTLs. A wide variety of T helper cell subsets with differing functional roles have been identified based on their function (Th1, Th2, Th17, etc.).

Following activation by APCs, and with $CD4^+$ T-cell help, CTLs develop a direct cell mediated cytotoxicity. Upon differentiation and activation, these T-cells undergo programmed cell death and/or exhaustion, preventing over-activation of immunity, thereby limiting autoimmune responses. These lymphocyte responses can also be regulated by LC ω −3 PUFAs, including promotion of $CD4^+$ Th1 cell differentiation[64] and the modulation of T-reg cells[65].

Numerous randomized clinical trials have reported anti-inflammatory activity by marine LC ω−3 PUFAs and improved clinical parameters in rheumatoid arthritis patients[66, 67]. These effects are mostly attributed to EPA, (C20:5) and DHA, (C22:6) via two mechanisms. First, they interfere with the enzymatic conversion of arachidonic acid (AA, C20:4) an ω−6 PUFA to pro–inflammatory prostaglandins (PGs) and leukotrienes (LTs). Second, EPA is a direct precursor in the biosynthetic pathway of anti-inflammatory PGs (series-3) and LTs (series-5). Dietary ω−3 LC-PUFAs replace AA in the phospholipid bilayer of cell and then alters the membrane composition and fluidity, as well as cell signaling, gene transcription and metabolism of proresolving mediators[40, 41, 68, 69]. A recent meta-analysis of nine clinical trials, with 475 colorectal cancer (CRC) patients, evaluated the effects of ω−3 PUFA on cytokines and/or acute phase proteins levels[70]. In a stratified analyses, a reduction in IL-6 levels was observed in surgical patients that received 0.2 g/kg of fish oil parenterally during the postoperative period and the albumin levels were increased in the surgical patients that received >2.5 g/d of EPA and DHA orally during the preoperative period. In patients undergoing chemotherapy, supplementation of 0.6 g/d of EPA and DHA for 9 week

significantly reduced C-reactive protein (CRP) levels, and the CRP:albumin ratio. The authors concluded that LC ω−3 PUFA supplementation has benefits on reducing some inflammatory mediators, but that these benefits were specific to distinct supplementation protocols based on duration, dose and route of administration.

Dietary PUFA Regulation of Myeloid Cell Function

The regulatory activity of PUFAs on immunity appears to affect myeloid cells. It has been demonstrated that a diet rich in ω−6 PUFAs enhanced the accumulation of MDSCs, which are negative immune regulators[71]. This was observed with both cultured murine bone marrow cells and *in vivo*, in mice fed diets enriched in ω−6 PUFAs. In these studies, mice were fed a linseed oil based diet containing 45% of the shorter ω−3 PUFA, ALA, or a sunflower oil diet containing 45% LA, an ω−6 PUFA. The results suggested that the bioactivity of PUFAs occurred through janus kinase-signal transducer and activator of transcription (JAK-STAT3) signalling, such that a JAK inhibitor almost completely inhibited the bioactivity of PUFAs on MDSCs. Thus, it was concluded that the immune modulatory activity of PUFAs may be mediated, in part, by diet.

High fat diets are associated with non-alcoholic fatty liver disease (NAFLD), and with Kupffer cells, which are hepatic resident macrophages, representing 20–25% of the non-parenchymal cells in the liver. NAFLD, which is characterized by chronic systemic low grade inflammation, including a critical contribution by Kupffer cells[72]. The increased production of proinflammatory cytokines and eicosanoids, by ω−6 PUFA metabolism, can enhance Kupffer cell secretion of inflammatory cytokines, resulting in NFκβ activation with further worsening of inflammation and fibrosis[73]. Recently, several studies have suggested that lipid accumulation in adipose tissues of obese hosts, promoted infiltrating macrophages with an M1 polarization shift; while M2 phenotype macrophages were found in lean adipose tissue[74, 75]. Thus, high-fat diets can decrease the frequency of Kupffer cells with an M1-predominant phenotype and result in increased secretion of pro-inflammatory cytokines. Further, ω−3 PUFAs polarize Kupffer cells/macrophages to a predominantly M1 phenotype while ω−6 PUFAs polarize Kupffer cells/macrophages to an M2 phenotype, in association with the activation of NFkβ signalling and peroxisome proliferator-activated receptors (PPAR)-γ respectively[76, 77]. The up-regulation of PPAR-γ induces macrophage polarization from an M1-predominant phenotype to an M2 phenotype[78]. Because dietary fish oil, LC ω−3 PUFA, results in decreased PGE-2 production, LC ω−3 PUFAs are anti-inflammatory, and enhance secretion of Th1-type cytokines, and decrease MHC II expression, NK cell activity, and lymphocyte proliferation. Consistent with this hypothesis, the culture of human neutrophils with the LC ω−3 PUFAs, EPA or DHA inhibits superoxide production and phagocytosis[79]. Similarly, the incubation of murine peritoneal macrophages with EPA or DHA has been reported to inhibit MHC II expression[80]. In one study, human monocytes were cultured with EPA or DHA, resulting in a decrease in the proportion of human leukocyte antigens-DR or DP (HLA-DR or –DP) positive monocytes following addition of IFN-γ[81] depressing Ag presentation[82]. Similarly, adding fish oil to rodent diets has been shown to decrease superoxide and hydrogen peroxide secretion by macrophages[83]. Experiments comparing diets with safflower oil versus fish oil have been found to decrease peak plasma levels of TNF-α, IL-1β, and IL-6 following lipopolysaccharide (LPS)

injection[84]. Indeed, parenteral nutrition that includes fish oil can decrease serum TNF-α, IL-6, and IL-8 levels in burned rats, compared with animals given ω−6 PUFA–rich parenteral nutrition[79]. However, these studies utilized super-pharmacologic doses, contrasting with most rodent studies using dietary fish oil in which EPA plus DHA comprise up to 30% of the lipid fatty acids and up to 12% of energy. Conclusions from studies, such as these, have been refined by using relatively low levels of EPA or DHA (4.4% of total FAs or 1.7% of dietary energy), documenting that these levels are sufficient to result in anti-inflammatory activities[85].

