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The Effects of n-3 Polyunsaturated Fatty Acid-Rich Salmon on Inflammatory Bowel Diseases

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1. Introduction

Inflammatory Bowel Disease (IBD) is a disorder of the gastrointestinal tract that is characterised by chronic inflammation, with high incidence in Westernised countries (Yamamoto et al., 2009). Long-chain n-3 polyunsaturated fatty acids (PUFA), in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are purported to be important for maintaining health and protection against disease (Connor, 2000). They exhibit beneficial effects with respect to cardiovascular diseases, rheumatoid arthritis, inflammatory diseases and neurodegenerative illnesses (Wahrburg, 2004). PUFA can modulate the inflammatory response (Calder, 2008) and could therefore be an important factor in the course of IBD. Several studies have tested the anti-inflammatory potential of pure n-3 PUFA extracts, fish oil and whole fish, however, the results of these studies are inconsistent (effects of dietary n-3 PUFA on animal models of colitis reviewed in Calder, 2008; effects of dietary n-3 PUFA in intervention studies with IBD patients reviewed in Ferguson et al., 2010). Nevertheless, experimental evidence (Knoch et al., 2009) has shown potential anti-inflammatory effects of dietary EPA supplementation, a nutrient which is found in high levels in salmon. Furthermore, New Zealand IBD patients recorded a higher tolerance to salmon compared with other foods on the basis of a food frequency questionnaire (Triggs et al., 2010) and salmon has shown beneficial effects for patients with mild IBD (Grimstad et al., 2011). Various factors play a role in the development of IBD, however, the focus of this review is the effect of dietary n-3 PUFA and n-3 PUFA-rich food such as salmon.

2. Background

2.1 Inflammation in inflammatory bowel disease

The inflammatory response is the beginning of an immunological process and is necessary to protect the body against invading pathogens and toxins. The response is typified by

activation/production of at least the following four classes of active molecules (Chapkin et al., 2009): (i) adhesions molecules (*e.g.* vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin) on the surface of endothelial cells, allowing leukocyte binding and subsequent diapedesis; (ii) inflammatory cytokines (*e.g.* tumor necrosis factor alpha (TNF α), interleukin (IL) 1, IL6 and IL8); (iii) arachidonic acid (AA)-derived eicosanoids; and (iv) inflammatory mediators (*e.g.* platelet activating factor). The activation/production of these molecules must be ordered and controlled to avoid excessive damage to host tissue and chronic inflammatory disorders (Calder, 2006). This defect in resolving inflammation and returning the target tissue back to homeostasis is a hallmark of IBD (Chapkin et al., 2009). While the rate of new cases of IBD is beginning to stabilise in high-incidence areas, including northern Europe and North America, countries with traditionally low occurrence rates (*e.g.* southern Europe, Asia and developing countries) are reporting an increased rate of new patients (Loftus, 2004). Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of IBD and although the two forms have distinctive characteristics, they share many common symptoms and can be difficult to distinguish clinically (Lee & Buchman, 2009; Teitelbaum & Allan Walker, 2001). The aetiology of IBD is largely unknown, but it is generally accepted that genetic factors and the environment play a role (Ferguson, 2010; Hanauer, 2006; Lee & Buchman, 2009). Furthermore, the tolerance of the mucosal immune system to the commensal intestinal microbiota is disrupted and dysregulation of the immune system occurs (Duchmann et al., 1995).

Observations in twin studies have highlighted that susceptibility to IBD, in particular CD, is inherited (Bouma & Strober, 2003). The genetics of IBD is complex and it is suggested that variations in key genes, for example single-nucleotide polymorphisms (SNPs), play a role. SNPs are genetic variations in the DNA sequence, whereby only a single nucleotide is changed. Approximately seven million common SNPs have been found across the human population (Hinds et al., 2005). While only a few of these may have a functional effect (Stover, 2006), some variations can affect health or even cause disease (Lee & Buchman, 2009). Currently, 99 susceptibility loci/genes are known to contribute susceptibly to IBD (Lees et al., 2011). One of the first susceptibility loci was found to be a polymorphism of the caspase recruitment domain family member 15 (CARD15) gene, which encodes the protein nucleotide-binding oligomerization domain 2 (NOD2) (Hugot et al., 1996; Hugot et al., 2001).

Environmental factors such as dietary changes, smoking, oral contraceptives, appendectomy and stress can affect the development of IBD (Krishnan & Korzenik, 2002; Loftus, 2004). In the last three decades, the incidence of IBD in Japan has increased sharply, correlating with changes in dietary preferences towards a Western-type diet (Yamamoto et al., 2009). This implies that dietary choice is an important factor in the development of IBD. The lipid profile of Western-type diets features excessive amounts of saturated fats and n-6 PUFA, but a deficiency of n-3 PUFA. This imbalance leads to an altered n-6/n-3 ratio, which may promote the pathogenesis of many diseases including IBD (Simopoulos, 2008). Thus increasing the n-3 PUFA intake and lowering the ratio of n-6/n-3 PUFA in the diet may reduce the risk of developing chronic diseases.

The molecular mechanisms underlying the interaction of nutrients including n-3 PUFA with an individual's genome are very complex, and also poorly understood (Stover, 2006; Weaver et al., 2009). To improve the understanding of these gene-diet interactions, the field of nutrigenomics has evolved with the aim of developing a personalised strategy for health maintenance or disease treatment (Ferguson, 2010). In nutrigenomics research, nutrients are

considered signalling molecules that can target the cellular sensor system and therefore subsequently influence gene expression, protein expression and metabolite production (Subbiah, 2008). These dietary signals can cause changes in the organism, tissue or single cells and subsequently influence homeostasis (Müller & Kersten, 2003).

