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Polyunsaturated Fatty Acids, Ulcerative Colitis and Cancer Prevention

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1. Introduction

Fatty acids (FA) – lipid constituents – are carboxylic acids that can be represented by the form RCO_2H . Most often, the group R is a long carbon chain, unbranched and with an even number of carbon atoms and may be saturated or contain one (monounsaturated) or more double bonds (polyunsaturated) (Calder et al. 2002). Fatty acids are often referred to by their common names, but they are correctly identified by a systematic nomenclature. This nomenclature indicates first the number of carbon atoms in the hydrocarbon chain, followed by the number of double bonds, and the position of the first double bond from the terminal methyl group, which is indicated by n-9, n-7, n-6 or n-3 (Figure 1). There are two main families of polyunsaturated FA (PUFA), n-6 (or w-6) and of n-3 (or w-3) (Curi et al. 2002).

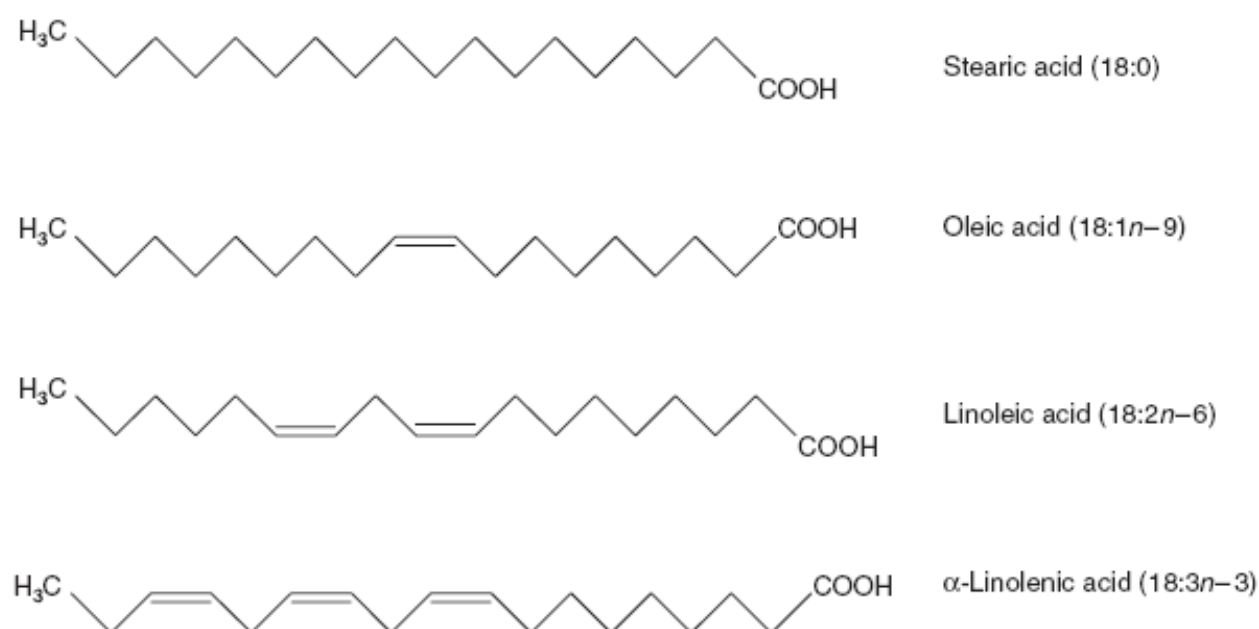


Fig. 1. Structure of some fatty acids (Sala-Vila et al. 2008).

Triacylglycerols (TAG), formed by three FA esterified to glycerol, are the main form of fat present in the human diet. TAG of animal origin are rich in saturated fatty acids and are characterised by being solid at ambient temperature (fats), while those of vegetable origin are rich in unsaturated fatty acids and liquid at room temperature (oils). TAG act as reserve lipids found in the form of oily microdroplets, emulsified in the cytosol (Lanning 1993). In addition to TAG, other lipids are present in small amounts in the diet, such as phospholipids, cholesterol, cholesterol esters and traces of free FA. Phospholipids are the major lipid components of the cell membrane, acting as structural elements, precursors of second messengers, and affecting the activity of some enzymes, such as phospholipase A2 and protein kinase C. Thus lipids, besides being a source of energy (immediate or reserve), act as key components of our body, both in terms of structure (cellular constituents) and function (Burr & Burr 1929, 1930).

Mammals synthesise saturated fatty acids from non-lipid precursors and unsaturated n-9 series and n-7; normally the diet provides adequate amounts of these fatty acids. However, the cell membrane also needs unsaturated FA of n-3 and n-6 families to maintain their structure, fluidity and function measures. As mammals lack the enzyme delta-12 desaturase and delta-15 (found in most plants), which insert double bonds at positions 3 and 6, they do not synthesise n-3 or n-6 PUFA. As such, these FA have to be consumed in the diet and are therefore called essential fatty acids (Semplecine & Valle 1994, Burr & Burr 1929).