T-cell Immunosuppression and PUFA

LC ω−6 PUFAs are proinflammatory[86] as they can be metabolized to AA and subsequently by COX-/LOX- to inflammatory lipid mediators including (PGs) and leukotrienes (LTs)[87]. These AA metabolites are well known for their tumor-promoting effects and the COX downstream molecule PGE-2 can enhance tumor growth by stimulating the development of tolerogenic DCs and Tregs. 5-LOX metabolites involve 4 series leukotrienes (*LTs*) and have a role in stimulating tumor growth and progression[88]. In contrast, the ω−3 fatty acids, EPA and DHA, modulate COX/LOX activities by forming less potent metabolites such as three series PGEs and five series LTs. Further, the lipoxygenase products from AA metabolism stimulate the expansion and differentiation of myeloid progenitor cells[89] such as MDSCs. Tolerogenic DCs contribute to T-cell regulatory functions by suppressing their activation via peripheral tolerance. In steady state conditions, tissue-resident immature DCs internalize/process and present Ags from tumors. These DCs, identified as DC2s, are poorly immunogenic, and do not secrete proinflammatory cytokines, and express low levels of costimulatory molecules. Further, DC2s secrete immunosuppressive cytokines, including IL-10 and TGF-β that are key mediators in the induction of T-reg cell differentiation. Indoleamine 2,3-dioxygenase (IDO) secretion by these DCs also contributes to immune tolerance[90]. Alternatively activated macrophages (M2s) are differentiated from monocytes by IL-4 stimulation. M2s facilitate tumor angiogenesis, support tumor progression, invasion and metastasis, and contribute to immunosuppression by secreting IL-10, facilitating the development of IL-4-secreting Th2 cells, and provide a positive feedback for the development of additional M2 macrophages. CCL22, produced by M2 macrophages, also recruit T-regs to suppress CTL functions. Further, PD-L1, expressed by M2 macrophages, contributes to the apoptosis of activated T-cells[91].

Similar to M2 macrophages, MDSCs; a heterogeneous population of immature myeloid cells with potent immunosuppressive activity also infiltrates tumors. MDSCs can be either of monocytic, granulocytic or immature origin[20, 92]. In the blood of cancer patients, MDSCs lack lineage (LIN) markers for lymphocytes (CD19 and CD3) and NK cells (CD56) and thus express an $LIN^{-}HLADR^{-}CD11b^{+}$ phenotype[93, 94] that can be further segregated based on expression of CD14 (monocytic), CD15 (granulocytic) or $CD33^{+}CD14\text{-}CD15^{-}$ (immature) expression[20, 95]. A positive correlation between the frequency of MDSCs and tumor stage has been reported for numerous tumor pathologies[92]. MDSCs inhibit T-cell activation via arginase, iNOS, ROS or reactive nitrogen species (RNS) as well as secretion of immunosuppressive cytokines[96]. Further, MDSCs deplete nutrients necessary for lymphocyte function, disrupt IL-2 receptor signaling, interfere with lymphocyte trafficking,

promote activation of T-regs by CD40-CD40L ligation, suppress CD3-zeta (ζ) expression and secrete IL-10 or TGF-β[97, 98].

T-regs are divided into 2 major populations, one that develops in the thymus[99] and one that is induced in the PB[100] by TGF-β. In homeostatic conditions, T-regs limit the induction and expression of autoimmunity, inhibit bystander tissue destruction and maintain tolerance to self-antigens[101]. In cancer patients, the T-reg frequency in the PB is increased compared to normal individuals[102]. In addition, there are high numbers of tumor infiltrating T-regs[103]. T-regs are phenotypically identified as $CD4^+$ T-cells that co-express forkhead box P3 (Foxp3) and CD25[102]. Further, T-regs can express one or more checkpoint inhibitory molecules; including, but not limited to, lymphocyte activating gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3 (TIM3), glucocorticoid-induced tumor necrosis factor receptor (GITR), cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), and programmed death-1 (PD-1), which can directly suppress immune cells[102, 104]. T-regs can also indirectly suppress effector T-cells by depleting local IL-2, which is needed for the survival of actively dividing effector T-cells[105]. Indirect suppression is also associated with the secretion of immunosuppressive cytokines, including IL-10 and TGF-β[106]. In contrast to immunosuppressive myeloid cells, recent research has focused on direct PUFA regulation of T-regs.

Diets Rich in ω−6 PUFAs Increase the Risk of Inflammatory Diseases

Numerous studies have suggested that dietary PUFAs regulate inflammatory responses. Western diets include fatty acids (FAs) from animal sources, which are mainly saturated fatty acids (SFAs) and FAs from plants that are predominantly ω−6 PUFAs. In contrast, some FAs derived from plant-based oils, and fatty fish consist mainly of ω−3 PUFA. Rodent and clinical studies have shown that hosts given diets rich in ω−6 PUFAs have an increased risk of inflammatory diseases, including asthma, rheumatoid arthritis and inflammatory bowel disease[107]. In contrast, diets with high levels of LC ω−3 PUFAs are anti-inflammatory, with a decreased risk of inflammatory diseases[107]. Further, PUFAs can be oxidized to either pro-inflammatory or pro-resolving lipid mediators (Figure 2), both of which have potent immune modulatory capacities[108]. Pro-inflammatory mediators, notably PGs and LTs, are secreted in response to “foreign” substances and cleared by pro-resolving lipid mediators, restoring tissue homeostasis[109]. Diets with high levels of the ω−3 PUFAs, shorter chain ALA, and more critically, LC EPA and DHA are associated with regulation of the incidence and severity of inflammation[70]. The beneficial effects of dietary FAs include the anti-inflammatory metabolites LTs, thromboxanes (TX), resolvins and a decrease in the levels of inflammatory cytokines. The ω−3 PUFAs differ from the ω−6 PUFAs based on the position of their double bonds in the acyl chain, such as linoleic acid (LA) as compared to arachidonic acid (AA) found with ω−6 PUFA containing diets. (Figure 2) However, the inflammatory and immune augmenting aspects of PUFAs are not clearly separated based on the number and placement of double bonds, counting from the methyl end of the FA (*i.e.*, ω−3 vs ω−6). The addition of the dietary shorter ω−3 PUFA, ALA, an essential FA, and the main precursor of LC ω−3 PUFAs, enhances secretion of superoxides from macrophages and neutrophils[110], resulting in cellular adhesion to endothelial cells[111] and pro-inflammatory effects *in vitro*. Further, ALA can slow the proliferation of rodent and human