2.2 Dietary intake of lipids

2.2.1 Fatty acids

Fatty acids form the major component of dietary fats, and dietary sources range from free fatty acids to phospholipids, sterols and triacylglycerol (TG) (Ratnayake & Galli, 2009). The term fatty acid describes a carboxylic acid with an aliphatic chain that can be saturated or unsaturated. The degree of un-saturation is addressed by the number of double bonds between the carbon atoms of a fatty acid. A fatty acid that contains two or more double bonds between the carbon atoms is classified as polyunsaturated, while monounsaturated fatty acids (MUFA) contain only one double bond. The classification into n-3 and n-6 PUFA is based on the position of the first double bond, starting from the terminal methyl end. In general, short-chain unsaturated fatty acids refer to 19 or fewer carbon atoms, long-chain to 20-24 carbon atoms and very-long-chain to 25 or more. The reactivity of fatty acids increases with double bonds; therefore, saturated fatty acids are more stable and have a longer shelf life than unsaturated ones (Ratnayake & Galli, 2009).

The dietary intake of lipids is predominately through TG, which is the vast majority of lipid found in vegetable oils and animal fats (Ratnayake & Galli, 2009). TG are characterised by a glycerol backbone connected to three molecules of fatty acids (sn-1, sn-2 and sn-3, starting from the top of the glycerol), whereby the three hydroxyl groups from the glycerol backbone form an ester bond with the carboxyl groups from fatty acids (Fahy et al., 2005). Nutritionally, the distribution of fatty acids over the three sn-positions changes biological activity and absorption pattern, whereas the composition of sn-2 is of importance due to facilitated absorption (Ratnayake & Galli, 2009). In Atlantic salmon, the TG in the depot fat comprise ~70% DHA on sn-2 position, whereas EPA is nearly randomly distributed (40% on sn-2) (Aursand et al., 1995). In order to be absorbed by the gastrointestinal tract lining, TG need to be digested, *i.e.* broken down into smaller components (Ratnayake & Galli, 2009). The small intestine is the main site for fat digestion, where the pancreatic lipase hydrolyses TG at sn-1 and sn-3 position, yielding final products of 2-monoacylglycerols and free fatty acids (Mu & Porsgaard, 2005). Free fatty acids are directly absorbed through the intestinal wall and 2-monoacylglycerols form micelles that further diffuse to the epithelial cells, where they leave the micelles and enter epithelial cells by diffusion. In the enterocytes, they are transported to the endoplasmic reticulum in association with a fatty acid binding protein (FABP) and are re-synthesised to TG. Newly synthesized TG are transported out of the enterocyte and enter the bloodstream *via* the lymph vessels in the form of chylomicrons. In the bloodstream, the TG of the chylomicrons are hydrolysed to free fatty acids and glycerol that then pass through the capillary walls to be used by cells as the major substrates for energy production and storage (Ratnayake & Galli, 2009). Some fatty acids (*e.g.* DHA, EPA and AA) have additional roles in modulating the structural and functional properties of cells (Galli & Calder, 2009).

2.2.2 Fatty acid metabolism

Due to its abundance in food, many human populations over-consume n-6, but consequently lack long-chain n-3 PUFA (Calder, 2006; Ratnayake & Galli, 2009), resulting in

an n-6/n-3 ratio of ~10:1 to 20-25:1, which may promote the pathogenesis of many diseases including inflammatory disorders (Simopoulos, 1991). Whereas humans evolved on a diet with a ratio of ~1:1 (Simopoulos, 2008), a ratio of 4:1 is recommended as optimal (Wall et al., 2010), but this may vary with disease state (Simopoulos, 2008). It has been suggested that lowering the n-6/n-3 ratio in the diet should be achieved by increasing the amount of n-3 PUFA rather than by simply reducing n-6 PUFA, which may reduce the risk of developing chronic diseases (Camuesco et al., 2005; Simopoulos, 2008). The long-chain PUFA AA, EPA and DHA are supplied to tissues from dietary sources, either *via* direct supplementation or *via* the consumption of the precursor PUFA linoleic acid (LA; n-6 pathway) and α -linolenic acid (ALA; n-3 pathway). LA and ALA cannot be synthesised in the human body, but can be metabolised to longer-chain fatty acids. This conversion of LA and ALA occurs *via* several elongation and desaturation steps (Fig. 1), with competition for the same enzymes on both pathways (Calder & Yaqoob, 2009). LA, the parent fatty acid on the n-6 PUFA pathway, is metabolised to AA, whereas ALA on the n-3 PUFA pathway is metabolised to EPA and further to DHA. However, as the conversion of ALA to EPA is limited and further conversion to DHA is even lower (Burdge & Calder, 2005; Garg et al., 2006), direct DHA and EPA supplementation is more effective than *de-novo* synthesis in increasing long-chain n-3 PUFA concentrations in the cell membrane (Hamilton et al., 2005).

3. Putative mechanisms of action

Long-chain PUFA are taken up by inflammatory cells and incorporated into membrane phospholipids (Leslie, 2004). Membrane phospholipids of inflammatory cells from humans consuming Western-type diets possess a relatively high amount (>20%) of n-6 PUFA, whereas long-chain n-3 PUFA represent less than 1% of fatty acids (Calder, 2006). The result