The PUFA most commonly consumed are linoleic acid (LA, 18:2 n-6) and α -linolenic acid (ALA, 18:3 n-3). These two FA can be converted to other unsaturated derivatives. Linoleic acid can be converted to γ -Lilolênico (18:3 n-6), Dihomo- γ -linolenic (20:3 n-6) and arachidonic acid (AA, 20:4 n-6) sequentially. Similarly, the α -linolenic acid (18:3 n-3) is converted into eicosapentaenoic acid (EPA, 20:5 n-3) and Docosapentaenoic acid (DHA, 22:5 n-3) (Calder 2003) (Figure 2). The main dietary sources of acids LA and ALA are oils which are rich in polyunsaturated fats. The PUFA of n-6 series are derived from plants found, for example, in soybean, sunflower and evening primrose oils. The PUFA of n-3 series are predominantly found in fish oils and marine mammals, and deep cold water fish, such as mackerel, sardines, trout, salmon and tuna (Connor 1996). This occurs because many marine plants, especially phytoplankton algae, also synthesize EPA and DHA from-linolenic acid- α . This synthesis of long-chain PUFA n-3 by marine algae, and their transfer through the food chain to fish, explains their abundance in some fish oils and marine mammals (Semplecine & Valle 1994).

Up until 1929, the FAs were viewed exclusively as efficient energy storage. Between 1929 and 1930, George and Mildred Burr published articles reporting the essentiality of PUFA. The authors found that the administration of diets completely devoid of fat in rats caused severe changes in relation to growth and the physiological functions of various organs, which were attributed to the lack of long-chain PUFA. Similar changes were observed in newborns undergoing a diet based on skimmed milk and then reversed by the administration of whole milk. These findings led to a systematic study being carried out by Hensen et al. In 1958, it was found that the administration of skimmed milk to infants was associated with diarrhoea and skin abnormalities, among other things. The supplementation of milk with linoleic acid reversed all symptoms. These observations therefore characterise the effects of PUFA deficiency in humans (Hensen et al. 1958, Holman et al. 1998). With the development of parenteral nutrition, which initially did not contain essential fatty acids, it became evident that a deficiency of n-type PUFA-6 caused the death of patients. This led the

FDA (Food and Drug Administration), in 1982, approving the supplementation of parenteral nutrition with PUFA n-6 (Holman et al. 1998).

