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The Impact of Macrophage Membrane Lipid Composition on Innate Immune Response Mechanisms

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1. Introduction

Most microorganisms that are encountered in the daily life of a healthy individual are detected and destroyed within minutes or hours by the defence mechanisms of the innate immunity. Macrophages play a key role in innate immunity because they can recognize, ingest and destroy many pathogens without the aid of an adaptive immune response. Macrophages recognize pathogens via cell-surface receptors that can discriminate between the surface molecules displayed by pathogens and those of the host (Bryant & Fitzgerald, 2009). Binding of bacteria to macrophage receptors stimulates phagocytosis and uptake of pathogens into intracellular vesicles, where they are destroyed (Groves et al., 2008). Upon phagocytosis macrophages produce a variety of toxic products that help to kill the engulfed microorganisms. The most important of these are antimicrobial peptides, nitric oxide (NO), the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), the hydroxyl radical ($^{\cdot}OH$), hypochlorite (OCl^-) and hypobromide (OBr^-), which are directly toxic to bacteria (Pourova et al., 2010; Robinson, 2009). In addition, activation of macrophage receptors triggers the production of pro-inflammatory cytokines and chemokines (including IL-1β, IL-6, TNF-α and CXCL8) (Hamilton et al., 1999) and the expression of co-stimulatory molecules such as B7.1 and B7.2 (Glaros et al. 2009), which orchestrates immune responses.

Fatty acids are indispensable to life for all organisms. They serve as a source of metabolic energy providing twice the energy density compared to carbohydrates or proteins. In addition, fatty acids are an integral part of cellular membranes. The heterogeneity of fatty acids in the membrane contributes to membrane fluidity as well as to the physical and chemical properties of various membrane domains (Stillwell & Wassall, 2003; Wassall & Stillwell, 2008). Numerous cellular functions critically rely on the dynamic characteristics of the membranes. Thus, fatty acids are important for signalling mechanisms as well as catalytic processes by membrane-associated enzymes (Stillwell & Wassall, 2003; Wassall & Stillwell, 2008). The oxygenated derivatives of some fatty acids include prostaglandins, prostacyclins, thromboxanes and leukotrienes, lipoxins, resolvins, protectins and marensins (Bannenberg & Serhan, 2010; Kohli & Levy, 2009; Löffler et al., 2007; Norling & Serhan, 2010). This group of biological messenger substances mediate numerous and diverse actions especially in the immune system (Bannenberg & Serhan, 2010; Kohli & Levy, 2009; Löffler et al., 2007; Norling & Serhan, 2010).

Diseases occur when a microorganism succeeds in evading or overwhelming innate host defences to establish a local site of infection, and then replicates there to allow its further transmission within the body. Immunocompromised individuals are in special danger in developing serious illness (Kamboj, et al., 2005; Prescott, 1991; Trautmann et al., 2005). Immune cell activity depends on numerous external as well as internal stimuli. One important factor modulating immune function is the diet. In particular, nutritional fatty acids have an impact on membrane fatty acid composition. Basic properties of membranes, including fatty acid chain order, phase behaviour, elastic compressibility, ion permeability, fusion, rapid flip-flop as well as protein function are determined by the lipid composition (Stillwell & Wassall, 2003; Wassall & Stillwell, 2008). Accordingly, changes in membrane fatty acid pattern may impact cell signalling pathways and membrane-associated enzymes via modulating membrane fluidity (Stillwell & Wassall, 2003; Wassall & Stillwell, 2008). The interrelation between dietary fatty acids, membrane composition and macrophage function provides a link between dietary fatty acid uptake, inflammation and immunity.

1.1 Innate immunity

The innate immunity is the frontline in the host`s immune response. After infection the innate immunity detects and destroys invading microorganisms within minutes or hours. Only if the pathogen overwhelms the innate immunity an adaptive immune response is needed.

A typical attribute of the innate immunity is its efficiency in fighting a wide variety of pathogens. The differentiation between self and non-self is based on a limited and invariant repertoire of pattern recognition receptors (PRRs) (Bryant & Fitzgerald, 2009). These receptors bind evolutionary conserved regular molecular structures, the so called pathogen-associated molecular patterns (PAMPs) (Bryant & Fitzgerald, 2009). In general, PAMPs represent typical structures on the surface of microorganisms, which are not found on host cells. This includes peptidoglycane, lipopolysaccharide (LPS), mannose-rich oligosaccharides and un-methylated GC-rich DNA (Mogensen, 2009).

The innate immunity is based on leucocytes of the myeloide cell line: macrophages, granulocytes (neutrophil, eosinophil, basophil), mast cells and dendritic cells. Macrophages and neutrophil granulocytes are predominantly phagocytes. They engulf pathogens and destroy them inside (Silva, 2010). Premature dendritic cells are phagocytes as well (Miloud et al., 2010). After maturing dendritic cells function as antigen presenting cells (Miloud et al., 2010). Eosinophil and basophil granulocytes as well as mast cells are characterized by a great amount of secretory granula (Boyce et al., 2009). Eosinophils are thought to play an important role in the immune defence against parasites (Boyce et al., 2009). Mast cells promote locale inflammation in tissues (Boyce et al., 2009).

1.2 Macrophages

Macrophages (figure 1) are migrating mononuclear phagocytes, which appear throughout the body. In particular, macrophages can be found in high numbers in connective tissue, in the submucosa of the intestinal tract, in the lung, in the liver, in the spleen and along specific blood vessels (Varol et al., 2009). Macrophages function as pathogen-recognitive and antigen-presentating scavenger cells (Russel et al., 2009). In addition, macrophages serve as a source of pro-inflammatory cytokines as IL-1β, IL-6, TNF-α and CXCL8 (Hamilton et al., 1999). The cells are crucial for engulfment and killing of invading microorganisms and for

orchestrating the immune response (Russel et al., 2009). At this, macrophages trigger the initiation of inflammatory processes via secretion of pro-inflammatory signal proteins, which activates further immune cells (Hamilton et al., 1999). A special function of macrophages is the clearance of the body from dead cells and cell debris (Russel et al., 2009).

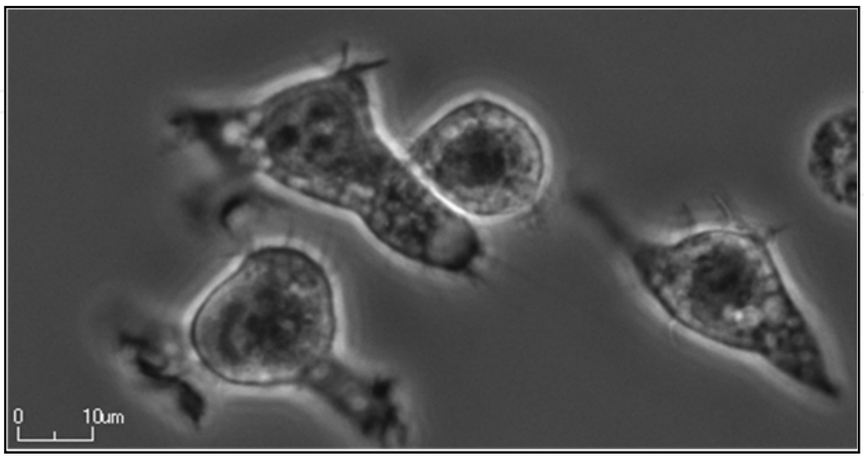


Fig. 1. Macrophages of the murine cell line RAW264.7 (phase-contrast).

Macrophages express several cell-surface receptors, which can discriminate numerous bacterial components as bacterial carbohydrates (mannose receptor, glucan receptor), bacterial lipids (LPS receptors) as well as other structures typically found on pathogen surfaces (Toll-like receptors, scavenger receptors) (Bryant & Fitzgerald, 2009). The binding of a bacterium to a macrophage receptor stimulates the engulfment of the pathogen into intracellular vesicles, a process known as phagocytosis (Groves et al., 2008) (figure 2). The phagocytosis is an active process. Initially, the receptor-bound pathogen is surrounded by the membrane of the phagocyte. This is followed by an internalisation of the pathogen into an intracellular vesicle, the so called phagosom. The destruction of the microorganism in the phagosom occurs via lowering of the pH (Haas, 2007). Furthermore, the phagosom fuses with lysosomes, which enables the killing of the pathogen via lysosomal enzymes (Haas, 2007).