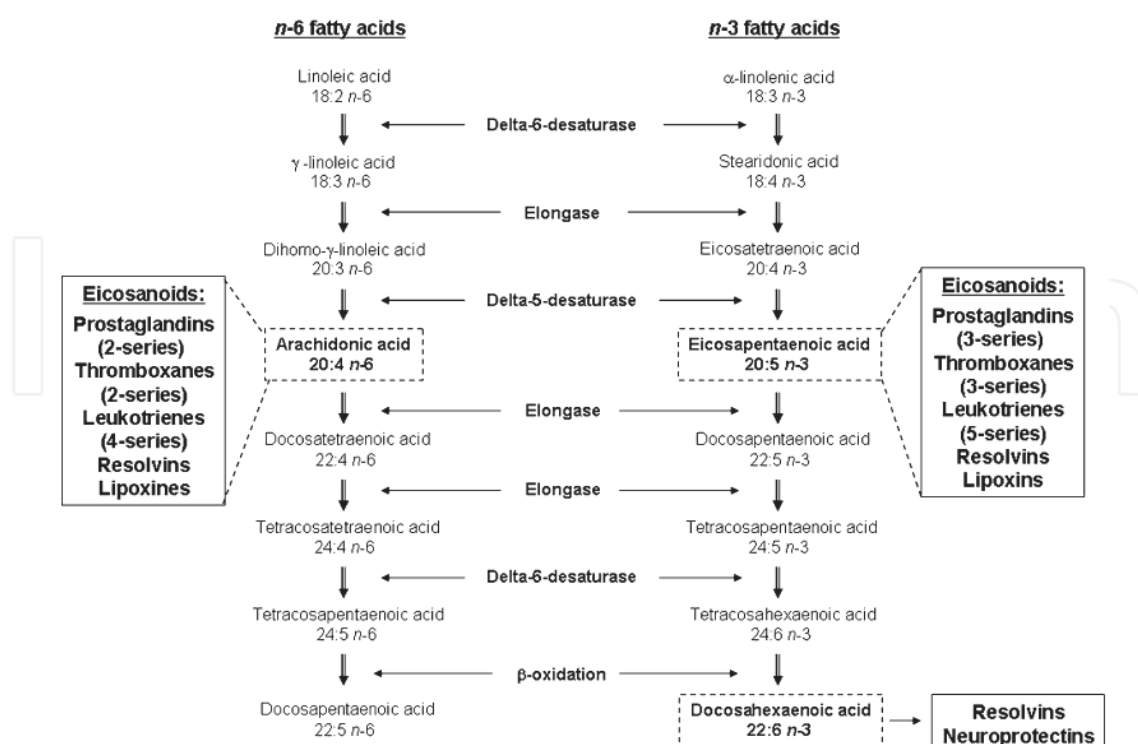


Fig. 1. Metabolism of n-6 and n-3 PUFA from precursor fatty acids (Wall et al., 2010)

is an unbalanced n-6/n-3 ratio which can promote a pro-inflammatory phenotype. The dietary intake of foods rich in EPA and DHA results in membrane replacement of n-6 PUFA in a time and dose-dependent manner, which may contribute to anti-inflammatory effects (Calder, 2009). How an elevated dietary intake of n-3 PUFA exerts its beneficial effects is not fully understood, but the putative mechanisms of action of n-3 PUFA are illustrated in Fig. 2. These include alterations in (i) cell membrane lipid bi-layer composition; (ii) gene expression; and (iii) lipid mediator metabolism (Chapkin et al., 2009). The overall physiological outcome depends on several factors, for example, the quantity and chemistry of the fat ingested, the cells present, cell-specific fatty acid metabolism (oxidative pathways, kinetics, and competing reactions) or the nature of the stimulus (Calder et al., 2009; Jump & Clarke, 1999). However, the different effects of DHA versus EPA are not well studied (Chapkin et al., 2009).

Lipid rafts are complex micro-domains in the cell membrane that appear to serve as platforms for receptor-mediated signal transduction (Calder & Yaqoob, 2007; Chapkin et al., 2009). When incorporated into cell membrane phospholipids, n-3 PUFA can increase membrane fluidity (Li et al., 2005), however, lipid rafts are far more sensitive to the incorporation of n-3 PUFA than non-raft domains (Rockett et al., 2011). A modulation of the lipid composition in rafts is associated with altered signalling pathways (Li et al., 2005; Schley et al., 2007; Stulnig et al., 2001).