lymphocytes following mitogen stimulation[112–114], supporting immunosuppressive activity by ALA. Consistent with these *in vitro* observations, studies in which rodents were given a high-fat diet, rich in ALA, resulted in a decreased mitogen-stimulation of lymphocyte proliferation and NK cell activity[115]. *In vitro* studies using the ω−6 PUFA; AA, have demonstrated increased inflammation associated changes, including enhanced superoxide release[110], neutrophil attachment to endothelial cells[111], and IL-1β secretion by macrophages[116]. Mice fed diets with high ω−6 PUFA levels, in a dose dependent manner, resulted in increased levels of LTE-4 and PGE-2 following zymosan stimulation *in vivo*[117]. Thus, diets high in AA result in increased angiotensinogen, IL-6 and monocyte chemoattractant protein (MCP)-1 and increased expression of the proinflammatory transcription factor; nuclear factor κβ (NFκβ)[118]. In other studies using rats fed diets with a high ALA composition for 8 weeks, a decreased superoxide production was observed by peritoneal macrophages in response to phorbol esters[119], and an increase in TNF secretion by resident macrophages, although no effect on TNF production was observed with inflammatory macrophages[120]. Thus, the effects of the shorter ω−3 PUFA, ALA on lymphocyte functions appears to be dependent on ALA levels and total PUFA diet content and composition[121]. These observations with ALA and ω−6 PUFA contrast with the bioactivity of the LC ω−3 PUFA with 20 or more carbon atoms such as EPA, and DHA, which are anti-inflammatory and immune augmenting[122]. Diets incorporating LC ω−3 PUFAs are anti-inflammatory, in part due to a decrease in metabolism of ω−6 PUFA into inflammatory eicosanoids, cytokines, and stimulation of ROS and NOS mediators[123]. Clinically, EPA and DHA dietary supplementation can decrease intestinal damage and improve gut histology in patients with inflammatory bowel disease[124], as well as decreased arthritic lesions including joint pain, number of tender and swollen joints, and duration of morning stiffness[125].

Dynamic Anti-inflammatory Activities of ω−3 PUFA

One of the challenges of dietary studies, with PUFA regulation of inflammation, is that obesity is associated with a chronic low-grade inflammation and increased levels of free fatty acids, pro-inflammatory cytokines, hormones and circulating macrophages[126, 127]. Adipose tissue can secrete metabolites that either promote or resolve an inflammatory response[128]. Additionally, excess energy is normally stored in adipose tissue[129], resulting in enlarged fat cells (hypertrophy) and increased numbers, primarily through hyperplasia of pre-adipocytes, to store the excess triglycerides (TG). This hypertrophy and hyperplasia of adipose cells increases oxygen consumption, resulting in hypoxia[129], activation of cellular stress pathways and autonomous inflammation due to pro-inflammatory cytokine secretion[129]. This also results in myeloid infiltration of adipose tissue, (including mammary glands), surrounding both dead and dying adipocytes, where they form crown-like structures (CLS) and a phenotypic shift of the adipose tissue macrophages, releasing pro-inflammatory cytokines that induce ROS and activate inflammatory signalling pathways in neighbouring adipocytes[130]. An example of the impact of differing dietary PUFA composition on CLS formation in mammary fat pad (MFP) is shown in Figure 3. MFPs from groups of mice receiving isocaloric and isolipidic diets containing either ω−3 PUFA (Figure 3A), or ω−6 PUFA (Figure 3B) diets by pair feeding for 20 weeks, were analyzed for CLS in 10 high

power fields per sample (N=10/group). The results from our studies showed that there was a significant increase in CLS in the mammary fat pad (MFP) of mice receiving ω−6 diets (Figure 3B) compared to the mice consuming ω−3 diets (Figure 3A). These observations are consistent with the recent report on hepatocyte secretion of dipeptidyl peptidase 4 and adipose inflammation including CLCs.[131]

Obesity contributes to the tumor microenvironment by increasing inflammation, and the presence of free fatty acids (FFAs)[132]. High levels of proinflammatory adipokines contribute to the content of inflammatory cell content within the tumor microenvironment[133, 134] through autocrine and paracrine activation of signalling pathways including NF-κβ[135], STAT3 and extracellular regulated kinase (ERK)1/2, all of which stimulate tumor cell proliferation, which can inhibit apoptosis[136]. In contrast, adiponectin, secreted by white adipose tissue, has anti-proliferative effects for breast cancer cells, but is down-regulated in obese patients[137]. Thus, low levels of adiponectin increase the risk of breast cancer in obese women[138].

A number of clinical trials have assessed the therapeutic activity of diets supplemented with fish oil in inflammatory diseases, including Crohn's disease, psoriasis, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, and lupus[139]. Many placebo-controlled, double-blinded trials with dietary fish oil, undertaken in patients with chronic inflammatory diseases, have documented significant benefits. The evidence for clinical activity by fish oil is greatest in rheumatoid arthritis, where LC ω−3 PUFA consumption results in a concentration-dependent decrease in inflammatory enzymes, including ones that degrade cartilage, COX-2, but not COX-1 expression and TNF-α and IL-1β expression in cultured articular chondrocytes[140]. The mechanisms of action with LC ω−3 PUFAs in patients with arthritis have been postulated to be a competition between the canonical ω−6 substrate AA resulting in eicosanoids with lower inflammatory activity[141]. Further, LC ω−3 PUFAs can be metabolized into anti-inflammatory, bioactive lipid mediators including resolvins, protectins and maresins, which can resolve inflammation with significantly more activity than their lipid precursors[142]. The associated paradigm shift, based on these observations, suggests that the resolving phase of inflammation is not passive, but involves actively downregulated endogenous anti-inflammatory mediators[143]. This contrasts with ω−6 PUFA metabolites, including PGD-2, LTD-4, LTC-4, and LTE-4, which mediate asthmatic bronchoconstriction. Although AA is a precursor to LTs and has a role in allergic inflammation, PGE-2 can also regulate macrophage and lymphocyte functions. Thus, dietary consumption of the ω−6 PUFA LA, as the precursor of AA, is causally linked to allergic diseases and supports a potential treatment strategy using LC ω−3 PUFAs[144].

Dietary ω−3 Regulation of Murine Tumor Growth

Clinically, a number of differing associations have been reported between PUFA consumption / composition and inflammation; due in part to confounding factors including genetic susceptibility, tissue microenvironments, stress, obesity, age, caloric intake and dietary duration. Murine models have suggested a number of mechanisms that associate dietary PUFA with tumor initiation and progression, secondary to systemic and tissue inflammation. These studies include a number of pathologic conditions such as infections,

autoimmune and inflammatory conditions, neoplasia and obesity with neutrophilia, splenomegaly and multifocal, hepatic extramedullary myelopoiesis (*i.e.*, the formation of myeloid tissue outside of the bone marrow)[5, 145]. These inflammatory conditions, in association with tumor initiation, are regulated by multiple risk factors, including hormones, obesity, diet, and age. However, following tumor initiation and growth, inflammation is controlled by tumor secretion of GFs, as well as, existing risk factors. Thus, the tumor inflammatory microenvironment is associated with cross talk between host immunity and tumor-secreted GFs. As an example, the cellular microenvironment of mammary glands incorporates, primarily, adipocytes, hormonal responsive epithelial cells, and stromal cells, as well as, infiltrating immune cells, resulting in mammary glands that can act as both an endocrine and as an immune organ[146]. This stimulates a progressive increase in tumor infiltrating inflammatory cells, including MDSCs, M2 macrophages, DC2s, and granulocytes, during tumor initiation and progression from normal tissue to dysplastic cells[147].