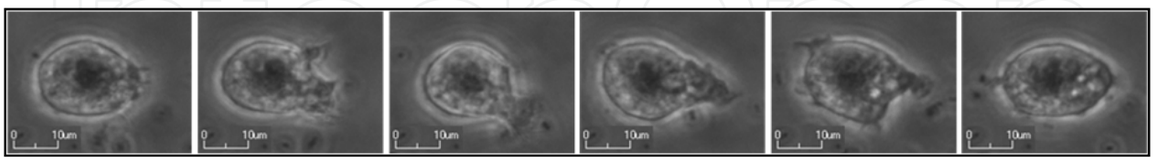


Fig. 2. Macrophage of the murine cell line RAW264.7 during phagocytosis (phase-contrast).

Macrophages produce a variety of toxic substances to kill engulfed microorganisms (figure 3). This includes antimicrobial peptides, nitric oxide (NO), the superoxide anion (O_2-) and hydrogen peroxide (H_2O_2) (Pourova et al., 2010; Robinson, 2009). Nitric oxide is generated by the inducible nitric oxide synthase (iNOS) (Pourova et al., 2010; Robinson, 2009). Superoxide is synthesized by a multicomponent, membrane-associated NADPH oxidase in a process known as the respiratory burst, and further converted by the enzyme superoxide dismutase into H_2O_2 (Pourova et al., 2010; Robinson, 2009). Based on H_2O_2 a range of toxic

chemicals, including the hydroxyl radical (·OH), hypochlorite (OCl^-) and hypobromide (OBr^-) are produced by chemical and enzymatic reactions (Pourova et al., 2010; Robinson, 2009). Moreover, the activation of macrophages receptors promotes the expression of co-stimulating molecules as B7.1 and B7.2 (Glaros et al. 2009).

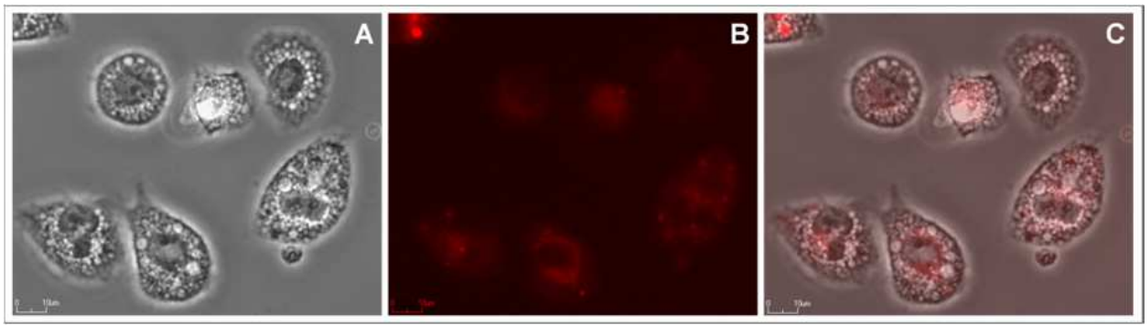


Fig. 3. Macrophages of the murine cell line RAW264.7 stimulated with phorbol-myristate-acetat (PMA). Intracellular respiratory burst is detected by the fluorogenic probe dihydrorhodamine 123.
A: Phase-contrast; B: Fluorescence channel Cy3; C: Overlay

2. Inflammation and bacterial resistance

2.1 Characteristics of an inflammation

An inflammation is defined as a local accumulation of fluid, plasma proteins and leucocytes caused by physical injuries, infections or locale immune reactions (Johnston et al., 2007). Characteristics of an inflammation are redness, swelling, heat and pain. During an acute inflammation the host actively fights invading microorganisms. This includes the inhibition of infection spread by means of physical barriers and the activation of the complement system (Johnston et al., 2007). The process is triggered by macrophage secreted cytokines (Johnston et al., 2007).

2.2 Bacterial resistance mechanisms

Several pathogens have evolved resistance mechanism to escape the immune defence (Johnston et al., 2007). Such persistent microorganisms are the cause of chronic infections. A chronic infection is a protracted process. Characteristics are an ongoing tissue damage accompanied with permanent proliferation processes (Germolec et al., 2010).
Bacterial resistance mechanisms are important factors of virulence, which have a significant impact on infection outcome. Via interaction with the immune system pathogens are able to modulate the defence mechanisms of the host thereby influencing the severity of disease (Veesenmeyer et al., 2009). Both the rate of pathogen elimination as well as the scale of tissue damage can be manipulated by the microorganisms. There is a multitude of bacterial resistance mechanisms. Typical examples are listed in table 1.
The impermeability of the membrane and the active transport of antimicrobial substances out of the cell impair the accumulation of antibiotics in the pathogens inside. Bacterial resistances against β-lactam antibiotics, fluoroquinolones, tetracyclines and aminoglycosides have been reported to be based on these mechanisms (Strateva & Yordanov, 2009).

Bacterial resistance mechanisms
Reduced permeability of the outer membrane
Constitutive (over-)expression of efflux channel proteins with broad substrate specifity
Biofilm formation
Quorum sensing

Table 1. Bacterial resistance mechanisms (Veesenmeyer et al., 2009; Strateva & Yordanov, 2009)

Via biofilm formation bacteria are able to colonise on all types of animal tissue, plants and inert surfaces (Boyen et al., 2009; Veesenmeyer et al., 2009). Furthermore, the resistance of the microorganisms against environmental conditions is improved. Biofilm formation hampers the killing of the pathogens by immune defence mechanisms or antimicrobial substances (Boyen et al., 2009; Veesenmeyer et al., 2009). As a consequence there are chronic infections, which are hard to treat by the means of antibiotics (Boyen et al., 2009; Veesenmeyer et al., 2009).
Quorum sensing is a communication mechanism, which is used by bacteria for collective coordination (Boyen et al., 2009). The microorganisms produce chemical signalling molecules as polypeptides (auto-inducing polypeptides. AIPs), N-acetyl-homoserine-lactone (auto inducer-1, AI-1) or furanosyl-borate-ester (auto inducer-2, AI-2) and secret them into the environment (Boyen et al., 2009). When exceeding a critical concentration the signal molecules modulate gene expression of the bacteria thus synchronising the behaviour of the whole population (Boyen et al., 2009). By this way quorum sensing promotes biofilm formation and manipulates virulence, mobility and sporulation of the microorganisms (Boyen et al., 2009).

2.3 Examples

2.3.1 *Rhodococcus equi*

Infections of immunocompetent humans with *R. equi* are rare. However, in case of immune-suppressing conditions as transplantations, cancer treatment and steroid medication pneumonia caused by *R. equi* have been observed (Kamboj, et al., 2005; Prescott, 1991). HIV positive people are particularly endangered. The mortality rate of infected AIDS patients is reported to be about 55% (Bell et al., 1998).
The facultative intracellular bacterium is known to survive extreme environmental conditions as low pH (Benoit, 2000) or oxidative stress (Benoit, 2002). In addition, *R. equi* blocks the process of phagosom maturation thus surviving and proliferating within macrophages (Fernandez-Mora et al., 2005). Internalised viable *R. equi* organisms prevent the fusion of their phagosom with lysosomes leading to an arrested phagosom neutral in pH and without lysosomal contents (Fernandez-Mora et al., 2005). The underlying mechanisms are not known, so far.