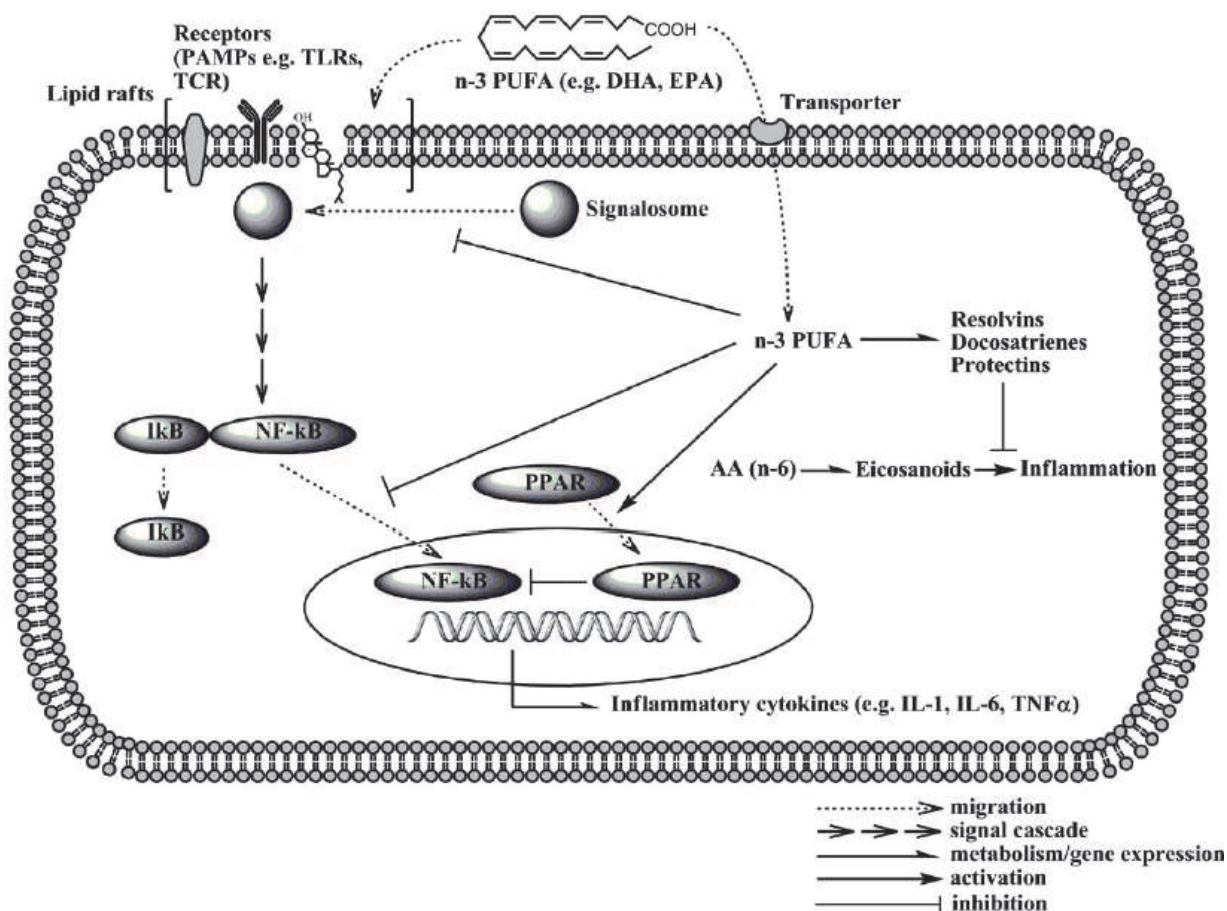


Fig. 2. Putative mechanism of action of PUFA. These include alterations in lipid mediator synthesis, gene expression, lipid composition in cell membrane and signal transduction (Chapkin et al., 2009)

Dietary n-3 PUFA can be transported into the cell *via* passive diffusion or active protein-mediated transport (Bordoni et al., 2006), depending on the chain size. Longer-chain fatty acids are actively transported *via* fatty acid transport proteins (FATP) 1-6 and/or CD36 (Bordoni et al., 2006; Heimerl et al., 2006). Inside the cell, n-3 PUFA can give rise to the anti-inflammatory lipid mediators resolvins and protectins (Serhan et al., 2008) and in turn competitively inhibit the production of mainly pro-inflammatory eicosanoids from AA. Furthermore, alterations in gene expression by n-3 PUFA can be mediated by interaction with transcription factors. For example, the activation of peroxisome proliferator-activated receptors (PPARs) can suppress nuclear factor-kappaB (NFκB) translocation and thereby inhibit the expression levels of pro-inflammatory cytokine genes (*e.g.* IL1 or TNFα) (Chapkin et al., 2009).

3.1 The formation of lipid mediators from fatty acids

Lipid mediators including eicosanoids, resolvins and protectins are regulators of inflammation and are generated from long-chain PUFA (Fig. 1) (Calder, 2009). The biological activity and potency of lipid mediators is dependent on the PUFA substrate. The n-6 PUFA AA gives rise to several eicosanoids (*e.g.* series-2 prostaglandins and thromboxanes, series-4 leukotrienes), hydroperoxy- and hydroxy-eicosatetraenoic derivatives and lipoxins. The majority of eicosanoids derived from AA are pro-inflammatory; however, prostaglandin E₂ and lipoxin have been shown to exert anti-inflammatory effects (Calder, 2008). EPA is the substrate for the anti-inflammatory eicosanoids and resolvins (*e.g.* series-3 prostaglandins and thromboxanes and series-5 leukotrienes) and hydroperoxy- and hydroxy-eicosapentaenoic derivatives. DHA gives rise to anti-inflammatory and pro-resolution mediators (*e.g.* resolvins and neuroprotectin) (Wall et al., 2010). The enzymes which catalyse these conversions are at least two cyclooxygenase (COX) and several lipoxygenase (LOX) enzymes (Calder et al., 2009), thus an elevated n-3 PUFA intake can lead to competitive inhibition of eicosanoid production from AA. Consequently, the pattern of lipid mediator production can be modulated towards a decrease in mainly pro-inflammatory eicosanoids from n-6 PUFA and an increase in anti-inflammatory resolvins from EPA and DHA (Calder, 2008; Calder, 2009).

3.2 Modulation of gene expression by polyunsaturated fatty acids

As well as altering lipid mediator synthesis, dietary fatty acids can affect gene expression and subsequently influence metabolism, growth and cell differentiation (Jump & Clarke, 1999). The mechanisms for these influences may be *via* intermediate molecules (*e.g.* transcription factors, nuclear hormone receptors and lipid secondary messengers) that subsequently alter gene expression, or a direct interaction with target genes (Deckelbaum et al., 2006). The expression levels of genes encoding several key proteins involved in inflammation, lipid metabolism and energy utilisation have been identified to be modulated by n-3 PUFA (Deckelbaum et al., 2006).