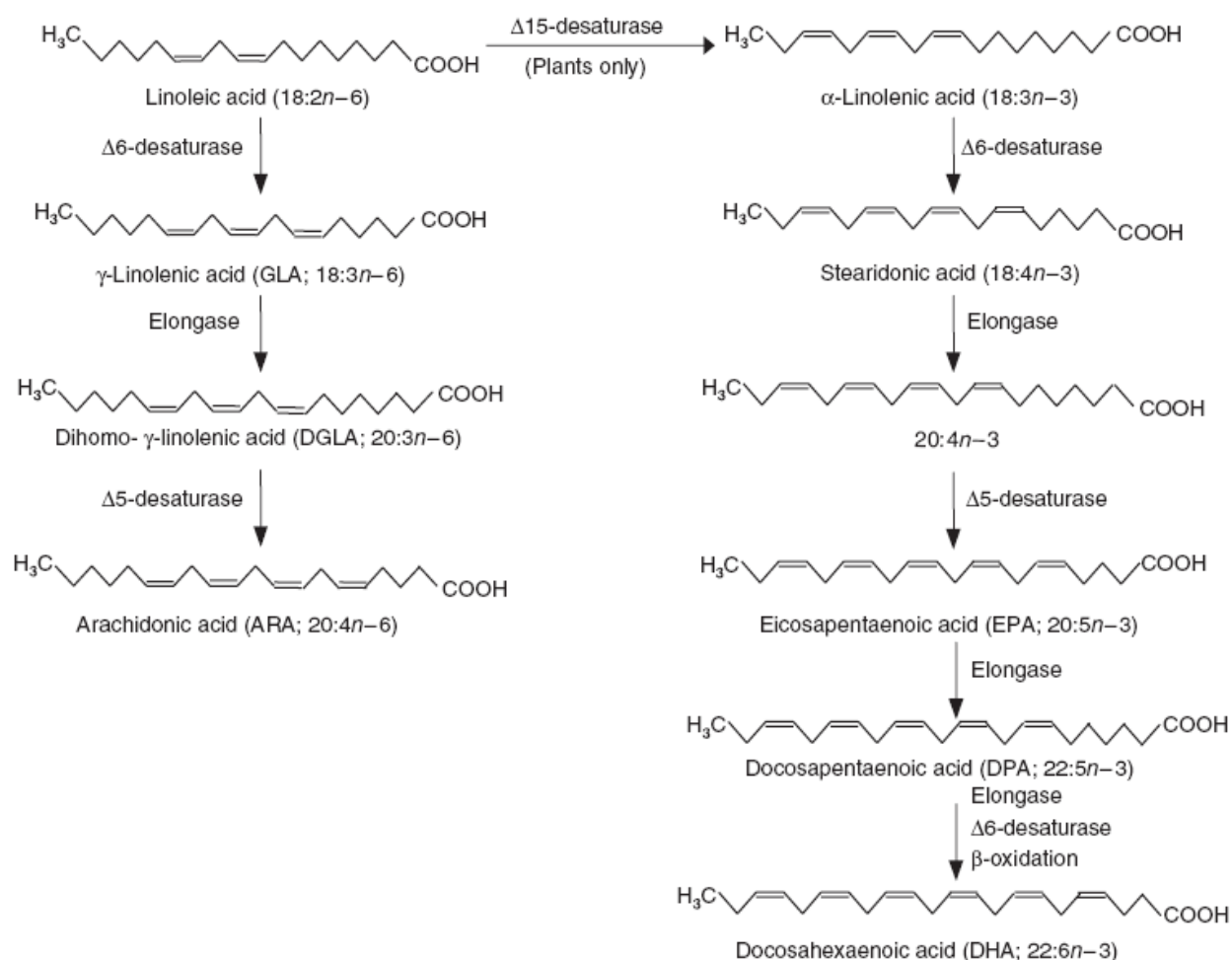


Fig. 2. Biosynthesis of some fatty acids (Sala-Vila et al. 2008)

2. Inflammation and PUFA

The relationship between inflammatory response and PUFA enriched diets has been investigated in recent years. Several studies show that PUFA can modify immunological and inflammatory reactions, and that it can be used as a complementary therapy in chronic diseases (Kinsella et al. 1990, Serhan et al. 2004).

Inflammation is a body's response to tissue injury, which can be triggered by mechanical stimuli, chemical or microbial invasion, as well as hypersensitivity reactions. This response includes complex processes that involve the immune system cells and biological mediators (Rankin et al. 2004). The acute phase response is characterised by increased blood flow and vascular permeability, increased accumulation of fluid, leukocytes and inflammatory mediators; meanwhile the chronic phase is characterised by the development of specific cellular and humoral immune responses against pathogens present at the site of injury (Saadi et al. 2002). Inflammation is characterised by redness, swelling, heat and pain. These signs occur primarily due to: vasodilatation, which allows increased blood flow to the

affected area; increased vascular permeability, which facilitates the diffusion of molecules such as antibodies; cytokines and other plasma proteins to the site of injury and cellular infiltration, which occur through chemotaxis and diapedesis and the direct movement of inflammatory cells through the vessel wall towards the site of inflammation. In addition, during the inflammatory response catabolic and metabolic changes may occur, as well as biosynthetic activation in various organs and enzyme systems and cells of the immune system.

The inflammatory response begins the process of immune elimination of invading pathogens and toxins for the repair of damaged tissue (Rang & Dale 1995). The nonspecific inflammatory response can be seen, for example, in the phagocytosis of bacteria or leftover tissue, the secretion of proteolytic enzymes, the production of reactive oxygen species and the secretion of molecular modulators. It can also be immune-mediated, where there is the participation of lymphocytes and antigen-presenting cells. This second type is closely associated with the onset and maintenance of chronic inflammation (Pompei et al. 1999).

The inflammatory process is controlled by cellular and molecular components. Among the cellular components are neutrophils, monocytes, lymphocytes, macrophages fixed, dendritic cells, mast cells and eosinophils. These cells accumulate in inflamed tissues and interact with the endothelial cells of the microcirculation. Different adhesion molecules participate in these interactions, including selectins, integrins and intercellular adhesion molecules (ICAM) (Rang & Dale 1995). Neutrophils constitute 60% of circulating leukocytes and act as the first line of cellular defence, and they may participate in both reactions as a nonspecific defence and as specific antigen reactions (Curi et al. 1997). Monocytes represent approximately 3-6% of circulating leukocytes in human blood, and they migrate to different tissues where they differentiate into macrophages in response to different stimuli. These cells participate in a variety of functions related to the host's defence, the most well known being the phagocytosis of microorganisms and cell debris, and cytotoxic activity against microorganisms, virus-infected cells and tumour cells (Curi et al. 2002).

The molecular components of inflammation include vasoactive substances (kinins, histamine), proinflammatory cytokines (such as Tumour Necrosis Factor (TNF), Interleukin (IL)-1 and IL-6), anti-inflammatory cytokines (such as IL-4, IL-10 and IL-13), chemokines, acute phase proteins, bioactive lipids (such as eicosanoids derived from AA), Platelet Activating Factor, diacylglycerol, ceramides, cAMP, and inositol triphosphate, amongst others.