2.3.2 *Pseudomonas aeruginosa*

P. aeruginosa is one of the leading hospital bugs in the world. According to estimates the microorganism accounts for 10 to 15% of all nosocomial infections (Blanc et al., 1998). *P.*

aeruginosa colonises burns and wounds as well as the respiratory tract and the urinary tract of immunocompromised individuals (Trautmann et al., 2005). Due to the natural resistance of the opportunistic pathogen against numerous antibiotics *P. aeruginosa* infections are often hard to treat (Strateva & Yordanov, 2009). Moreover, the microorganism has a remarkably ability to acquire further resistance mechanisms against antimicrobial substances by the means of mutations (Strateva & Yordanov, 2009). Another notorious characteristic of *P. aeruginosa* is the biofilm formation (Boyen et al., 2009). The colonisation of surfaces of surgical implants, endotracheal tubes, catheters as well as the respiratory tract of individuals suffering from cystic fibrosis becomes an increasing medical problem. Further virulence factors of *P. aeruginosa* include the secretion of a number of toxins and the expression of flagella and type IV pili, which are of importance for surface attachment (Veesenmeyer et al., 2009). Two quorum sensing mechanisms of *P. aeruginosa* have been identified, so far: Las and Rhl (Veesenmeyer et al., 2009). A Pseudomonas quinolone signal (PQS) acts as mediator between the two systems (Pesci et al., 1999). Quorum sensing controls about 350 genes of *P. aeruginosa* (approximately 6% of the entire genome) modulating toxin synthesis and biofilm formation (Veesenmeyer et al., 2009).

3. Fatty acids and cellular membranes

3.1 Fatty acids

Fatty acids are composed of a hydrocarbon chain and a carboxyl group. Most naturally occurring fatty acids have a chain of an even number of carbon atoms. Fatty acids may be saturated or unsaturated depending on the existence of double bonds. In almost every unsaturated fatty acid the double bonds are in *cis* configuration (Löffler et al., 2007). This means that the adjacent hydrogen atoms are on the same side of the double bond resulting in a rigid binding, which restricts the conformational freedom of the fatty acid. The more *cis* double bonds a chain has, the less flexible it is. Thus, *cis* bonds limit the ability of a fatty acid to be closely packed (Stillwell & Wassall, 2003). Since fatty acids are parts of triglycerides in lipid droplets as well as of phospholipids in lipid bilayers the number of *cis* bonds of a fatty acid has an impact on basic physical properties of fat or biological membranes (Stillwell & Wassall, 2003).

Depending on the position of the double bonds unsaturated fatty acids are classified in several fatty acid families: n3, n6, n7 and n9. This terminology is based on the first double bond relative to the end of the hydrocarbon chain. For example, the term n3 signifies that the first unsaturation exist at the third carbon-carbon bond from the terminal methyl end of the chain. A transformation of a fatty acid from one family to another is not possible (Löffler et al., 2007). Animals and humans lack the ability to introduce double bonds in fatty acids beyond carbon 9. So, the fatty acids linoleic acid (C18:2n6) and linolenic acid (C18:3n3) are essential to the animal and human organisms (Löffler et al., 2007). Important examples of the n3, the n6, the n7 and the n9 family are listed in table 2.

Fatty acids are of great importance as membrane compound and in energy metabolism in the animal and human organisms. They can be found both as free fatty acids and as parts of acylglycerols, phospholipids, sphingolipids and cholesterol esters. Furthermore, some fatty acids serve as precursors of eicosanoid synthesis.

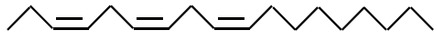
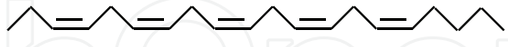
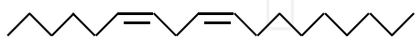
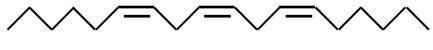
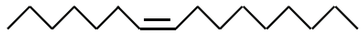
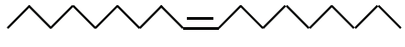
Non-scientific name	Chemical formula	Structural formula
N3 family		
Linolenic acid (LNA)	C18:3n3	
Eicosapentaenoic acid (EPA)	C20:5n3	
Docosahexaenoic acid (DHA)	C20:6n3	
N6 family		
Linoleic acid (LA)	C18:2n6	
Gamma-linolenic acid (γ-LNA)	C18:3n6	
Arachidonic acid (AA)	C20:4n6	
N7 family		
Palmitoleic acid	C17:1n7	
N9 family		
Oleic acid (OA)	C18:1n9	

Table 2. Important examples of the n3, the n6, the n7 and the n9 fatty acid family

3.2 Cellular membranes

Cellular membranes are essential to life for all living beings. In prokaryotic organisms the plasma membrane separates the inner of the cell from the environment. In eukaryotic organisms beyond that there are additional intracellular membranes which encompass the cell organelles leading to a compartmentalisation of the cell. Furthermore, in eukaryotic organisms there are numerous membrane-enclosed vesicles, which ensure the directed exchange of materials and membrane components between the compartments of the cell as well as between the cell and the environment.

Membranes serve diverse functions in prokaryotic and eukaryotic cells. The plasma membrane is selectively-permeable to ions and organic molecules thus controlling the movement of substances in and out the cell. Biological membranes are involved in a variety of cellular processes as cell adhesion, ion conductivity and cell signalling. Moreover, membranes serve as an attachment surface both extracellular and intracellular.

The basic structure of biological membranes is a lipid bilayer, which is composed of phospholipids and sphingolipids. Further components of cellular membranes are cholesterol and proteins. Cholesterol crucially impacts the viscosity of the membrane. The hydrophobic interactions between the sterol scaffold of the cholesterol and the acyl chains of the phospholipids reduce the deformability of the lipid bilayer as well as the permeability of the membrane for small hydrophilic molecules (Quinn & Wolf, 2009). The proteins are the key to the overall functions of the membranes. They are either embedded into the membrane (integral proteins) or associated to it (peripheral and lipid-anchored proteins). Actions of membrane proteins include cell-cell contact, surface recognition, cytoskeleton contact, signalling, enzymatic activity and the transport of substances across the membrane.

Beside cholesterol the physical and chemical properties of biological membranes are determined by the fatty acid pattern. The packing density of saturated fatty acids differs widely from the packing density of unsaturated fatty acids (Stillwell & Wassall, 2003). An increase in the proportion of unsaturated fatty acids therefore results in a weakening in the intermolecular hydrophobic interactions (Stillwell & Wassall, 2003). In this way basal properties of biological membranes are modulated including the assembly of the acyl chains, the fluidity, permeability and compressibility of the membrane, melting and flip-flop mechanisms as well as the function of membrane proteins (Stillwell & Wassall, 2003; Wassall & Stillwell, 2008).

3.3 Lipid rafts

The phospholipids and sphingolipids are not distributed evenly in cellular membranes. Via lateral interactions among one another as well as with proteins specific micro domains are formed, the so called lipid rafts. Lipid rafts are structurally and functionally distinct domains that can be distinguished within the cell membrane due to their specific lipid compositions (Henderson et al., 2004; Lingwood & Simons, 2010; Pike, 2003; Tresset, 2009). Sphingolipids, cholesterol and saturated fatty acids predominate in the rafts (Pike, 2003). This allows for a tight packing of the acyl chains. The remaining liquid-ordered domain is characterized by a reduced fluidity compared to the surrounding plasma membrane.

Lipid rafts have been defined as "small (10-200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalise cellular processes" (Pike, 2006). A variety of proteins has been shown to be enriched in membrane rafts such as GPI-anchored proteins, flotillin, receptor tyrosine kinases and G protein-coupled receptors (Pike, 2003). The spatial proximity of the proteins in the rafts enables a better coordination and an increased efficiency of proceeding reactions. Taking the dynamic nature of membrane domains into account the rafts have been supposed to scaffold certain molecules while excluding others thus function as a unique signalling platform (Ye et al., 2010). Further cellular processes lipid rafts have been implicated include membrane trafficking, molecular sorting, internalisation processes as well as membrane-cytoskeleton interactions (Simons & Toomre, 2000).

A number of macrophage functions have been shown to interrelate with membrane rafts. Examples include the endotoxin-mediated activation of macrophages, the MHCII-mediated presentation of antigens, phagocytosis as well as the production of pro-inflammatory cytokines (Gaus et al., 2005). Furthermore, lipid rafts have been shown to be used as target by a wide variety of pathogens to invade host cells (Hartlova et al., 2010). Bacterial toxins have been demonstrated to enter cells via certain toxin-associated receptors, which are known to be concentrated in membrane rafts (Van & Leo, 2002). Thus, the domains play an important role in infectious biology.