3.2.1 Gene expression changes underlying intestinal inflammation

Differences in gene expression and metabolic pathways underlying intestinal inflammation can be characterised when inflamed colon tissue from interleukin-10 gene-deficient (*Il10*^{-/-}) mice is compared to colon tissue from healthy control mice. The gene expression levels in *Il10*^{-/-} mice on a control diet were mainly increased in the inflammatory and immune

response pathway, with pro-inflammatory genes encoding cytokines (*e.g.* $Il1\beta$ and $TNF\alpha$) or chemokine receptors (*e.g.* $Ccr5$) as examples (Table 2) (Knoch et al., 2009). Decreased expression levels were observed for genes involved in fatty acid metabolism and xenobiotic metabolism (Table 1) (Knoch et al., 2009). The decreased expression levels of genes associated with fatty acid oxidation may have a role in disease progression (Knoch et al., 2009) and have also been observed in colon tissue of IBD patients (Heimerl et al., 2006). Decreased mRNA levels of genes involved in xenobiotic metabolism were observed in $Il10^{-/-}$ mice. Detoxification and biotransformation alter xenobiotics, *i.e.* foreign compounds (Jakoby & Ziegler, 1990), and a dysfunction of these mechanisms exposes enterocytes to toxic luminal antigens (Langmann & Schmitz, 2006), promoting local injury (Sartor, 1995) and contributing to the pathophysiology of IBD (Crotty, 1994; Langmann & Schmitz, 2006). Expression levels of genes encoding tight junction proteins were decreased in colon tissue of $Il10^{-/-}$ mice (Knoch et al., 2009). Tight junctions are intercellular barriers that regulate the transport of large molecules between the intestinal epithelial cells (Balda et al., 1992) and a dysfunction leads to impaired intestinal integrity and increased permeability ('leaky gut') (Forster, 2008). A non-invasive method to assess intestinal permeability is the urinary measurement after an oral dose of sugar probes, for example sucralose, mannitol and lactulose (Arrieta et al., 2006; Farhadi et al., 2003). In $Il10^{-/-}$ mice, it was found that the ratio of lactulose/mannitol, a marker of small intestinal barrier permeability, was increased compared to control mice (Arrieta et al., 2009). The urinary excretion of sucralose, which indicates colonic damage, was also increased in $Il10^{-/-}$ mice.

Gene family (genes) down-regulated in the $Il10^{-/-}$ mouse compared to WT	Pathways influenced in the $Il10^{-/-}$ mouse compared to WT	The effect of PUFA on gene expression during intestinal inflammation		Reference
		EPA ($Il10^{-/-}$)	AA ($Il10^{-/-}$)	
ATP-binding cassette (Abca1, Abcb1 α (mdr1a), Abcc3)	Xenobiotic metabolism	Up	Up	A, C
Cytochrome P450 (Cyp2c40, Cyp2e1)	Xenobiotic metabolism	Up	Up	A, B, C
Glutathione S-transferase (Gsta4, Gstt1, Gstm1)	Xenobiotic metabolism	Up	Up	A, B, C
Interleukin (Il6)	Immune and inflammatory response	Down*	Down	B
Peroxisome proliferator-activated receptor (PPAR α)	Immune and inflammatory response	Up		A, C

Table 1. Selected genes and their associated pathways that are down-regulated in the $Il10^{-/-}$ mouse model, compared to wild-type (WT) mice, and the effects of polyunsaturated fatty acids in mouse models of intestinal inflammation (Table constructed with information from (A) Knoch et al., 2009; (B) Knoch et al., 2010a; (C) Reiff et al., 2009). (*) indicates a non-significant change.

Gene family (genes) up-regulated in the <i>Il10</i> ^{-/-} mouse compared to WT	Pathways influenced in the <i>Il10</i> ^{-/-} mouse compared to WT	The effect of PUFA on gene expression during intestinal inflammation			Reference
		EPA (<i>Il10</i> ^{-/-})	AA (<i>Il10</i> ^{-/-})	DHA (BALB/c + DSS)	
S100 calcium binding protein (S100a8, S100a9)	Oxidative stress response	Up*	Down	Down	A, B
Tumor necrosis factor alpha (TNF α)	Immune and inflammatory response	Down*	Down		B, C, D, E
Tumor necrosis factor receptor superfamily, member 1b (Tnfrsf1 β)	Immune and inflammatory response	Down	Down*	Down	A, B, D, E
Prostaglandin-endoperoxide synthase 2 (COX-2) (PTGS2)	Immune and inflammatory response	Down*	Down		C
Chemokine (C-C motif) receptor (Ccr5, Ccr7)	Immune and inflammatory response	Down			B
Interleukin (Il1 β)	Immune and inflammatory response		Down	Down	A, B, C
Matrix metalloproteinase (Mmp3, Mmp9, Mmp13)	Leukocyte extravasation signalling		Down	Down	A, B, C

Table 2. Selected genes and their associated pathways that are up-regulated in the *Il10*^{-/-} mouse model, compared to wild-type (WT) mice, and the effects of polyunsaturated fatty acids in mouse models of intestinal inflammation (Table constructed with information from (A) Cho et al., 2011; (B) Knoch et al., 2009; (C) Knoch et al., 2010a; (D) Knoch et al., 2010b; (E) Reiff et al., 2009). (*) indicates a non-significant change.

3.2.2 Modulation of gene expression by polyunsaturated fatty acids

PUFA-enriched diets were partly able to reduce expression levels of genes associated with inflammation (Table 1 and Table 2) (Cho et al., 2011; Deckelbaum et al., 2006; Knoch et al., 2009; Knoch et al., 2010a; Knoch et al., 2010b; Reiff et al., 2009). As illustrated in Table 1, expression levels of the PPAR α gene were increased by EPA-enriched diets. This is supported by a study in a pig model of IBD, where dietary LA increased colonic PPAR γ gene expression levels and dietary n-3 PUFA activated PPAR δ (Bassaganya-Riera & Hontecillas, 2006). In this study (Bassaganya-Riera & Hontecillas, 2006), the onset of

experimental IBD was either delayed (PPAR γ activation) or colonic regeneration and clinical remission accelerated (PPAR δ activation). The expression levels of the gene encoding for the S100a8 protein, associated with neutrophil activation (Ryckman et al., 2003), was increased in UC patients compared to healthy subjects (Dieckgraefe et al., 2000). Its expression level was also increased in mice with experimental colitis compared to healthy mice; DHA- and AA-enriched diets were able to reduce increased S100a8 gene expression levels in *Il10*^{-/-} mice, however, EPA-enriched diets were not (Cho et al., 2011; Knoch et al., 2009).