The role of dietary PUFA during tumor progression and metastasis has been examined in syngeneic, and xenograft mammary cancer models. In a xenograft model using MDA-MB-435 tumor cells, athymic nude mice were injected with tumor cells following establishment of the mice on diets of either LA, EPA or DHA. These studies revealed significantly delayed tumor growth and metastasis in the mice fed an EPA or DHA diet, including a reduction in AA levels in the tumor membrane phospholipids[148]. The results from one of our studies are shown in (Figure 4). In this study, two groups of mice received diets differing in PUFA composition using pair fed, isocaloric and isolipidic liquid diets (unpublished results). Ten weeks following initiation of the diets, the mice received orthotopic injections of 4T1 mammary tumor cells. The results show that mice consuming a LC ω−3 PUFA diet had significantly slower growing tumors (Figure 4A) and prolonged survival (Figure 4B) compared to the mice receiving an ω−6 PUFA diet. Interestingly, when subgroups of mice were autopsied 35 days post orthotopic injection, the mice consuming the ω−6 based diets were observed to have a significantly greater number and frequency of pulmonary, hepatic, renal, cardiac and bone marrow metastases. Inhibition of inflammatory cells, as discussed elsewhere in this review, is associated with slower growth of primary tumors and potentially a reduction in the frequency of metastases. This suggests that dietary PUFA composition is not only critical to tumor initiation, but also modulates tumor growth and the extent of metastasis and metastatic sites. Further, in murine studies, when EPA and DHA are provided as neoadjuvant therapy, the number of pulmonary metastases are significantly decreased compared to mice on an LA diet[149]. Similar immune-augmenting and therapeutic activities were reported in studies with R3230RC and MCF-7 breast adenocarcinoma tumor models[150, 151], including a reduced number of MDSCs[152]. In a tumor survival study, mice were switched from an 8% corn oil (1% ALA) diet to an 8% canola oil (10% ALA) diet, when the mice had developed an average primary tumor volume of 60 mm^3. In this study, tumor growth was significantly lower in mice fed the ω−3, canola oil diet as compared to the ω−6, corn oil cohort.[153] Based on these and other preclinical studies, it appears that dietary intervention may be used with therapeutic intent.

Murine studies with interventions using LC ω−3 PUFA and autochthonous, chemically induced mammary tumors support these observations. In an autochthonous 7, 12-

dimethylbenz (α) anthracene (DMBA) induced mammary tumor model, mice on a fish oil diet had a significantly reduced tumor incidence, growth and metastasis[154, 155]. The LC ω−3 diet affected tumor induction and growth that correlated with reduced AA serum levels, suppressed tumor cell proliferation, protection against DNA single strand breaks, and an increase in apoptosis marker expression[155–157]. Similarly, in a tumor model with N-methyl-N-nitrosourea (MNU)-induced rat mammary tumors, diets with varying fat composition were compared, including an SFA diet, a monounsaturated fat (MUFA) diet, an ω−6 PUFA alone diet or diets with different ratios of ω−6 : ω−3 PUFA diets. It was found that a diet incorporating a 1:1 ratio of ω−6 : ω−3 PUFA was most effective in preventing mammary tumor development as compared to the other dietary groups. Studies into causal relationships revealed that this diet group had decreased transcription of cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX) in mammary tissues and PPAR-γ levels[158]. Together, these and other studies directly support a role for LC ω−3 PUFA in controlling the inflammatory tumor microenvironment by the upregulation of PPAR-γ[157, 158]. When dietary LC ω−3 PUFA content was increased to an ω−6 : ω−3 ratio of 1:14.6, as compared to 1:0.7, a 60% decrease in tumor growth was observed[159]. Similar studies, using a therapy model with orthotopic 4T1 mammary tumors, in which a 5% fish oil diet was initiated when the hosts had developed primary tumors that were 8–10 mm^3 in diameter, resulted in significantly reduced growth and metastasis, which correlated with decreased tumor cell proliferation[160].

The ability of LC ω−3 PUFAs to downregulate inflammatory mediators and increase proteins, associated with apoptosis, supports the importance of exogenous regulation of the tumor microenvironment. However, the regulatory mechanisms are unclear. *In-vivo* studies, focused on cellular phenotypes, have examined the effect of dietary LC ω−3 PUFA on inflammatory cells in animal models with both LPS and tumor induced inflammation. However, the majority of murine models use diets that are not isocaloric and are rarely pair-fed, raising questions regarding mechanisms based on obesity verses dietary composition. Since obesity itself is inflammatory, clarifying the effects of obesity associated inflammation, as opposed to diet regulation, is crucial to determining the actual effects of dietary components in tumor initiation and progression. Thus, the use of an animal model using an isocaloric, isolipidic liquid diet that allows pair feeding and controlled dietary caloric intake is required to assess dietary impacts on weight and adipose changes, as well as dissociate effects between obesity and dietary composition, such as PUFA composition.

Dietary LC ω−3 PUFA and Improved Cancer Patient Outcomes

The local tumor microenvironment includes tumor cells, extracellular matrix; endothelial cells, stromal cells, fibroblasts, adipocytes and critically infiltrating inflammatory and adaptive immune cells. These microenvironmental elements have a role in regulating tumorigenesis, tumor growth, invasion and metastasis. The infiltrating immune cells, particularly CTLs, serve as regulatory factors in the tumor microenvironment[161, 162]. In cancer patients, it has been documented that the infiltration of immune cells provided an independent positive prognostic factor using immunohistochemistry (IHC) and hematoxylineosin (HE) staining.[163] Studies, into the type of infiltrating immune cells (*e.g.*, $CD3^+$, $CD8^+$, and $FOXP3^+$ T lymphocytes) and the density or location of infiltrating T-cells,

contribute to a prognostic correlation with positive outcomes for patients with CRC[50, 164–170]. This correlation is also observed in a variety of other tumors, including ovarian cancer and breast cancer[171–174]. These studies have been extended clinically to include a meta-analysis assessing the impact of tumor-infiltrating inflammatory cells on outcomes, including a meta study incorporating 30 studies involving 2,988 patients.[175] These studies examined the associations between CRC survival and generalized tumor inflammatory infiltrates (N=12) and T lymphocyte subsets (N=18). Pooled analyses revealed that a significant, generalized tumor inflammatory infiltrate was associated with improved cancer-specific survival (CS), OS and DFS. Stratification by cellular location and T lymphocyte subset indicated that in the tumor microenvironment, $CD3^+$, $CD8^+$ and $FoxP3^+$ cellular infiltrates were not significant prognostic markers for OS or CS. In contrast, a high frequency of infiltrating $CD8^+$, but not $CD3^+$ or $FoxP3^+$ T-cell cells were predictive of an increased OS. Furthermore, a high frequency of tumor infiltrating $CD3^+$ cells at the invasive tumor margin was also associated with improved OS and DFS.[175]