4. Fatty acid dependent modulation of the immune system

4.1 Fatty acids and the immune system

Fatty acids, in particular polyunsaturated fatty acids (PUFAs), possess immune modulating properties. PUFAs are shown to modulate the proliferative activity of neutrophil granulocytes (Prescott, 1984), macrophages (Hughes & Pinder, 2000), T cells (Anderson & Fritsche, 2004) and dendritic cells (Zeyda et al., 2005). Furthermore, impacts on the respiratory burst, the production of cytokines as well as the expression of adhesion

molecules have been described (Calder, 1998; Calder, 2006a). Of note, the effects triggered by the fatty acids depend on the fatty acid family. N3 fatty acids such as eicosapentaenoic acid (C20:5n3; table 2) and docosahexaenoic acid (C22:6n3; table 2) are thought to act anti-inflammatory (Calder, 2006a; Schmitz & Ecker, 2008). In contrast, fatty acids from the n6 family such as linoleic acid (C18:2n6; table 2) and arachidonic acid (C20:4n6; table 2) are described to act pro-inflammatory (Calder, 2006a; Schmitz & Ecker, 2008).
The interaction between fatty acids and the immune system is based on three known mechanisms (Benatti et al., 2004; Capkin et al, 2009): First, some fatty acids, e.g. eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid, serve as precursors for the production of immune-modulating effectors. Second, fatty acids directly interact with intracellular receptors such as peroxisome proliferator-activated receptors (PPARs) or retinoid X receptors (RXRs) as well as G protein-coupled receptors (GPR120) (Oh et al., 2010). Third, the fatty acid composition of cell membranes modulates basic properties of the membrane thus influencing the activity of immune cells. A molecular model displaying the functional mechanisms, which underlay the interaction of fatty acids and the immune system, is shown in figure 4.

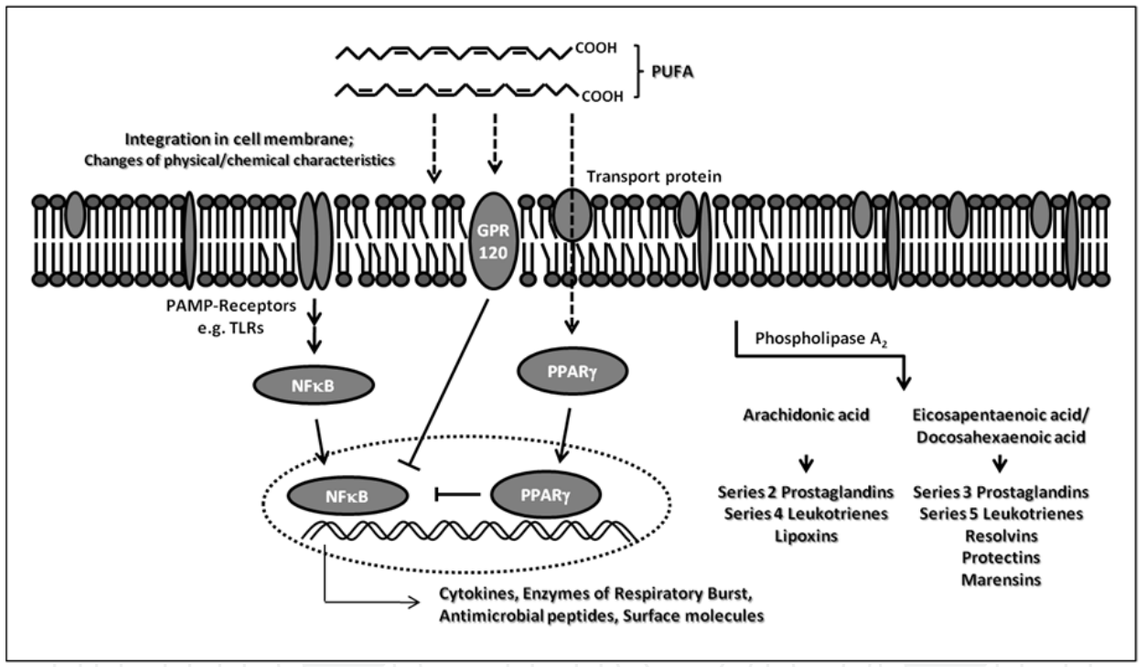


Fig. 4. Molecular model displaying the functional mechanisms, which underlay the interaction of fatty acids and the immune system

4.2 Eicosanoids, lipoxins, resolvins, protectins and marensins

Unsaturated fatty acids serve as precursors for the synthesis of several signal molecules and tissue hormones. These lipid mediators include the eicosanoids, the lipoxins, the resolvins, the protectins and the marensins.
There are four families of eicosanoids: prostaglandins, prostacyclins, thromboxanes and leukotrienes (Löffler et al., 2007). Each of these families can further be divided into separate series depending on the fatty acid family they derive from. The eicosanoid series differ widely in their biological activity. In general, n6 eicosanoids act pro-inflammatory, n3 eicosanoids are much less inflammatory (Lee, 1984; Lee, 1988).

Eicosanoids are synthesized in almost every animal and human tissue modulating numerous hormonal and other stimuli. The several physiological effects are triggered by specific membrane receptors of target cells and target tissues (Löffler et al., 2007). Acting as immune-modulators and neurotransmitters among others they influence the contraction of smooth muscle cells (vasoconstriction / vasodilatation), the experience of pain and the platelet aggregation (Löffler et al., 2007). Moreover, eicosanoids play an important role in hypersensitivity reactions and inflammatory processes (Benatti et al., 2004). An overview on the biological effects of major eicosanoids is shown in table 3.

Substance	Biological activity
Prostaglandin E_2	Bronchodilatation, Vasodilatation, Inducing of inflammation, fever and pain, Activation of osteoclasts, Inhibition of chloride secretion in the stomach and of lipolysis in fat tissue
Prostaglandin D_2	Bronchoconstriction, Promotion of sleep
Prostaglandin $F_{2\alpha}$	Bronchoconstriction, Vasoconstriction, Constriction of smooth muscle cells
Thromboxane A_2	Bronchoconstriction, Vasoconstriction, Platelet aggregation
Prostacyclin I_2	Vasodilatation, Increasing of vascular permeability, Inhibition of platelet aggregation, Inducing of inflammation

Table 3. Biological effects of major eicosanoids (Löffler et al., 2007)

The half-life of eicosanoids is about seconds to minutes. Thus, eicosanoids are considered as tissue hormones acting in an autocrine and paracrine manner (Löffler et al., 2007). The effect profile of eicosanoids therefore crucially depends on the type of eicosanoid receptors, which are expressed in close proximity to the eicosanoid-producing cell. In general, eicosanoid receptors are seven transmembrane receptors, which are also known as G protein-coupled receptors (Löffler et al., 2007). Subject to the type of receptor ligand binding results either in the modulation of the adenylate cyclase, which is followed by increased or decreased intracellular cAMP concentrations, or in an activation of the phosphatidylinositol cycle, which manipulates the concentration of cellular calcium (Löffler et al., 2007).

Depending on the fatty acid, which is used as precursor, eicosanoid synthesis results in discrete mediators. The n6 PUFA arachidonic acid is the substrate for production of series 2 prostaglandins and series 4 leukotrienes (Benatti et al., 2004). Starting from the n3 PUFA eicosapentaenoic acid series 3 prostaglandins and series 5 leukotrienes are formed (Benatti et al., 2004). In comparison to the arachidonic acid derivates series 3 prostaglandins and series 5 leukotrienes are notably less inflammatory. As an example: the leukotriene B_5 has been reported to have a 10 to 100 times reduced biological activity than the leukotriene B_4 (Lee et al., 1984; Lee et al., 1988).