3. Inflammatory bowel disease and carcinogenesis

Inflammatory bowel diseases (IBDs) are chronic disorders of the gastrointestinal (GI), which generally refer to two conditions, namely ulcerative colitis and Crohn's disease (Galvez et al. 2006). IBDs are characterised by chronic diarrhoea, malabsorption, mucosal barrier dysfunction and inflammatory intestinal process, being incurable clinically (Benedetti & Plum 1996). Ulcerative colitis encompasses a spectrum of diffuse inflammation and the continuous surface of the colon, which begins in the rectum and may extend to the proximal level. Crohn's disease is characterised by transmural inflammation affecting any asymmetric portion of the GI tract, from the mouth to the anus (Benedetti & Plum 1996).

IBDs cause nutritional deficiencies, such as calorie and protein malnutrition, and deficiencies in vitamins, minerals and trace elements. This underscores the importance of

nutritional therapy in their treatment (Ferguson et al. 2007, Pizato et al. 2005, Razack et al. 2007). Malnutrition is common in these patients, and interventions through adequate nutritional therapy so as to restore the nutritional status have been associated with an improved recovery process involving the improvement of the immune system during periods of the exacerbation of the disease (Razack et al. 2007). Several characteristics contribute to the malnutrition observed in patients: 1) there is a decrease in the oral intake of nutrients associated with abdominal pain and anorexia; 2) the mucosal inflammation associated with diarrhoea leads to a loss of protein, minerals, blood, electrolytes and trace elements. In addition, multiple resections or bacterial overgrowth in the colon can cause adverse effects, such as the poor nutritional absorption of micronutrients; 3) drug therapies can lead to malnutrition. For example, sulfasalazine reduces the absorption of folic acid, and corticosteroids reduce calcium absorption and adversely affect the protein metabolism (Wild et al. 2007).

Although much progress has been made in understanding IBD, its aetiology is not fully elucidated. However, it is believed that there is involvement of immune factors, both genetic and environmental (Laroux et al. 2001, Cheon et al. 2006, Sainathan et al. 2008). Some studies have suggested that IBDs represent an inappropriate and exaggerated response of the intestinal mucosal immune system to normal intestinal microflora – in genetically susceptible individuals – which can be attributed in part to an imbalance between effector T cells (T eff) cells and T regulatory cells (T reg). (Sanchez-Muñoz et al. 2008, Ma et al. 2007). Effector T cells are helper T lymphocytes (lymph CD4 +) and cytolytic T lymphocytes (lymph CD8 +) that are activated during the adaptive or acquired immune response. The helper T cells secrete cytokines, whose function is to stimulate the proliferation and differentiation of T cells, as well as other cells including B lymphocytes, macrophages and other leukocytes (Sanchez-Muñoz et al. 2008, Sainathan et al. 2008). Cytolytic T lymphocytes destroy cells that produce antigens, such as cells infected by viruses or other intracellular microbes. Since regulatory T cells are cells capable of blocking the activation and effector function of T lymphocytes (Abbas & Lichtman 2005), some studies indicate that the suppressive action of these cells is linked to the secretion of immunosuppressive cytokines, such as IL-10 and Transforming Growth Factor Beta (TGF- β). TGF- β inhibits the proliferation of T and B cells, whereas IL-10 inhibits macrophage activation and is the main antagonist of Macrophage Activating Factor and Interferon Gamma (IFN- γ) (Sanchez-Muñoz et al. 2008).

The innate immune response in IBDs also plays an important role. This response is the first line of defence of the immune system, attended by phagocytic cells, natural killer cells, blood proteins, and including fractions of complements and other mediators of inflammation such as cytokines (Abbas & Lichtman 2005). Cytokines are polypeptides – produced mainly by immune cells – that facilitate communication between cells, stimulate the proliferation of antigen-specific effector cells, and mediate systemic inflammation and local roads in the endocrine, paracrine and autocrine (Muños-Sanchez et al. 2008). Dendritic cells and activated macrophages secrete various cytokines that regulate the inflammatory response. Once secreted, these cytokines promote the differentiation of T cells, activating the adaptive immune response (Abbas & Lichtman 2005). The T-helper cells or CD4 + T cells can differentiate into subpopulations of effector T cells that produce different sets of cytokines and, therefore, play different effector functions. The most well-defined subpopulations of effector T cells are T helper cells type 1 (Th1) and type 2 (Th2) (Abbas &

Lichtman 2005, Fuss et al. 2004). IFN- γ is associated with Th1 cells, while IL-4 and IL-5 are associated with Th2 cells. Today it is clear that individual cells can express various mixtures of cytokines, and that there may be many sub-populations with heterogeneous patterns of cytokine production. However, chronic immune reactions are often dominated by either Th1 or Th2 populations (Kampen et al. 2005). These sub-populations show differences in the expression of several cytokine receptors, and these differences may reflect the activation state of the cell, determine their effectors' functions, and participate in the development and expansion of their sub-populations (Abbas & Lichtman 2005). IBDs can cause an imbalance between regulatory T cells and T effector cells Th1/ Th2. The lack of appropriate regulation of T cells and the overproduction of effector T cells are related to the development and exacerbation of IBDs (Muños-Sanchez et al. 2008, Zhang et al. 2005).