Consistent with the effect of LC ω−3FA on tumor infiltrating immune cells, is an inverse relationship between dietary LC ω−3FA consumption and the risk of developing CRC, as reported within case-control studies by Murff et al.[176] and Habermann et al.[177]. However, the benefits were limited such that, in one study[176] an increased ω−3 PUFA intake was associated with a reduced risk of colorectal adenomas in women, whereas in another trial[178] an inverse association was observed between low DHA intake and an increase in the risk of CRC in patients with specific genetic variants that resulted in higher levels of proinflammatory mediators. More recently, a relationship between LC ω−3FA intake and survival in the CALGB 89803 randomised trial of adjuvant chemotherapy for completely resected stage III CRC (n=1,264) was investigated retrospectively[178]. Patients in the highest quartile of LC ω−3FA dietary intake had an increased disease-free survival (DFS) compared with the lowest quartile. Notably, this relationship appeared to be greater for patients with high CRC COX-2 expression[178]. Numerous clinical studies have examined adjuvant supplemental therapy with LC ω−3FA[179]. In one positive example breast cancer patients with high dietary DHA had a significantly longer time to disease progression and survival as compared to patients with lower incorporation of supplemented DHA[180].

IHC analyses of infiltrating immune cells, particularly $CD3^+$ T lymphocytes in the primary tumor, provide a biomarker predicting good clinical outcomes in most cancer pathologies[181–183]. Furthermore, basic histological quantification of T lymphocyte density, cytotoxicity and memory, by $CD3^+$, $CD8^+$, and $CD45RO^+$ markers respectively, demonstrate that an increase in T lymphocyte infiltration was associated with significant improvements in a patient's DFS and OS[165, 182, 184]. In CRC, identifying the location of infiltrating CTLs, assessed as $CD3^+CD8^+$ T-cells in two areas within the center (CT) and invading margin (IM) of the primary tumor, provides an accurate prediction of clinical outcomes[165]. The quantification of the density, phenotype, and location (CT or IM) of infiltrating CTL results in what has been termed an Immunoscore[185–187]. Indeed, the analysis of $CD3^+$ cell infiltration surpasses the gold standard of diagnosis by tumor-stage, lymph node, and metastatic invasion. The assessment, of a tumor Immunoscore, subsets patients into five categories based on the location in the tumor (CT and IM) of $CD3^+$ and $CD8^+$ T-cells.[188, 189].

In addition to leukocytic infiltration of tumors, circulating hematological inflammatory markers, including the neutrophil–lymphocyte ratio (NLR), can predict the survival of cancer patients[190]. This has been extensively studied, documenting the prognostic value of the NLR in multiple, but not all, tumor pathologies and disease stages. Over 60 studies (>37,000 patients) have been examined to assess the prognostic value of the NLR[191]. In parallel with these studies, there are reports of a relationship between plasma proinflammatory cytokine levels and elevated NLR (>5)[192, 193] providing insight into underlying mechanisms. Further, there is potentially a relationship between the frequency of circulating myeloid cells and an elevated NLR and an increase in peritumoral macrophages[192]. Together, these observations suggest that the NLR reflects, in part, innate immunity and myeloid cell infiltration of tumors, providing an easily measurable biomarker that is predictive of OS and progression free survival (PFS).

TILs occur primarily at the tumor interface with the surrounding stroma[194]. Thus, while infiltrating leukocytes may have prognostic significance, subsets of infiltrating cells, may be a more accurate predictor. As discussed above, infiltrating $CD8^+$ T-cells, are a critical component of tumor-specific adaptive immunity. CTLs are a cellular mediator that can be prognostic of positive outcomes. Further, immunosuppressive myeloid cells, including MDSCs, DC2s and M2 macrophages, emphasize the criticality of assessing the infiltrating myeloid cell-to-$CD8^+$ lymphocyte ratio in cancer tissues. Several studies have focused on this parameter, concluding that infiltrating $CD66^+$ myeloid cells provide an independent prognostic factor for poor DFS and OS[195]. This observation has been extended with the finding that the infiltrating NLR (iNLR) determined as a $CD66^+$: $CD8^+$ cell ratio, documents a relationship with OS and tumor stage[196].

In association with immunoregulatory properties, a patient's lifestyle, preceding and following diagnosis and therapeutic interventions, may help control cancer initiation, progression[38], and responses to therapeutic interventions[197]. Specifically, patients who consume a high-fat diet; one with high levels of saturated fat, or one with high levels of ω−6 PUFAs, frequently exhibit neutrophilia, that can facilitate tumor initiation and progression, resulting in poor outcomes[198, 199]. Conversely, diets that contain a high ω−3 PUFA content have been associated with lower inflammation, lower EMM and better clinical outcomes[5]. We posit, herein, that dietary LC ω−3 PUFA may increase the infiltration of tumor specific CTLs, decrease myeloid cell infiltration and improve intraturmoral survival of T-cells, contributing to improved patient outcomes.