Beside eicosanoids there is a genus of specialized pro-resolving mediators (SPM). The several families of these distinct local mediators include the lipoxins, the resolvins, the protectins and the marensins (Bannenberg & Serhan, 2010; Kohli & Levy, 2009; Norling & Serhan, 2010). SPM play a key role in the endogenous down-regulation of inflammation. For a long time inflammation resolution has been thought to occur passively by a dilution of pro-inflammatory signals and mediators. Only recently it has emerged, that instead it is an active process, which is orchestrated by a distinct set of chemical effectors (Serhan et al.,

2008). In resolving tissues an alteration in PUFA metabolism has been observed. A class switching in lipid mediator generation occurs, that leads to a change in enzymatic PUFA conversion from pro-inflammatory eicosanoids to pro-resolving mediators (Levy et al., 2001). SPM are derived from the n6 PUFA arachidonic acid and the n3 PUFAs eicosapentaenoic acid and docosahexaenoic acid as well (Bannenberg & Serhan, 2010; Kohli & Levy, 2009; Norling & Serhan, 2010). They exert influence at even picomolar to nanomolar concentrations (Serhan, 2005; Spite, 2009). Biological actions of SPM include the down-regulation of cell adhesion molecules, the reduction of chemotaxis, transendothelial migration and neutrophil activation, the stimulation non-phlogistic phagocytosis of apoptotic neutrophils and macrophages as well as the removal of inflammatory leukocytes (Bannenberg & Serhan, 2010). In table 4 there is an overview regarding the biological activities of major SPM.

The first SPM identified are the lipoxins (Serhan, 2005). Lipoxins are enzymatically generated by lipoxygenase from the n6 PUFA arachidonic acid, a process, which is triggerd by aspirin (Chiang, 2004). The potent anti-inflammatory effectors are special important in slowing down neutrophil-mediated tissue injury. They limit the recruitment and the adhesion of neutrophils to the site of inflammation. Furthermore, lipoxins force the phagocytosis of apoptotic neutrophils (Bannenberg & Serhan, 2010; Norling & Serhan, 2010). Major lipoxins are Lipoxin A_4 (LXA_4) and Lipoxin B_4 (LXB_4).

Resolvins are bioactive metabolites, which are synthesized from the enzymatic conversion of the n3 PUFA eicosapentaenoic acid and docosahexaenoic acid. The term resolvin is derived from 'resolution phase interaction products' (Serhan & Chiang, 2008). Depending on the fatty acid they are produced from resolvins are categorized as either E-series (from eicosapentaenoic acid) or D-series (from docosahexaenoic acid) (Serhan & Chiang, 2008). Aspirin-triggered forms have been described for each family (Serhan & Chiang). The E-series resolvins currently comprise Resolvin E1 (RvE1) and Resolvin E2 (RvE2). The D-series resolvins include Resolvin D1 (RvD1), Resolvin D2 (RvD2), Resolvin D3 (RvD3) and Resolvin D4 (RvD4). In general, resolvins efficiently block the synthesis of pro-inflammatory mediators, regulate the entry of neutrophils to inflammatory sites and help to clear neutrophils from mucosal surfaces (Norling & Serhan, 2010). At this, the bioactivity of the anti-inflammatory effectors has been shown to be highly stereoselective both *in vitro* and *in vivo* (Levy, 2010).

The n3 PUFA docosahexaenoic acid serves also as precursor for the synthesis of protectins. Protectins are characterized by their anti-inflammatory and protective actions, especially in neuronal tissues (Hong et al., 2003). As lipoxins and resolvins, protectins stop the infiltration of neutrophils and activate the resolution of inflammation (Hong et al., 2003; Serhan et al., 2006). The major protectin, Protectin D1 (PD1) has been shown to possess protective actions in the lung and in renal tissues thereby preserving them against injury and inflammation (Bannenberg & Serhan, 2010; Kohli & Levy, 2009; Levy, 2010; Norling & Serhan, 2010).

Recently, macrophages have been identified to synthesize anti-inflammatory and pro-resolving mediators from docosahexaenoic acid in a separate biosynthetic pathway (Norling & Serhan, 2010). These effectors have been termed maresins, for 'macrophage mediators in resolving inflammation' (Norling & Serhan, 2010). The production of marensins is triggered during phagocytosis (Bannenberg & Serhan, 2010). So far, Marensin 1 (MaR1), the major marensin, is known to reduce neutrophil migration and to stimulate phagocytosis by macrophages (Bannenberg & Serhan, 2010).

Substance	Biological activity
Resolvin E1	Decreasing of migration, pro-inflammatory signalling and infiltration of neutrophils; Stimulation of phagocytosis of apoptotic neutrophils by macrophages; Promotion of healing of diseased tissue
Resolvin E2	Decreasing of neutrophil infiltration
Resolvin D1	Decreasing of neutrophil infiltration; Protection from tissue damage and loss of function
Protectin D1	Decreasing of neutrophil infiltration and pro-inflammatory signalling; Stimulation of phagocytosis of apoptotic neutrophils by macrophages; Protection from tissue damage and loss of function

Table 4. Biological effects of major specialized pro-resolving mediators (SPM) (Kohli & Levy, 2009; Norling & Serhan, 2010)

The type of eicosanoids and specialized pro-resolving mediators produced depend on the fatty acid composition of the cell membrane. The main phospholipase, the phospholipas A2, preferably liberates the n6 PUFA arachidonic acid from membrane phospholipids, which acts as substrate for the synthesis of series 2 prostaglandin, series 4 leukotrienes and lipoxins (Löffler et al., 2007). Intake of n3 PUFA, such as eicosapentaenoic acid and docosahexaenoic acid, leads to increased levels of these fatty acids in the cell membrane. Products of eicosapentaenoic acid and docosahexaenoic acid are series 3 prostaglandins, series 5 leukotrienes, resolvins, protectins and marensins.

4.3 Interaction of fatty acids with nuclear receptors and G protein-coupled receptors

Fatty acids regulate gene expression via interaction with nuclear receptors and G protein-coupled receptors (GPCRs). Nuclear receptors are defined as intracellular ligand-inducible transcription factors, which modulate gene expression in response to hydrophobic endogenous and exogenous chemicals (Khan & Heuvel, 2003). Functions affected include the fatty acid metabolism, the reproductive development and the detoxification of substances (Khan & Heuvel, 2003). In general, nuclear receptors consist of distinct functional domains. The N-terminal A/B domain, has a weak transactivation activity (activation function 1 (AF-1)) (Bordoni et al., 2006; Khan & Heuvel, 2003). Adjacent there is the C domain, which is important for DNA binding (Bordoni et al., 2006; Khan & Heuvel, 2003). The DNA binding domain is the most conserved region of the nuclear receptor superfamily. It is composed of two zinc fingers, which bind to response elements (NREs) in their target promoters (Bordoni et al., 2006; Khan & Heuvel, 2003). The flanking D domain is a hinge region. This region may allow for conformational changes in the receptor structure following ligand binding (Bordoni et al., 2006; Khan & Heuvel, 2003). The C-terminal E/F domain contains the ligand binding site, which in every nuclear receptor is comprised of 10 to 13 α-helixes that form a hydrophobic binding cavity (Bordoni et al., 2006; Khan & Heuvel, 2003). At the extreme C-terminus there is the ligand-dependend transactivation function-2 (AF-2) (Bordoni et al., 2006; Khan & Heuvel, 2003). Furthermore, this region also contains nuclear localisation signals and protein interaction surfaces for dimerization with heat shock proteins, co-regulators and other transcription factors (Bordoni et al., 2006; Khan & Heuvel, 2003).

So far, five transcription factor families have been described to be modulated in their activity by fatty acids: peroxisome proliferator-activated receptors (PPARs), retinoid X receptors (RXRs), liver X receptors (LXRs), the hepatic nuclear factor 4 α (HNF-4α) and

sterol regulatory element binding proteins (SREBPs) (Bordoni et al., 2006). The interaction between fatty acids and nuclear receptors is of importance in regulating lipid and glucose metabolism at this modulating the expression of specific enzymes as well as of fatty acid transporters (Bordoni et al., 2006). Beside, based on PPARs there is also a regulation of inflammation and immune response (Bishop-Bailey & Bystrom, 2009).