Patients with IBDs, particularly ulcerative colitis, are at risk of developing cancer that is 10 times higher than that of the general population, indicating that chronic intestinal inflammation is an important risk factor for developing colon cancer (Gommeaux et al. 2007). Some studies have shown that the risk of developing cancer increases exponentially with the duration of the illness, and the extent and intensity of inflammation in the intestinal mucosa (Burstein & Fearon 2008).

The process of carcinogenesis seems to involve a sequence of events, where the chronically inflamed and hyperplastic epithelium progresses to initially flat foci of dysplasia, adenoma and finally to adenocarcinoma. Uncontrolled inflammation is associated with oxidative stress and oxidative cell damage. During cell proliferation, oxidative DNA lesions induce mutations that are commonly observed in oncogenesis and tumour suppressor genes, such as p53 (Gommeaux et al. 2007, Seril et al. 2003). It is likely that the cells of the colonic mucosa, persistently subjected to oxidizing agents, suffer progressive oxidative damage in their DNA, which can cause mutations in tumour suppressor genes (p53), oncogenes (k-ras) and genes that encode the repair of proteins (MSH2 and MLH1) (Gommeaux et al. 2007). The initiation of carcinogenesis is caused by an irreversible alteration of the DNA through the reaction of this molecule with carcinogenic substances. Thus, mechanisms of carcinogen detoxification, DNA repair, and the elimination of cells that have modified DNA (apoptosis, for example), are important for protection against cancer initiation (Brown et al. 1994). For initiation to occur requires not only the modification of DNA, but also its replication and cell proliferation, so that the original mutation can be fixed. Most human cancers originate from epithelial cells (carcinoma), as these are exposed to carcinogens (in the air or in food) and they are rapidly proliferating (Bartsch et al. 1996). In general, electrophilic substances are carcinogens or are metabolised to carcinogens substances during the process of detoxification. Such substances are attracted to molecules with high electron densities – such as DNA bases – which end up calling and leading to the formation of adducts (Bartsch et al., 2006).

The basis of the DNA which is more susceptible to this type of attack is guanine, but the adducts thereby formed have been reported in other bases. Being formed in DNA by specific chemical mechanisms, such adducts may lead to mutations in proto-oncogenesis or tumour suppressor genes, and they start the process of carcinogenesis (Lehman et al. 1994, Kinzler et al. 1996).

It is well established that inflammation facilitates the progression of normal cells to malignant cells, the production of pro-inflammatory cytokines such as TNF, IL-1, IL-6, IL-23 and reactive oxygen species (ROS) and nitrogen (Bartsch et al. 2006, Roessner et. al. 2008).

ROS – which are the cellular consequences of oxidative stress – may cause DNA oxidation, resulting in damage to all four bases and in the deoxy-ribose-molecule triggering the appearance of genetic mutations and initiating colorectal carcinogenesis (Chapkin et al. 2007).

With the large number of cytokines and growth factors released during inflammation, the immune cells and nonimmune cells may influence the process of carcinogenesis (Fantini et al. 2008). These mediators activate NF- κ B, inducible nitric oxide synthase, and cyclooxygenase-2-related signalling pathways, which are associated with the delay or suppression of the apoptosis of intestinal epithelial cells and the modulation of angiogenesis (Chapkin et al. 2007, Fantini et al. 2008). Apoptosis – programmed cell death – is the mechanism by which the intestine eliminates cells with irreparable DNA damage, and the inhibition of this response is a characteristic of colon cancer (Bancroft et al. 2003).

The integrity of DNA is vital for cell division, and oxidative changes may interfere with transcription, translation and DNA replication, and may also increase mutations, senescence and cell death (Miranda et al. 2008).

4. Inflammatory bowel disease and dietary fatty acids

Epidemiological studies have been conducted in an attempt to correlate nutritional factors with chronic diseases and carcinogenesis on set. In this context, we can observe in recent years a drastic alteration in dietetic habits, mainly in lipids' composition and contents (Wild et al. 2007), leading to an association with the type and amount of fatty acid intake by diet, and the development of diseases (Figler et al. 2007). Asian countries that have changed from a traditional diet (i.e. high in fish and cruciferous vegetables) to a Western diet lifestyle (i.e. high in red meat and saturated fat), such as Singaporean Chinese (who have had a historically low risk for colorectal cancer), have doubled this risk in the past three decades, after dietetic modification (Stern et al. 2009).

Linoleic acid intake, in western countries, increased considerably in the 20th century, followed by vegetable oil and margarine introduction, which resulted in a significant rise in the n-6:n-3 PUFA ratio in the diet (Calder 2008). The incidence of IBDs is higher in western populations and has increased in developing countries which have adopted industrialised urban lifestyles associated with changes in dietetic habits, including an increased fast food intake with high lipids content (Wild et al. 2007).

PUFA n-6 and n-3 are incorporated in cell membrane phospholipids and can influence immunological and inflammatory responses by modifying fluidity, the antioxidant defence system and the inflammatory mediators (Calder 2008, Kinsella et al. 1990, Simopoulos 2003).