The transcription factors NF κ B and PPARs are reported to be modulated in inflammatory states and by dietary PUFA (Calder, 2008; Chapkin et al., 2009; Wall et al., 2010). NF κ B is a regulator of the inflammatory response and oxidative stress (Hassan et al., 2010) and its activation is triggered by extracellular inflammatory stimuli, followed by translocation of NF κ B to the nucleus and an increase in expression levels of genes associated with inflammation (e.g. the cytokines IL1, IL6 or TNF α) (Calder, 2008). Fatty acids and eicosanoids are natural ligands of PPARs. When activated by ligand binding, PPARs dimerise with the retinoid X receptor (RXR) and the dimer subsequently binds to specific response elements (PPREs) within promoter regions of target genes, thus modulating transcription of the genes (Berger & Moller, 2002). The three isoforms PPAR α , PPAR β/γ and PPAR δ are encoded by different genes and exhibit broad, isotype-specific tissue expression patterns (Michalik et al., 2006). PPAR γ activity can be inhibited by TNF α which consequently is associated with the pathogenesis of inflammation (Ye, 2008). PPAR α was shown to be an important transcriptional regulator in the small intestine (Buenger et al., 2007) and reduced NF κ B gene expression levels (Knoch et al., 2009). DHA and EPA are natural ligands of PPAR α and its activation can trigger fatty acid oxidation, thus a deficiency in PPAR α resulted in a dysfunction of hepatic fatty acid uptake and oxidation in an animal model (Lee & Kim, 2010).

3.3 Modulation of protein expression by polyunsaturated fatty acids

The analysis of gene expression explains only a part of the observed phenotype, as the increase or decrease of expression levels of a gene that code for a certain protein does not necessarily result in changed protein abundance (Ideker et al., 2001). Several influences, including the degradation of mRNA, post-translational modifications and the rate of degradation of the protein, can affect protein abundance. While there is published research on the effects of fatty acids on gene expression, there is less data available on its effects on protein expression. Proteomic analysis for IBD patients exists (Shkoda et al., 2007; Zhao et al., 2011) and has identified distinctive patterns in protein expression compared to healthy subjects. The studies showed that the biological processes inflammatory response and oxidative stress, signal transduction, energy generation including lipid metabolism and cell apoptosis were influenced (Shkoda et al., 2007; Zhao et al., 2011). How n-3 PUFA can influence protein expression in *Il10*^{-/-} mice should therefore provide further insights into the putative molecular mechanisms behind the observed phenotypical changes between *Il10*^{-/-} and control mice.

4. The role of foods in IBD

Minor components in foods such as antioxidants or PUFA are necessary for several processes in the human body (Visioli et al., 2003). The use of pure extracts of these

components has occasionally been promoted and the effects of these single nutrients have been reviewed. For example, curcumin (a polyphenolic compound found in some foods such as the spice turmeric), reduced histological signs of colonic inflammation and the expression levels of genes in pro-inflammatory pathways in a mouse model of IBD (Nones et al., 2009). The influences of dietary PUFA supplementation on mice with chronic colitis were studied by Knoch et al. (2009; 2010a) and Roy et al. (2007). The results of these experiments showed mild anti-inflammatory effects for both n-3 and n-6 PUFA, the former *via* the activation of a PPAR α transcription factor. However, single nutrients may exert different protective effects than whole foods which provide these components. Possible anti-inflammatory features of extracted long-chain n-3 PUFA (Calder, 2009; Knoch et al., 2009; Knoch et al., 2010a; Roy et al., 2007) may function differently when in a food matrix (Kris-Etherton & Hill, 2008). Dietary n-3 PUFA can be ingested as highly purified extracts of single n-3 PUFA, fish oil (mixture of PUFA) or marine fish (nutrient package and rich in n-3 PUFA). One of the advantages in the consumption of whole fish is nutritional diversity, which favours possible synergistic effects (He, 2009; Rudkowska et al., 2010).

4.1 The benefits of dietary fish intake

Compared to other foods, marine fish (especially salmon and tuna) are naturally rich in long-chain n-3 PUFA (Mozaffarian, 2006). Early evidence of potential health benefits of fish was found in the dietary habits of Greenland Eskimos (Bang et al., 1976). The food consumed by Eskimos is mostly of marine origin and provides high amounts of long-chain n-3 PUFA including EPA and DHA. An important correlation between dietary fish intake and a lower risk of coronary atherosclerotic diseases was found (Bang et al., 1976).

Long-chain n-3 PUFA accumulates in fish through the food chain (Sargent, 1997). The basis of the food chain is marine phytoplankton, which synthesises long-chain n-3 PUFA by conversion of LA to ALA (Hamilton et al., 2005). The uptake of phytoplankton by marine zooplankton leads to the accumulation of n-3 PUFA in the phospholipids of cellular membranes and through the ingestion of zooplankton, n-3 PUFA accumulates in fish. In general, deep water fish including salmon, herring, mackerel or tuna are classified as oily fish, with the main fat storage being the flesh. The lipid reserves of lean fish, for example cod, haddock or whiting, are in the liver. Cod liver is therefore a rich source of n-3 PUFA, as well as the fillets of salmon, herring etc. (Sargent, 1997). The n-3 PUFA content in fish varies with species, age, size, reproduction stage, season, geographical location and diet (Larsen et al., 2010).