PPARs were identified 1990 as transcription factors (Issemann & Green, 1990). In 1992 linoleic acid (C18:2n6; table 2) and arachidonic acid were demonstrated to activate PPARs (Gottlicher et al., 1992). There are three PPAR family members: PPARα (NR1C1), PPARβ/δ (NR1C2; NUC1; FAAR fatty acid-activated receptor) and PPARγ (NR1C3). The isotypes are distinguished from each other by their tissue distribution and their differential activation (Grimaldi, 2001). PPARs are implicated in a number of biological processes, such as the regulation of lipid metabolism (uptake, activation, oxidation and esterification of fatty acids), development, cell proliferation and differentiation as well as inflammatory responses Escher & Wahli, 2000). PPARs exert their effects on gene expression as heterodimers with RXRs (Kliewer et al., 1992). The PPAR/RXR heterodimer binds to specific PPAR response elements (PPRE), which located in the promoter of target genes (Issemann et al., 1993). The consensus sequence consists of a direct repeat of the hexamer AGGTCA separated by single-nucleotide spacer, the so called direct repeat (DR-1) (Ijpenberg et al., 1997). The conformational change that occurs upon ligand binding leads to the dissociation of co-repressors as nuclear receptor co-repressor (NCoR) and silencing mediator for retinoid- and thyroid-hormone receptors (SMRT) (Feige et al., 2006). In addition, activated PPARs fascilitate the recruitment of co-activators, chromatin remodelling factors and of the transcription machinery (Bishop-Bailey & Bystrom, 2009). The activity of the PPARs can be modulated by phosporylation, nitration, ubiquitylation and sumoylation (Bordoni et al., 2006).

PPARα is mainly expressed in liver, intestinal tract, kidney, heart and brown adipose tissue (Bordoni et al., 2006). The receptor is of importance in fatty acid transport and oxidation, cell proliferation and inflammatory crosstalk (Bordoni et al., 2006). Synthetic ligands of PPARα have been shown to impair cytokine synthesis of phorbol ester stimulated monocytes (Jiang at el., 1998).

PPARβ/δ is almost ubiquitously expressed (Bishop-Bailey & Bystrom, 2009). It is implicated in the fatty acid oxidation of many tissues (Bishop-Bailey & Bystrom, 2009). Furthermore, PPARβ/δ has been reported to be involved in cell proliferation and development, wound healing, myelination of nerves as well as the adaptive response of skeletal muscle to exercise (Bordoni et al., 2006). In macrophages the receptor controls the inflammatory status at this diminishing the expression of pro-inflammatory cytokines and receptors as IL-1β, IL-6, TNF-α, macrophage inflammatory protein 1β, the MCP-1 receptor CC-chemokine receptor-2 and VCAM-1 (Bishop-Bailey & Bystrom, 2009).

PPARγ is expressed in various isoforms, which show tissue and differentiation specifity (Bishop-Bailey & Bystrom, 2009). The receptor plays a role in glucose homeostasis, lipid metabolism, cell proliferation and inflammation (Feige et al., 2006). PPARγ is the predominant PPAR receptor expressed by cells of the myeloid line (Stulnig, 2003). It is essential for differentiation of adipocytes and macrophages (Khan & Heuvel, 2003). Expression of PPARγ is upregulated during macrophage activation (Huang et al., 1999). Genes regulated include lipoprotein lipase, CD36 and scavenger receptors (Khan & Heuvel, 2003; Yaqoob, 2003). As with PPARα, synthetic ligands of PPARγ have been demonstrated to suppress production of IL-1β, IL-6, TNF-α as well as the inducible nitric oxide synthase

(iNOS), matrix metalloprotease-9 and scavenger receptor A (Jiang at el., 1998; Ricote et al., 1998; Yang et al., 2000). PPARγ is activated by unsaturated fatty acids, the prostaglandin 15-deoxy PGJ_2 and non-steriodal anti-inflammatory drugs (NSAIDS) (Grimaldi, 2005; Khan & Heuvel, 2003; Stulnig, 2003).

Beside nuclear receptors recently five G protein-coupled receptors have been described, which can be activated by free fatty acids: GPR40 binding long-chain fatty acids, GPR41 binding short-chain fatty acids, GPR43 binding short-chain fatty acids, GPR84 binding medium-chain fatty acids and GPR120 binding long-chain fatty acids (Oh et al., 2010). From the perspective of immune modulation GPR120 emerges as a receptor of particular interest. In contrast to the other receptors of the family of fatty acid sensing GPCRs GPR120 is the only one, which is highly expressed in adipose tissue and macrophages (Oh et al., 2010). Moreover, ligand stimulation of GPR120 by the n3 PUFA DHA and EPA has been reported to result in potent anti-inflammatory effects, including inhibition of IL-6, TNF-α and MCP-1 mRNA expression and secretion (Oh et al., 2010). Activation of GPR120 by n3 fatty acids leads to a coupling of GPR120 to the adaptor protein β-arrestin2, which is followed by receptor and β-arrestin2 internalization (Oh et al., 2010). In the cytoplasm the GPR120/β-arrestin2 complex can associate with the TGF-beta activated kinase 1 binding protein 1 (TAB1) at this blocking the association of TAB1 with the TGF-beta activated kinase 1 (TAK1) (Oh et al., 2010). Thus, there is an inhibition of TAK1 activation and downstream signalling to the IKKβ/NFκB and JNK/AP1 system resulting in the inhibition of Toll-like receptor 2/3 and 4 as well as TNF-α action (Oh et al., 2010).

4.4 Fatty acid composition of cellular membranes

The lipid composition of cellular membranes is known to depend on the availability of fatty acids (Calder et al., 1994). Supplementation of cells with PUFAs results in an incorporation of the fatty acids into membrane phospholipids (Schmutzler et al., 2010; Schumann & Fuhrmann, 2010; Walloschke et al., 2010). Beyond that, the PUFAs were metabolized leading to an increase of the desaturation and elongation products of the fatty acids added (Schmutzler et al., 2010; Schumann & Fuhrmann, 2010; Walloschke et al., 2009). The enhanced proportion of unsaturated fatty acids in the cell membrane is accompanied by a heightening of the Methylene Bridge Index (MBI) of the lipid bilayer and an increasing of membrane fluidity (Schmutzler et al., 2010; Schumann & Fuhrmann, 2010; Walloschke et al., 2009). The MBI is calculated based on the ratio of a fatty acid (weight %) and the number of its bis-allyl-methylene positions (Kelley et al., 1995). The higher the MBI, the more fluid the membrane. Moreover, membranes with a heightened MBI are predicted to have an increased susceptibility against radical reactions (Kelley et al., 1995).

The modulation of membrane fluidity makes an impact on the activity of membrane-bound enzymes and also on the function of membrane receptors thus affecting signal transduction (Benatti et al., 2004; Calder et al., 1994). Many key proteins of signal transduction, as Toll-like receptors or Nod-like receptors, are localized in lipid rafts (Pike, 2003). After binding of the ligand, the activated receptor complexes are compartmentalized in the lipid rafts (Jury et al., 2007). At this, the lipid rafts facilitate the association of signal transduction molecules (Jury et al., 2007; Pike, 2003).

The membrane fluidity necessary for an optimal cell response is assumed to fall within particular boundaries (Calder et al., 1994). Changes in the lipid composition of the plasma membrane therefore directly affect cellular reactions on signals from the environmental.

Accordingly, there is a correlation between the activity of immune cells and the fatty acid pattern of their cell membrane.
Of note, the availability of fatty acids is modulated by the diet. The connection between the dietary intake of fatty acids and inflammation was first drawn in the late 1970s. Epidemiological observation showed that native Greenland Eskimos (Dyerberg & Bang, 1979) and Japanese (Hirai et al, 1980), which have a high intake of n3 PUFA from seafood, have a low incidence for myocardial infarction, chronic inflammation and autoimmune disorders. To date, there are numerous studies, which have investigated the effects of the amount and the type of fat in the diet on cellular physiology (Calder, 2006b; Galli & Calder, 2009). It is now well accepted that the fatty acid composition of body cells, including immune cells, is sensitive to alteration according to the fatty acid composition of the diet (Calder, 2001). In particular, proportions of PUFAs of the n3 and the n6 family are readily modified thus providing a link between dietary PUFA intake, inflammation and immunity (Calder, 2001). The findings from these studies led health care professionals to encourage the general population to consume more n3 fatty acids.