N-3 PUFA, EPA and DHA competitively inhibit AA oxygenation by cyclooxygenase, decreasing the synthesis of eicosanoids from series 2 and 4 from AA, with a concomitant increase in prostaglandin (PG), tromboxanes (TX) from 3 series and leukotrienes from 5 series (Yaqoob & Calder 1995). On the other hand, an excessive amount of n-6 PUFA, in diet poor in n-3 PUFA, can contribute to PGE₂, TXA₂ and LTB₄ overproduction – potent inflammatory mediators. Eicosanoids produced from EPA (n-3 PUFA) are, in general, less active in inflammatory process than derived AA eicosanoids (Calder 1996, 1998, Kikuchi et al. 1998).

The inflammatory response is designed to remove the inciting stimulus and resolve tissue damage. However, excessive inflammatory response can cause local tissue damage and

remodelling, which may lead to a significant and chronic injury. Therefore, acute inflammation in healthy individuals is self-limited and has an active termination program (Seki et al. 2009). In the past, it was believed that this termination program was a passive mechanism but, nowadays, it is known that the process of the resolution of inflammation is an active and well controlled event. In part, this is due to the formation of newly endogenous mediators that act as local autacoids stimulating proresolving mechanisms (Serhan 2007, Gilroy et al. 2004). These proresolving mediators are derived from essential fatty acids, and include lipoxins (LX) from AA and resolvins (Rv) and protectins from EPA and DHA (Gilroy et al. 2004), that are biosynthesised in inflammatory exudates during spontaneous resolution (Figure 3).

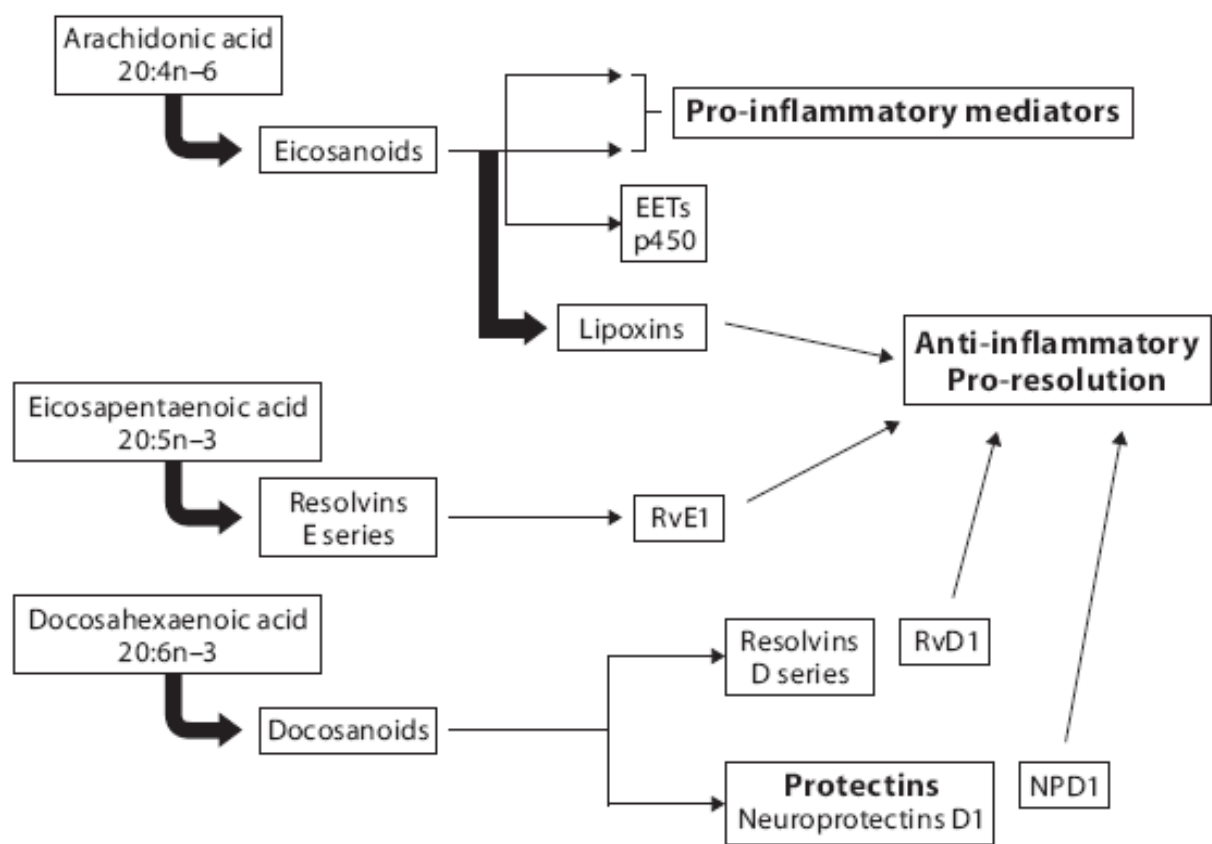


Fig. 3. News inflammatory mediators (Galli & Calder 2009)