Epidemiological studies into the incidence and progression of breast cancer in American women of Japanese descent, have been compared to that of women in Japan. The results from one study indicated a significantly higher breast cancer incidence in American women compared to Japanese women[200]. This conclusion was supported by the observation that children from Japanese immigrants to America, but not the immigrants themselves, had breast cancer rates similar to the general American population[201]. In the 1990s, dietary components were found to be implicated in these different incidences[202]. These relatively weak correlative epidemiologic studies were considered plausible, as preclinical experiments demonstrated that LC ω−3 PUFAs could reduce pro-inflammatory cytokines, inflammation and cancer development[203]. Similarly, high fat diets have been shown to increase the risk of

breast cancer and aggressive prostate cancers[204]. Case–controlled studies have documented an inverse relationship between the dietary ω−6 and LC ω−3 PUFAs ratio and the incidence of breast cancer, supporting the importance of the relative ratio of ω−6 and LC ω−3 LC-PUFAs in the diet[205]. In an epidemiological study of 56,007 French women over 8 years, the risk of breast cancer was reported to be unrelated to dietary PUFA consumption overall. Rather, a significant risk was associated with the ratio of dietary ω−6 vs. LC ω−3 PUFAs, which was inversely related to LC ω−3 PUFA levels in women with the highest intake of ω −6 PUFAs, indicating interactions due to PUFA consumption[206]. The decreased risk of developing breast cancer with LC ω−3 PUFA consumption was confirmed in a case controlled study[207], where a population based study showed all-cause mortality was reduced 16–34% in women consuming high levels of LC ω−3 PUFAs[208]. Indeed, in the last 20 years, data has accumulated suggesting that high ω−6 PUFA consumption is pro-inflammatory, likely involving COX-2 secretion and NFκβ activation, resulting in an increased incidence of cancer and all-cause mortality. In contrast, a high consumption of LC ω−3 PUFA is protective against neoplasia, resulting in the downregulation of NFκβ, a decreased incidence of cancer and neoplasia associated all-cause mortality[209]. Indeed, in a meta-analysis of 11 independent prospective studies, it was suggested that a decrease in the dietary ω−6 : LC ω −3 PUFA ratio significantly lowered the risk of breast cancer[210]. Even though some studies have shown no association between a heightened diet of ω−6 : LC ω−3 fatty acid ratios and breast cancer development, the risk of developing breast cancer was directly associated with increasing ω−6 : LC ω−3 PUFA ratios[211].

Recent studies have investigated the underlying mechanisms in these observations, and their relationship to innate and acquired immune cells in the tumor microenvironment. The regulatory activity of LC ω−3 PUFA on macrophage functions, has been documented with the use of antagonists to GPR120, which is expressed by some myeloid cell populations and acts as a PUFA receptor[212]. This is supportive of a role for LC ω−3 PUFA mediation of anti-inflammatory effects via this receptor. However, the nuclear receptor PPAR-γ also acts as a receptor for PUFAs and the regulatory mechanisms of LC ω−3 and ω−6 PUFA on obesity[213], postmenopausal breast cancer[214] and microenvironmental inflammation[64], suggesting a need for additional studies. Changes in the lipid content of cell membranes associated with LC ω−3 and ω−6 PUFA consumption may regulate oncogenic signalling via the regulating of lipid raft profiles and a reduction in cytokine production[215]. Further, PUFAs contribute to the regulation of BM and extramedullary hematopoiesis at sites such as the spleen[216, 217] and may also induce the expansion of MDSCs[71].

Summary

Dietary consumption of PUFAs may not only affect inflammation and the incidence and progression of neoplasia, but also may provide an interventional strategy with positive clinical outcomes for cancer patients and patients with other pathologies via the regulation of inflammation. In general, increased dietary ω−6 PUFA consumption is associated with a heightened risk of breast cancer due to direct effects on the mammary gland and promotion of a pro-inflammatory tumor microenvironment. In contrast, dietary LC ω−3 PUFAs have protective effects and suppress ω−6 PUFA associated inflammation. The nutritional recommendation has been that individuals should decrease dietary ω−6 PUFA intake and

increase LC ω−3 PUFA consumption with an intake of at least 500 mg/day of dietary LC ω −3 PUFA[218], easily achievable with 2 weekly servings of oily fish, supporting prevention of cancer and cardiac disease and a dietary ratio of ω−6 : ω−3 PUFA of approximately 8:1 or lower[219]. PPAR-γ and GPR120 agonists also have potential use as neoplastic chemopreventive drugs; although their use, initially, is perhaps better targeted towards either high-risk individuals or as a therapeutic intervention. Regardless, there remains a compelling need to document that both pharmacophores and dietary regulation of PUFAs have clinically significant anti-cancer activities. Future trials should address this question as well as the impact on tumor infiltrating cells subtypes. We stress that translational/preclinical studies should utilize isocaloric and isolipidic, pair fed diets to control the regulation of immunity and inflammation by obesity versus dietary FAs. Further, great care must be taken to differentiate dietary control of tumor growth as opposed to metastasis, as these biologic parameters are interrelated. In our experience, fatty diets impact not only primary tumor growth, but also the extent and critically, sites of metastasis, all of which are typically unstudied but clinically and highly relevant since they are often the ultimate cause of the patient's demise.

Acknowledgements:

James E. Talmadge, Timothy R. McGuire and John Graham Sharp are members of the Fred and Pamela Buffet Cancer Center supported by 30CA036727. John Graham Sharp and Timothy R. McGuire receive support via the Children's Hospital/UNMC Pediatric Cancer Research Group, from the State of Nebraska. Agricultural Research Division and Office of Research and Economic Development, University of Nebraska-Lincoln, National Institutes of Health, RO1-DK07076

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Highlights:

- This review discusses the relationships between dietary PUFAs, lipid mediators, inflammation and neoplasia and experimental strategies to improve our understanding of these relationships.
- Discusses the need for isocaloric, isolipidic and pair-fed models to separate mechanisms based on obesity verses dietary composition
- Discusses our understanding of dietary PUFAs regulation of inflammation and neoplastic progression as an interventional strategy for cancer patients.
- Discusses recent findings on PUFA regulation of not only tumor initiation, but also tumor growth and the extent and sites of metastasis.

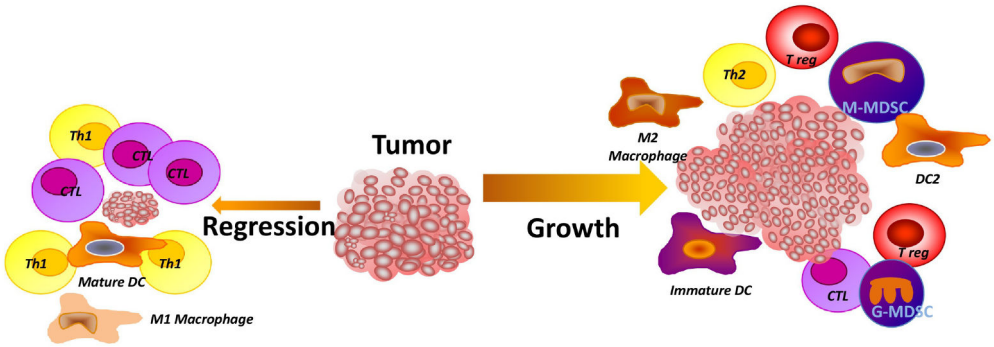

Fig. 1.