5. Conclusion

The importance of lipid bilayers for the overall processes of life is increasingly realized. Plasma membranes are just more than compartmentalization elements separating the inside of a cell from the surrounding environment. They have numerous functions in cell adhesion, ion conductivity and cell signalling acting as an attachment surface for intracellular and extracellular.
Infection processes and immune defence greatly depend on cellular membrane interactions. In an initial step of infection pathogens, as bacteria and viruses, as well as bacterial toxins, need to get inside the host cell (Murphy et al., 2008). The internalization enables the pathogens to proliferate and to poison the cell (Murphy et al., 2008). Thus, the attachment of pathogens to cellular surfaces and the binding to a cell-surface receptor are critical in the course of infection processes. Moreover, the mutual communication between immune cells crucially depends on signal molecules binding to cellular receptors as well as on direct membrane-membrane interactions. Stimulation of membrane receptors via cytokines and chemokines and direct cell-cell contacts are of importance in activating immune cells thus triggering immune defence (Murphy et al., 2008). Likewise, completion of the immune response after successful extinction of the pathogens is mediated by membrane-dependent signal transduction processes (Murphy et al., 2008). A further mechanism in immune defence, which involves the interaction between the plasma membranes of both pathogen and host, is the phagocytosis of pathogens by macrophages and dendritic cells.
Of note, membranes are very flexible in their overall composition. Depending on cell type and tissue the proportion of phospholipids and sphingolipids varies greatly. The same is the case with membrane proteins. There are numerous highly specialised mechanisms that allow for the particular allocation of membrane lipids and membrane proteins according to the requirements and functions of a cell. Beyond that, the lipid bilayer is characterized by an asymmetry in the distribution of phospholipids and sphingolipids between the inner and the outer leaflet (Löffler et al., 2007). This asymmetry is determined by the balance of specific transport proteins (Löffler et al., 2007). The disruption of the lipid asymmetry is a piece in the substrate recognition of macrophages (Löffler et al., 2007).

However, the lipid composition of cellular membranes, including immune cells, can be modulated depending on the availability of fatty acids, providing a link between the diet and the immune defence (Calder et al., 1994). In particular, highly unsaturated fatty acids are immediately incorporated into the lipid bilayer (Schumann & Fuhrmann, 2010). The physical properties of membranes are highly reliant on the fatty acid pattern. Features modulated include the fatty acid chain order, the phase behaviour, the elastic compressibility, the ion permeability, the fusion, the rapid flip-flop and several protein functions thus affecting cell signal transduction (Stillwell & Wassall, 2003; Wassall & Stillwell, 2008). Moreover, the unsaturated fatty acids of membrane phospholipids serve as substrate for the synthesis of lipid signal molecules, as eicosanoids, lipoxins, resolvins, protectins and marensins, which are known to efficiently modulate immune defence mechanisms (Bannenberg & Serhan, 2010; Kohli & Levy, 2009; Löffler et al., 2007; Norling & Serhan, 2010). Beside, the fatty acids also act as ligands for several nuclear receptors and G protein-coupled receptors thus directly influencing the immune system (Bordoni et al., 2006). This key position of fatty acids, in particular of PUFAs of the n3 and the n6 family, makes them particular promising in the supportive therapy of chronic diseases linked to persistent pathogens.

6. References

Anderson, M.J. & Fritsche, K.L. (2004). Dietary polyunsaturated fatty acids modulate in vivo, antigen-driven CD4+T-cell proliferation in mice. *Journal of Nutrition*, Vol.2004, No.8 (August 2004), pp. 1978-1983, ISSN 0022-3166

Bannenberg, G. & Serhan, C.N. (2010). Specialized pro-resolving mediators in the inflammatory resonse: An update. *Biochimica et Biophysica Acta*, Vol.1801, No.12 (December 2010), pp. 1260-1273, ISSN 1388-1981

Bell, K.S., Philp, J.C., Aw, D.W. & Christofi, N. (1998). The genus Rhodococcus. *Journal of Applied Microbiology*, Vol.85, No.2 (August 1998), pp. 195-210, ISSN 1364-5072

Benatti, P., Peluso G., Nicolai, R. & Calvani, M. (2004). Polyunsaturated fatty acids: niochemical, nutritional and epigenetic properties. *Journal of the American College of Nutrition*, Vol.23, No.4 (August 2004), pp. 281-302, ISSN 0731-5724

Benoit, S., Benachour, A., Taouji, S., Auffray, Y. & Hartke, A. (2002). H_2O_2, which causes macrophage-related stress, triggers induction of expression of virulence-associated plasmid determinants in Rhodococcus equi. *International Immunology*, Vol.70, No.7 (July 2002), pp. 3768-3776, ISSN 0019-9567

Benoit, S., Taouji, S., Benachour, A. & Hartke, A. (2000). Resistance of Rhodococcus equi to acid pH. *International Journal of Food Microbiology*, Vol.55, No.1-3 (April 2000), pp. 295-298, ISSN 0168-1605

Blanc, D.S., Petignat, C., Janin, B., Bille, J. & Francioli, P. (1998). Frequency and molecular diversity of Pseudomonas aeruginosa upon admission and during hospitalization: a prospective epidemiologic study. *Clinical Microbiological Infections*, Vol.4, No.5 (May 1998), pp. 242-247, ISSN 1469-0691

Bishop-Bailey, D. & Bystrom, J. (2009). Emerging role of peroxisome proliferator-activated receptor-β/δ in inflammation. *Pharmacology and Therapeutics*, Vol.124, No.2 (November 2009), pp. 141-150, ISSN 0163-7258

Bordoni, A., Di Nunzio, M., Danesi, F. & Biagi, P.L. (2006). Polyunsaturated fatty acids:From diet to binding to PPARs and other nuclear receptors. *Genes and Nutrition*, Vol.1, No.2 (June 2006), pp. 95-106, ISSN 1555-8932

Boyce, J.A., Broide, D., Matsumoto, K. & Bochner, B.S. (2009). Advances in mechanisms of asthma, allergy, and immunology in 2008. *Journal of Allergy and Clinical Immunology*, Vol.123, No.3 (March 2009), pp. 569-574, ISSN 0091-6749

Boyen, F., Eeckhaut, V., Van, I.F., Pasmans, F., Ducatelle, R. & Hasebrouck, F. (2009). Quorum sensing in veterinary pathogens: mechanisms, clinical importance and future perspectives. *Veterinary Microbiology*, Vol.135, No.3-4 (March 2009), pp. 187-195, ISSN 0378-1135

Bryant, C. & Fitzgerald, K.A. (2009). Molecular mechanisms involved in inflammasome activation. *Trends in Cell Biology*, Vol.19, No.9 (September 2009), pp. 455-464, ISSN 0962-8924

Calder, P.C. (2001). Polyunsaturated fatty acids, inflammation and immunity. *Lipids*, Vol.36, No.9 (September 2001), pp. 1007-1024, ISSN 0024-4201

Calder, P.C. (2006a). Polyunsaturated fatty acids and inflammation. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Vol.75, No.3 (September 2006), pp. 197-202, ISSN 0952-3278

Calder, P.C. (2006b). n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *American Journal of Clinical Nutrition*, Vol.83, No.6 (June 2006), pp. 1505S-1519S, ISSN 0002-9165

Calder, P.C., Yaqoob, P., Harvey, D.J., Watts, A. & Newsholme, E.A. (1994). Incorporation of fatty acids by concanavalin A-stimulated lymphocytes and the effect on fatty acid composition and membrane fluidity. *Biochemical Journal*, Vol.300, No.2 (June 1994), pp. 509-518, ISSN 0264-6021

Chapkin, R.S., Kim, W., Lupton, J.R. & McMurray, D.N. (2009). Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. *Prostaglandins, Leukotriens and Essential Fatty Acids*, Vol.81, No.2-3 (August-September 2009), pp. 187-191, ISSN 1532-2823

Chiang, N., Bermudez, E.A., Ridker, P.M., Hurwitz, S. & Serhan, C.N. (2004). Aspirin triggers anti-inflammatory 15-epi-lipoxin A_4 and inhibits thromboxane in a randomized human trial. *Proceedings of the National Academy of Science of the United States of America*, Vol.101, No.42 (October 2004), pp. 15178-15183, ISSN 0027-8424

Dyerberg, J. & Bang, H.O. (1979). Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. *Lancet*, Vol.2, No.8140 (September 1979), pp. 433-435, ISSN 0140-6736