The process of the resolution of inflammation has become a topic of interest because of expanding views of their action, particularly in chronic disorders where unresolved inflammation is a key factor leading to colon carcinogenesis. These newly identified LXs and Rvs have proven to be potent regulators of both leukocyte and cytokine production, thereby regulating the events of interest in inflammation and resolution. In light of the existing knowledge of the interconnected pathways of pro-inflammatory mediators (leukotrienes, chemokines (IL8, SDF-1 α , MIP-1 α , MCP-1,2 etc), and cytokines (IL3, IL6, IL12, IL-1 β , GM-CSF, B94, TNF- α etc)), the anti-inflammatory properties of pro-resolving mediators in preventing the chronic inflammation which leads to carcinogenesis requires further study. Clinical trials have demonstrated the beneficial effects of fish oil supplementation – rich in EPA and DHA – in chronic and acute inflammatory conditions (Innis et al. 2006, Simopoulos

et al. 2002, Harbige 1998, MacLean 2005). Fish oil supplementation seems to increase apoptosis on top of colonic crypts, where tumours and polyps are usually developed (Paulsen et al. 1997; Courtney et al. 2006, Hong et al. 2005). Bégin et al. (1991) showed that under some specific conditions, long chain PUFA – mainly GLA, AA, EPA, and DHA – are the most effective for inducing tumour cell death. However, this effect depends upon the type of cancer cells tested and the concentration of the fatty acid used.

The role of n-3 and n-6 PUFA on cancer development has been extensively investigated in epidemiological and experimental studies. The contrasting role of these fatty acids in carcinogenesis – n-3 as protectors and n-6 as promoters – remains as an intriguing question in the fields of nutritional and cancer research (Eder et al. 2008).

In rats with colitis induced by Dextran Sulphate Sodium (DSS), our group showed that a normal fat PUFA rich diet, with a balance on the n-6:n-3 ratio, can increase IL-10 cytokine – an immunoregulatory cytokine that influences the immunological system – both on the innate and cell-mediated response, reduce disease activity and the loss of weight, improve the histological score and protect against DNA damage (Barros et al., 2010). IL-10 is considered an immunoregulatory cytokine which exerts effects in both the innate immune response and in the adaptive immune response. IL-10 Knockout animals, for example, develop colitis spontaneously, and 30 to 60% of these animals show invasive carcinoma of the colon between 3 and 6 months of age (Hegazi et al. 2006, McCafferty et al. 2000). These animals have two important characteristics: 1) an increased intestinal permeability in an early age, and before the onset of the disease; 2) the development of colitis, dependent on the microbiological presence in the intestinal lumen. These characteristics suggest that the colitis observed in these animals can develop as a consequence of the high intestinal permeability that increases in the luminal agent's mucosal immune system (Arrieta et al. 2008). Some studies have demonstrated the role of IL-10 on gastrointestinal mucosal homeostasis maintenance. The mechanism by which this cytokine regulates mucosal inflammation is probably multifactorial; however, it is associated with reduced antigen presentation (Hegazi et al. 2006, McCafferty et al. 2000), an increased release of IFN- γ and IL-12 – a cytokine that inhibits the differentiation of T lymphocytes into Th1 lymphocytes (Rennick & Fort 2000). There is strong evidence that IL-10 promotes the differentiation and the increase of the activity of the regulatory T cells (Hegazi et al. 2006). *In vitro* studies have demonstrated that the administration of IL-10 reduces the release of pro-inflammatory cytokines in lamina propria mononuclear cells amongst patients with Crohn's Disease. In addition, high doses of IL-10 administered intraperitoneally into mice with colitis, induced by Trinitrobenzenesulphonic acid (TNBS), are able to restore the tolerance of the lamina propria mononuclear cells (Duchmann et al. 1996).

Considering the abundance of fatty acids in cells and its susceptibility to oxidation, PUFA are – for the oxidants – more likely targets than DNA (Shimizu et al., 2001, Wagner et al., 1994). It is estimated that approximately 60 molecules of linoleic acid and 200 of arachidonic acid are consumed by oxidants that react with the lipid bilayer. Autocatalytic oxidation triggers a cascade that generates numerous genotoxic substances, and such damage to lipids has important implications for the integrity of DNA (Wagner et al., 1994). The peroxidation of membrane lipids initiates autocatalytic breaks with the consequent formation of cytotoxic and genotoxic metabolites, such as malondialdehyde and hydroxynonenal. The degradation of these products can interfere with intracellular signalling cascades, involving replication and cell death (Eder et al. 2008).

The dietary lipids that are related to the pro-oxidative attack of the colonic epithelial cells may be an important contributor to carcinogenesis (Nowak et al. 2007, Udilova et al. 2003). So far, there is still no specific treatment for IBDs and the best strategy to regulate the exacerbated inflammatory response is to interfere with the multiple phases of the inflammatory cascade with anti-inflammatory and immunosuppressive drugs. These drugs, however, have serious side-effects that limit their use (Stein et al., 2000). Dietary treatment may be an alternative to drug therapy (Camuesco et al., 2005, Nowak et al., 2007).