The advantage of whole fish consumption compared to supplements is nutritional diversity. A common problem in IBD is malnutrition, caused by for example poor dietary intake or impaired nutrient absorption (O'Sullivan & O'Morain, 2006). Fish could compensate for the micronutrient deficiencies and provide a mechanism to elevate the levels of several minerals and vitamins. Of particular clinical relevance are deficiencies in calcium, vitamin D and B12, folate (Goh & O'Morain, 2003), zinc (Hendricks & Walker, 1988) and vitamin B6 (Saibeni et al., 2003), which are all contained in fish (Sidhu, 2003). Several of these micronutrients were able to suppress inflammation in rodents with experimental colitis. For example, vitamin E protected the rat colon from oxidative stress, which is associated with inflammation (González et al., 2001). Oxidised PUFA can activate transcription factors such as NF κ B and subsequently trigger pro-inflammatory gene expression, whereby vitamin E as an antioxidant compound in salmon might prevent oxidation and in turn NF κ B activation

(Calder et al., 2009). The supplementation of vitamin D and calcium showed protective effects in *Il10^{-/-}* mice (associated with TNF α pathway) (Zhu et al., 2005) and selenium protected rats with experimental colitis (Tirosh et al., 2007). Furthermore, fish is also an excellent source of amino acids, such as taurine, arginine and glutamine, which may contribute to anti-inflammatory effects (He, 2009; Rudkowska et al., 2010).

A positive association of salmon with IBD has been identified among New Zealand CD patients (Triggs et al., 2010). 446 patients rated food items and their effects on disease symptoms. No single food item was considered beneficial in all cases, however a small number of foods were frequently perceived to be beneficial, including white fish, salmon and tuna. These results indicated that salmon was perceived to be one of the most beneficial foods for those patients. Furthermore, intervention studies involving patients with active CD showed a favourable influence of salmon on IBD. After 8 weeks of a dietary intake of 600 g Atlantic salmon per week, the clinical colitis activity index was improved and the n-3/n-6 ratio increased (Grimstad et al., 2011). Another study (Pot et al., 2010) revealed that after 6 months, patients with previous colorectal adenomas or non-active UC showed partially decreased inflammation markers. The patients consumed either fatty (farmed salmon) or lean fish (Icelandic cod) in 2 x 150 g portions per week. Interestingly, the consumption of cod (lean fish) showed the same results as the salmon group, suggesting that not only oily fish, but also lean fish can exert anti-inflammatory effects (Pot et al., 2010).

4.2 Whole foods vs. supplements

Bioavailability is defined as “the proportion of a drug or other substance which enters the circulation when introduced into the body and so is able to have an active effect” (Oxford Dictionaries, 2010). Dietary n-3 PUFA can be provided by fatty fish, fish oil capsules or *via* foods enriched with n-3 PUFA (e.g. milk and meat) (Kitessa et al., 2001; Knowles et al., 2004; Ponnampalam et al., 2002), however its bioavailability may differ between these formats. Fish intake may increase the bioavailability of n-3 PUFA because: (i) the ingestion of whole foods is followed by a more effective activation of digestion/absorption in the intestine compared to capsules (Elvevoll et al., 2006; Galli & Calder, 2009; Visioli et al., 2003); (ii) lipids in fish are mostly in form of TG, with n-3 PUFA mostly in position sn-2, which facilitates absorption (Aursand et al., 1995; Ratnayake & Galli, 2009); and (iii) the bioavailability of EPA is improved when co-ingested with a high-fat meal (Lawson & Hughes, 1988a). Human studies have found that the n-3 PUFA within salmon are more efficient at increasing n-3 PUFA levels in serum and plasma compared to fish oil capsules (Elvevoll et al., 2006; Visioli et al., 2003). However, this contrasts to results from Arterburn et al. (2008), who found that algal-oil capsules and cooked salmon are nutritionally equivalent sources of DHA, thus representing an alternative to fish. The results of these studies (Arterburn et al., 2008; Elvevoll et al., 2006; Visioli et al., 2003) may depend on several factors, for example genetic differences in the individual subjects, but also on the oxidation rate of n-3 PUFA in capsules or differences in encapsulation (e.g. hard vs. soft gelatine capsules) (Ferguson et al., 2010).

5. Limitations

Dietary recommendations of two servings of fish per week require unlimited sources of fish. However, wild-caught fish are finite and some species are already classified as over-fished

(Naylor et al., 2000). Producing farmed fish in aquacultures may not be sustainable long-term. Apart from water pollution or habitat destruction, aquacultures require large inputs of wild fish for feed (Jenkins et al., 2009; Naylor et al., 2000). For example, the production of one kilogram of farmed fish, raised on feeds fortified with fish meal and oil, requires approximately three kilograms of wild fish (Naylor et al., 2000). To lower fish input in feed, n-3 PUFA-rich fish oil was replaced by n-3 PUFA-deficient vegetable oil. However, this resulted in lower levels of n-3 PUFA in salmon flesh, which would therefore not serve the purpose of increasing DHA and EPA in the human diet.

For those who do not wish to consume fish, enrichment of foods which are not naturally rich in long-chain n-3 PUFA is an option (Bermingham et al., 2008; Calder & Yaqoob, 2009; Whelan et al., 2009). These include n-3 PUFA-enriched eggs, meat (Knowles et al., 2004; Ponnampalam et al., 2002) or milk (Kitessa et al., 2001) that can be produced by bio-fortification (feeding the animal n-3 PUFA-rich feeds) or post-harvest modification of foods (n-3 PUFA-rich oils into foods) (Bermingham et al., 2008; Whelan et al., 2009). However in most cases, fish oils are used for elevating the n-3 PUFA levels. In order to reduce pressure on wild fish stocks, it is important to find an alternative source of n-3 PUFA. A possible solution could be DHA-rich algal oil, which is considered as plant-derived, thus also appropriate for vegetarians for direct supplementation (Whelan & Rust, 2006).