Leukocytes that infiltrate a tumor can regulate their growth rate, progression and may facilitate metastasis. Tumor regression is associated with tumor infiltration by dendritic cells (DCs), cytotoxic T cells (CTL) and type 1 T-helper cells (Th-1). Contrasting with this, tumor growth is facilitated by immune mediated immunosuppression and neoangiogenesis in association with infiltration by myeloid-derived suppressor cells, (MDSCs), immature DCs, pDCs, M2 macrophages, as well as T regulatory (T-reg) cells and a low frequency of $CD4^+$ and $CD8^+$ effector T cells. Further, the expansion of and infiltration by myeloid cell populations, including immunosuppressive sub-populations, is regulated in part, by colony stimulating factors (CSFs), and chemokines secreted by tumor cells, dietary ω−6 poly-unsaturated fatty acids (PUFAs) and saturated fatty acids (SFAs).

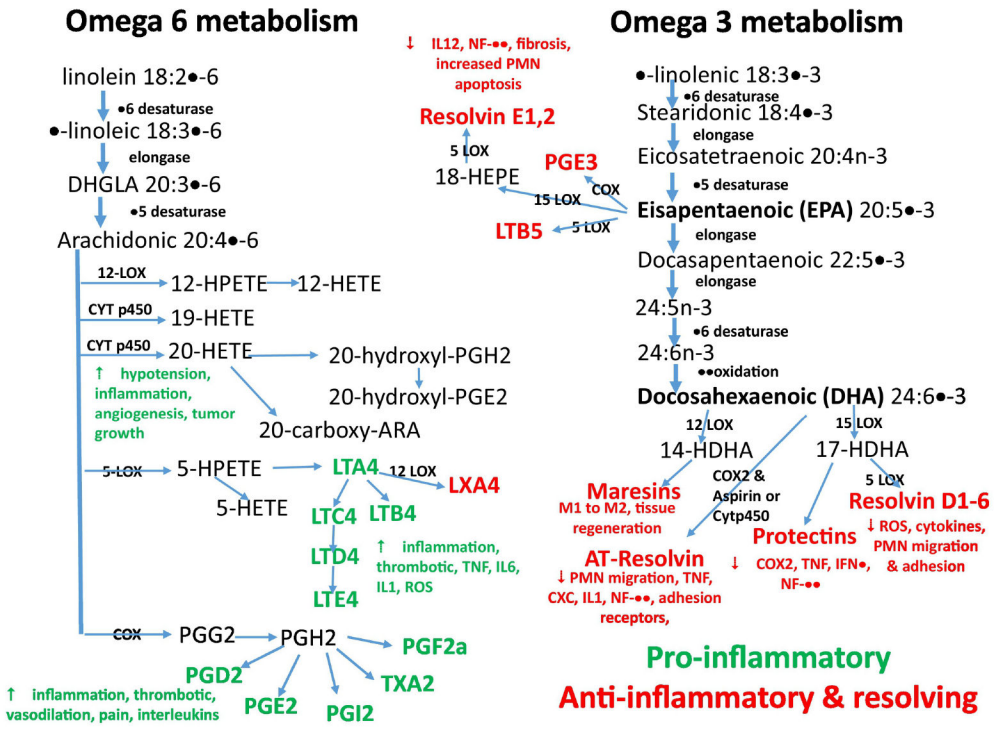

Fig. 2.

This figure is an outline of eicosanoid mediator synthesis pathways from arachidonic acid (AA) and resolvin related mediators from α-linolenic acid (ALA) and their inflammatory and anti-inflammatory functions. COX, cyclooxygenase; CYT p450 cytochrome, p450; chemokine subtype, CXC; HETE, hydroxyeicosatetraenoic acid; HDHA, hydroxyldocosahexaenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; HPDHA, hydroperoxydocosahexaenoic acid; HPEPE, hydroperoxyeicosapentaenoic acid; IL, interleukin, IFN, interferon; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; PG, prostaglandin; PMN, polymorphonuclear leukocytes; ROS, reactive oxygen synthetase; TNF, tumor necrosis factor, TX, thromboxane.

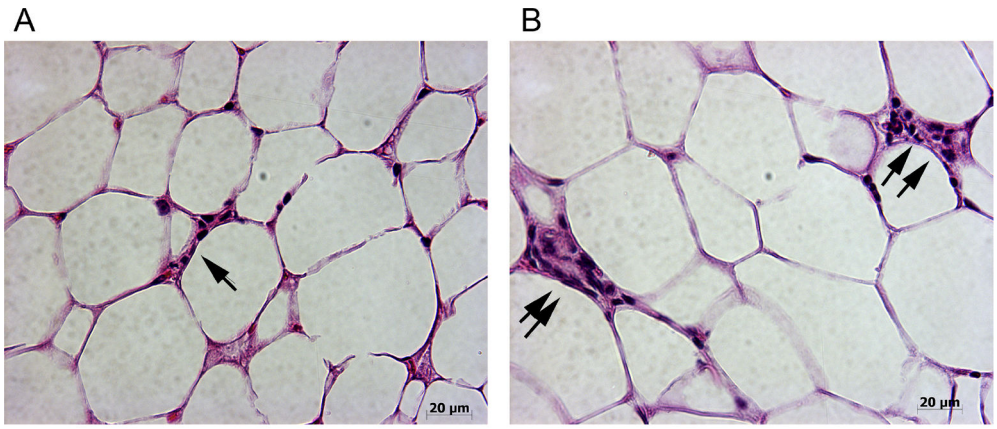

Fig. 3:

Dietary PUFA regulation of mammary adipose tissue inflammation

Crown-like-structures (CLS) were analysed in H & E stained sections of mammary fat pad from mice that received the differing PUFA composition diets for 20 weeks[5]. MFP from mice fed ω−3 diet (Fig. 3A) and ω−6 diet (Fig. 3B). Mice given the ω−3 diet had fewer and smaller CLS relative to mice given an ω−6 diet. Single arrow indicates small CLS and double arrows indicated large CLS. Note the difference in size of the adipocytes in the MFPs of mice on the different diets, i.e. the adipocytes are significantly larger in the mice given ω −6 diets. Images were taken at 400x magnification.