Although the high intake of PUFA has been related to colorectal cancer, several studies show that, besides the genotoxic effects of lipid peroxidation, epigenetic factors may also be responsible for an increased cancer risk after excessive PUFA intake (Nystrom et al. 2009). Using a model of DSS colitis and a high fat diet (20%), in our laboratory, we did not observe an exacerbation of experimental ulcerative colitis in relation to the diet control group (5%). Besides, the great balance in the n-6:n-3 PUFA ratio (2:1) caused beneficial effects on both pro- and anti-inflammatory cytokine balance and protected the DNA against damage (Barros et al. 2010).

Sasasuki et al. (2010) in an epidemiological study where it was inquired as to whether the intake of n-3 and n-6 PUFA are related to a decreased risk of colorectal cancer development. They found that, in a population with high fish consumption and a wide range of n-3 PUFA intakes, the PUFAs originating with marine consumption may be inversely related to the risk of cancer in proximal sites of the large bowel. On the other hand, Dahm et al. (2010), in a case-control study nested within seven prospective UK cohort studies, comprising 579 cases of the incidence of colorectal cancer and 1996 matched controls, did not find any association between total dietary fat, saturated, monounsaturated and PUFA intakes, and colorectal cancer risk.

5. Polymorphisms

Conclusive evidence between colorectal cancer and PUFA in epidemiological studies may be related to genetic influence. The relationship between genes and the environment has been recognised as central to knowledge of disease and health. During the last two decades, advances in molecular biology have demonstrated that genetic factors determine disease susceptibility, while environmental factors determine whether or not genetically susceptible individuals will be affected (Simopoulos et al. 2008, Paolini-Giacobini et al. 2003). In this context, nutritional aspects are beginning to be considered as one of the most important environmental factors (Simopoulos et al. 2008). Several studies have shown the mechanisms by which genes may influence the metabolism of nutrients, as well as the mechanisms by which nutrients can influence gene expression (Simopoulos et al. 2008, Paolini-Giacobini et al. 2003, Calder 2007). With advances in science, and emphasis on the study of nutrigenomics and nutrigenetics, it has been shown that certain nutrients can influence the inflammatory response, accelerating or regressing the development of many diseases (Heller et al. 2002, Weiss et al. 2002, Mayer et al. 2003, Paolini-Giacobini et al. 2003, Simopoulos et al. 2008).

Stern et al. (2009), from the Singapore Chinese Health Study, through analyses taking into account variants in genes that are relevant for the proposed PUFAs mechanism of action – hypothesised that the genes which play key roles in the pathways that repair PUFA-induced damage might modify the effect of these FA on colorectal cancer. This study also showed that diets high in marine n-3 PUFA were positively associated with colorectal cancer risk

(Stern et al. 2009). However, using a subset of this prospective cohort, Stern et al. (2009) reported that the marine n-3 PUFA association with rectal cancer is confined to those who carry the PARP codon 762 Ala allele. The PARP protein plays an important role in maintaining genomic stability, apoptosis, and in regulating transcription.

In this regard, some studies have shown that genetic variability in the FADS1-FADS-2 gene cluster, and the encoding delta-5 (D5D) and delta-6 (D6D) desaturases, have been associated with plasma long-chain PUFA and lipid levels in adults (Bokor et al. 2010). Desaturases and elongases catalyse the conversion of PUFAs in humans. The D5D and D6D desaturases are known to be the key enzyme of this pathway. Both desaturases are expressed in a majority of human tissue, with the highest levels in liver, but also with major amounts in the brain, the heart and the lungs. The hypothesis that they play a key role in inflammatory diseases is strengthened by functional studies in mice, where selective D5D and D6D inhibitors showed an anti-inflammatory response.

Several single nucleotide polymorphisms (SNP) in FADS genes were reported in humans, and some showed association between FADS SNPs and fatty acids in serum or plasma phospholipids, and erythrocyte membrane and adipose tissue (Schaeffer et al. 2006, Malerba et al. 2008, Rzehak et al. 2009), demonstrating that these concentrations are influenced not only by diet, but also to a large extent by genetic variants common in the world population (Koletzko et al. 2011).

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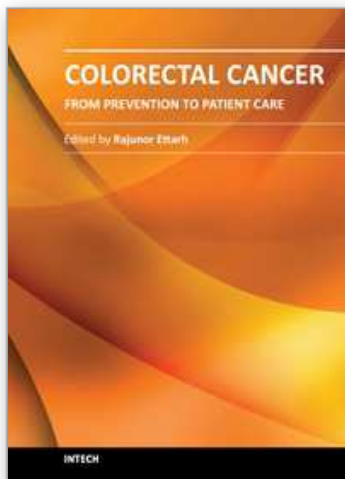
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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