Evidence for the protective effects of n-3 PUFA is inconsistent, possibly due to various factors (Ferguson et al., 2010). *In vitro* models can not mimic the complexity of an entire organism, which makes the use of animal models necessary. However, disease pathogenesis differs across animal models, thus making it difficult to compare results (Hegazi et al., 2003; Hegazi et al., 2006). Diets enriched with n-3 PUFA which are fed to animals differ in their sources and range from highly purified extracts of single PUFA (*i.e.* DHA or EPA) to fish oil and marine fish. Although these sources generally represent an excess of n-3 PUFA, bioavailability might change with the form provided (*e.g.* free fatty acids, ethyl esters, TG or embedded in a food matrix) (Lawson & Hughes, 1988b). Additionally, the time point of supplying the PUFA diets may be an important factor for the outcome of the study (Ramakers et al., 2008). As a preventive approach, the feeding of diets prior to colitis induction could exert different effects when compared with a therapeutic approach, in which the diets are fed when colitis is already present (Ramakers et al., 2008). An important factor is the dose of the supplemented n-3 PUFA. Trebble et al. (2003) demonstrated that the production of the pro-inflammatory cytokines TNF α and IL6 by cells appear to follow a 'U-shaped' dose response when n-3 PUFA supplementation was present. In this study, the supplementation of dietary fish oil in healthy humans resulted in a significantly decreased TNF α and IL6 production of the peripheral blood mononuclear cells at the lowest level (0.3 g n-3 PUFA per day). A maximum inhibition was observed at intermediate levels (1.0 g n-3 PUFA per day), but the least inhibition at highest supplementation levels (2.0 g n-3 PUFA per day). Thus, the dose of the dietary n-3 PUFA may considerably influence the outcome of n-3 PUFA supplementation studies (Treble et al., 2003). A possible explanation for the observations might be found in the molecular mechanisms by which n-3 PUFA influences cell function, *i.e.* altered eicosanoid synthesis, signal transduction or gene expression. It is hypothesised that those mechanisms have maximum effects at different intake levels of n-3 PUFA and thus a 'U-shaped' dose-response curve results (Treble et al., 2003).

6. Conclusion

Fish is high in protein, low in saturated fat and it provides high amounts of n-3 PUFA (He, 2009). Therefore, as part of a healthy lifestyle, fish should be consumed at least twice per week, and one of these servings should be oily fish (Kris-Etherton & Hill, 2008; Scientific Advisory Committee on Nutrition/Committee on Toxicity, 2004). The underlying molecular mechanisms by which salmon-containing diets influence intestinal inflammation are not well known. In *Il10^{-/-}* mice, pure EPA can reduce colon inflammation and regulate gene and protein expression involved in various pathways (Knoch et al., 2009), leaving a unique dietary signature. A genome-wide approach can be applied with the use of 'omics'-technologies - transcriptomics (gene expression analysis) and proteomics (protein expression analysis) - to identify metabolic pathways and key gene/protein regulatory 'hubs' which are responsive to n-3 PUFA-enriched diets, and through which anti-inflammatory effects are exerted. A metabolomic approach can be used to identify metabolites in mouse urine and plasma samples that are influenced by the n-3 PUFA-enriched diets. These metabolites could serve as biomarkers for future human clinical intervention studies to assess the effect of these diets non-invasively. Future studies need to determine if the dietary intake of salmon is more beneficial than fish oil (mixture of n-3 PUFA) or single n-3 PUFA (*i.e.* DHA or EPA). Further, if the intake of fish has anti-inflammatory effects, can these be attributed to DHA or EPA, a combination, or synergistic effects with other nutrients?

7. Acknowledgement

This study is part of Nutrigenomics New Zealand, a collaboration between AgResearch, Plant and Food Research, and The University of Auckland, and is primarily funded by the New Zealand Ministry of Science and Innovation (MSI). Nadja Berger's PhD Fellowship is funded by AgResearch within the Nutrigenomics New Zealand partnership. The authors would like to thank Denise Martin and Dr Matthew Barnett (AgResearch) for manuscript reviewing.

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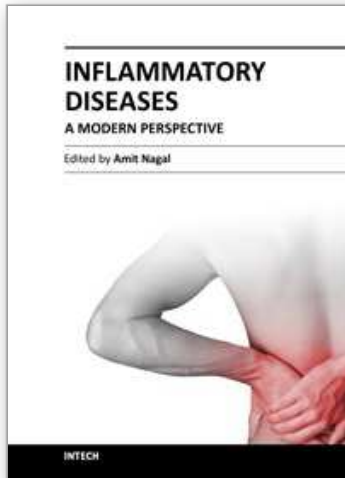
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Inflammatory Diseases - A Modern Perspective

Edited by Dr. Amit Nagal

ISBN 978-953-307-444-3

Hard cover, 240 pages

Publisher InTech

Published online 16, December, 2011

Published in print edition December, 2011

"Inflammatory Diseases - A Modern Perspective" represents an extended and thoroughly revised collection of papers on inflammation. This book explores a wide range of topics relevant to inflammation and inflammatory diseases while its main objective is to help in understanding the molecular mechanism and a concrete review of inflammation. One of the interesting things about this book is its diversity in topics which include pharmacology, medicine, rational drug design, microbiology and biochemistry. Each topic focuses on inflammation and its related disease thus giving a unique platform which integrates all the useful information regarding inflammation.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Nicole C. Roy, Nadja Berger, Emma N. Bermingham, Warren C. McNabb and Janine M. Cooney (2011). The Effects of n-3 Polyunsaturated Fatty Acid-Rich Salmon on Inflammatory Bowel Diseases, *Inflammatory Diseases - A Modern Perspective*, Dr. Amit Nagal (Ed.), ISBN: 978-953-307-444-3, InTech, Available from: <http://www.intechopen.com/books/inflammatory-diseases-a-modern-perspective/the-effects-of-n-3-polyunsaturated-fatty-acid-rich-salmon-on-inflammatory-bowel-diseases>

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