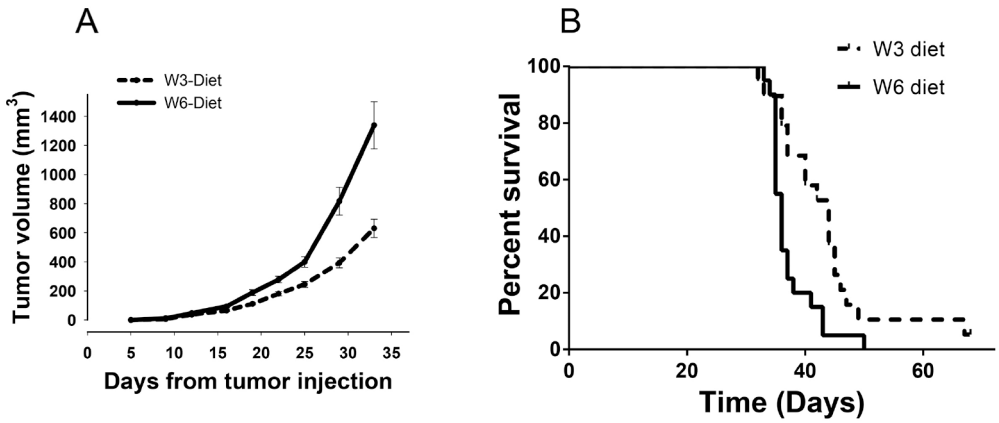

Fig. 4: Dietary PUFA regulation of mammary tumor growth and survival:

Groups of mice fed ω−6 and ω−3 diets for 10 weeks[5], were injected orthotopically with 4T1 cells. Tumor volume was recorded twice a week and plotted with average tumor volume per dietary group (Fig. 4A) (n=20). Survival days were compared between the dietary groups (Fig. 4B) (n=20) ($p<0.05$).

Table 1

Tumor Inhibitory Cellular Mediators

Cellular Mediators	Functions	Molecular Mediators
Cluster of differentiation 4 positive ($CD4^+$) T helper 1 cell (Th1)	Immune recognition of tumor associate antigens (TAAs) bound to major histocompatibility complex (MHC) class II molecules; contribution to dendritic cell (DC) and macrophage activation; natural killer (NK) and natural killer T cell (NKT) cell activation; cytotoxic T-lymphocyte (CTL) generation; induction of B-cell differentiation.	IL-2, interferon gamma (IFN-γ). interleukin 12 (IL-12), tumor necrosis factor-beta (TNF-β),
$CD8^+$ CTL	Immune recognition of TAAs bound to MHC class I molecules;	perforin, granzyme B, Fas ligand (FasL); IFN-γ, IL-2,
M1 (classically activated macrophages)	TAA presentation; expression of co-stimulatory molecules; Fc gamma receptor (FcR)-mediated antibody -dependent cellular cytotoxicity (ADCC).	IL-1β and TNF-α.; release of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS)
$CD4^+$ Th17	Stimulation and expansion of Th1 and CTLs	IFN-γ, IL-2, TNF, chemokine ligand 20 (CCL20), chemokine ligand (CXCL)9, CXCL10
Dendritic cell 1 (DC1) ($CD11c^+$, conventional DCs) mature DCs	Immunogenic cross-presentation of TAAs; expression of costimulatory molecules such as CD40, CD80, and CD86	IFNs, TNF-α, IL-1, IL-4, IL-6, IL-10, IL-12, and IL-23.
NK cells	Recognition of cells with down-regulated or absent MHC expression; cytotoxicity through perforin granzyme and other mechanisms	perforin, granzyme B, FasL; IFN-γ, IL-2, TNF-β
Gamma/delta T-cells (γ/δ T-cells)	Immune recognition of tumor-derived phosphoantigens or stress ligands; contact-dependent cytokine production, tumor and viral cytotoxicity	IFN-γ, TNF, IL-17, FasL, perforin, granzyme
NKT cells	Immune recognition through both NK membrane receptors and an invariant CD1d restricted T-cell receptor (TCR);	IFN-γ, IL-4, perforin, granzyme B and FasL
B-cells	Immune recognition of soluble and membrane TAAs; expression of co-stimulatory molecules; ADCC and Ag presentation	secretion of TAA-specific antibodies; IL-12, TNF-β

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Table 2

Pro-tumorigenic cellular mediators

Cellular Mediators	Functions	Molecular Mediators
Regulatory T-cell/cluster of differentiation 4 positive, T helper 2 cell (T-reg/$CD4^+$ Th2)	Mediate immune homeostasis via suppression of inflammation and cytotoxic T-lymphocyte type T1 T-helper cells (CTL Th1) responses, and maintenance of peripheral tolerance	Expression of lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin mucin 3 (TIM-3), glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein (GITR), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1); local consumption of interleukin 2 (IL-2), secretion of IL-10, IL-4, IL-35, IL-5, IL-6, transforming growth factor beta (TGF-β), granzyme B, and perforin
Cluster of differentiation 8 positive ($CD8^+$)	Inhibition of CTL and $CD4^+$ Th1 responses	IL-4, IL-5, IL-10
T helper 17 cells (Th17)	Promoting angiogenesis via VEGF production, neutrophil recruitment/infiltration	IL-8, IL-6, vascular endothelial cell growth factor (VEGF), prostaglandin E2 (PGE2), TGF-β, chemokine ligand 1 (CXCL1), CXCL5, CXCL8, and IL-1
Myeloid-derived suppressor cells (MDSC), granulocyte-like (G-MDSC), monocyte-like (M-MDSC) and inhibitor (iMDSC),	Depletion of arginine; disruption of interleukin-2 (IL-2) receptor signaling; inhibit lymphocyte trafficking; increase T-reg activation by CD40-CD40L, inhibit T-cell function and antigen presentation, stimulate neovascularization, downregulation of CD3ζ	Reactive oxygen species (ROS), nitrate oxide synthetase (NOS), arginase 1 (Arg1), IL-10, TGF-β
Regulatory B cells (B-regs)	Inhibition of T-cell function	Secretion of IL-10 and TGF-β.
M2, tumor associated macrophages (TAM) alternatively activated macrophages (Macs)	Promote angiogenesis, activate Th2 and CD8 cells, support tumor progression	Secretion of arginase, cyclo-oxygenase 2 (COX2), IL-10, chemokine ligand 22 (CCL22), programmed death-ligand 1 (PDL1)
Dendritic cell 2 (DC2) $CD123^+$, plasmacytoid (pDC)	Low levels of co-stimulatory molecule expression.	Secretion of IL-10, IDO, and TGF-β
Granulocytes	Increased secretion of toxic peptides	Secretion of ROS, atopic mediators, and IL-4

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