Escher, P. & Wahli, W. (2000). Peroxisome proliferator-activated receptors: insight into multiple cellular functions. *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis*, Vol.448, No.2 (March 2000), pp. 121-138, ISSN 0027-5107

Feige, J.N., Gelman, L., Michalik, L., Desvergne, B. & Wahli, W. (2006). From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. *Progress in Lipid Research*. Vol.45, No.2 (March 2006), pp. 120-159, ISSN 0163-7827

Fernandez-Mora, E., Polidori, M., Luhrmann, A., Schaible, U.E. & Haas, A. (2005). Maturation of Rhodococcus equi-containing vacuoles is arrested after completion of

the early endosome stage. *Traffic*, Vol.6, No.8 (August 2005), pp. 635-653, ISSN 1398-9219

Galli, C. & Calder, P.C. (2009). Effects of fat and fatty acid intake on inflammatory and immune responses: a critical review. *Annals of Nutrition and Metabolism*, Vol.55, No.1-3 (September 2009), pp. 123-139, ISSN 0250-6807

Gaus, K., Rodriguez, M., Ruberu, K.R., Gelissen, I., Sloane, T.M., Kritharides, L. & Jessup, W. (2005). Domain-specific lipid distribution in macrophage plasma membranes. *Journal of Lipid Research*, Vol.46, No.7 (July 2005), pp. 1526-1538, ISSN 0022-2275

Germolec, D.R., Frawley, R.P. & Evans, E. (2010). Markers of inflammation. *Methods in Molecular Biology*, Vol.598 (February 2010), pp. 53-73, ISSN 1940-6029

Glaros, T. Larsen, M. & Li, L. (2009). Macrophaes and fibroblasts during inflammation, tissue damage and organ injury. *Frontiers in Biosciences*, Vol.12 (January 2009), pp. 3988-3993, ISSN 1093-9946

Gottlicher, M., Widmark, E., Li, Q. & Gustafsson, J.A. (1992). Fatty acids activate a chimera of the clofibric acid-activated receptor and the glucocorticoid receptor. *Proceedings of the national Academy of Sciences of the United States of America*, Vol.89, No.10 (May 1992), pp. 4653-4657, ISSN 0027-8424

Grimaldi, P.A. (2001). Fatty acid regulation of gene expression. *Current Opinion in Clinical Nutrition and Metabolic Care*, Vol.4, No.5 (September 2001), pp. 433-437, ISSN 1363-1950

Groves, E., Dart, A.E., Covarelli, V. & Caron, E. (2008). Molecular mechanisms of phagocytic uptake in mammalien cells. *Cellular and Molecular Life Sciences*, Vol. 65, No.13 (July 2008), pp. 1957-1976, ISSN 1420-682X

Haas, A. (2007). The phagosome: compartment with a license to kill. *Traffic*, Vol.8, No.4 (April 2007), pp. 311-330, ISSN 1398-9219

Hamilton, T.A., Ohmori, Y., Tebo, J.M. & Kishore, R. (1999). Regulation of macrophage gene expression by pro- and anti-inflammatory cytokines, *Pathobiology*, Vol.67, No.5-6 (1999), pp. 241-244, ISSN 1015-2008

Hartlova, A., Cerveny, L., Hubalek, M., Krocova, Z. & Stulnig, J. (2010). Membrane rafts: a potential gateway for bacterial entry into host cells. *Microbiology and Immunology*, Vol.54, No.4 (April 2010), pp. 237-245, ISSN 0385-5600

Henderson, R.M., Edwardson, J.M., Geisse, N.A. & Saslowsky, D.E. (2004). Lipid rafts: feeling is believing. *News in Physiological Sciences*, Vol.19 (April 2004), pp. 39-43, ISSN 0886-1714

Hirai, A., Hamazaki, T., Terano, T., Nishikawa, T., Tamura, Y., Kumagai, A. & Sajiki, J. (1980). Eicosapentaenoic acid and platelet function in Japanese. *Lancet*, Vol.2, No.8204 (November 1980), pp. 1132-1133, ISSN 0140-6736

Hong, S., Gronert, K., Devchand, P., Moussignac, R.-L. & Cerhan, C.N. (2003). Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood and glial cells: autacoids in anti-inflammation. *Journal of Biologcal Chemistry*, Vol.278, No.17 (April 2003), pp. 14677-14687, ISSN 0021-9258

Huang, J.T., Welch, J.S., Ricote, M., Binder, C.J., Wilson, T.M., Kelly, C., Witztum, J.L., Funk, C.D., Conrad, D. & Glass, C.K. (1999). Interleukin-4-dependent production of PPAR-gamma ligands in macrophages by 12/15-lipoxygenase. *Nature*, Vol.400, No.6742 (July 1999), pp. 378-382, ISSN 0028-0836

Hughes, D.A. & Pinder, A.C. (2000). n-3 polyunsaturated fatty acids inhibit the antigen-presenting function of human monocytes. *American Journal of Clinical Nutrition*, Vol.71, No.1 (January 2000), pp. 357S-360S, ISSN 0002-9165

Ijpenberg, A., Jeannin, E., Wahli, W. & Desvergne, B. (1997). Polarity and specific sequence requirements of peroxisome proliferator-activated receptor (PPAR)/retinoid X receptor heterodimer binding to DNA. A functional analysis of the malic enzyme gene PPAR response element. *Journal of Biological Chemistry*, Vol.272, No.32 (August 1997), pp. 20108-20117, ISSN 0021-9258

Issemann, I. & Green, S. (1990). Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*, Vol.347, No.6294 (October 1990), pp. 645-650, ISSN 0028-0836

Issemann, I., Prince, R.A., Tugwood, J.D. & Green, S. (1993).The peroxisome proliferator-activated receptor:retinoid X receptor heterodimer is activated by fatty acids and fibrate hypolipidaemic drugs. *Journal of Molecular Endokrinology*, Vol.11, No.1 (August 1993), pp. 37-47, ISSN 0952-5041

Jiang, C., Ting, A.T. & Seed, B. (1998). PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature*, Vol.391, No.6662 (January 1998), pp. 82-86, ISSN 0028-0836

Johnston, J.B., Rahman, M.M. & McFadden, G. (2007). Strategies that modulate inflammasomes: insights from host-pathogen interactions. *Seminars in Immunopathology*, Vol.29, No.3 (September 2007), pp. 261-274, ISSN 1863-2297

Jury, E.C., Flores-Borja, F. & Kabouridis, P.S. (2007). Lipid rafts in T cell signaling and disease. *Seminars in cell & developmental biology*, Vol.18, No.5 (October 2007), pp. 608-615, ISSN 1084-9521

Kamboj, M., Kalra, A. & Kak, V. (2005). Rhodococcus brain abscess in a patient without HIV. *Journal of Clinical Pathology*, Vol.58, No.4 (April 2005), pp. 423-425, ISSN 0021-9746

Kelley, E.E., Buettner, G.R. & Burns, C.P. (1995). Relative alpha-tocopherol deficiency in cultured cells: free radical lipid peroxidation, lipid peroxidizability, and cellular polyunsaturated fatty acid content. *Archives of Biochemistry and Biophysics*, Vol.319, No.1 (May 1995), pp. 102-109, ISSN 0003-9861

Khan, S.A. & Heuvel, J.P.V. (2003). Reviews:Current Topics – Role of nuclear receptors in the regulation of gene expression by dietary fatty acids (Review). *Journal of Nutritional Biochemistry*, Vol.14, No.10 (October 2003), pp. 554-567, ISSN 0955-2863

Kliewer, S.A., Umesono, K., Noonan, D.J., Heyman, R.A. & Evans, R.M. (1992). Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature*. Vol.358, No.6389, pp. 771-774, ISSN 0028-0836

Kohli, P. & Levy, B.D. (2009). Resolvins and protectins: mediating solutions to inflammation. *British Journal of Pharmacology*, Vol.158, No.4 (October 2009), pp. 960-971, ISSN 0007-1188

Lee, T.H., Menica-Huerta, J.M., Shih, C., Corey, E.J., Lewis, R.A. & Austen, K.F. (1984). Characterization and biologic properties of 5,12-dihydroxy derivates of eicosapentaenoic acid, including leukotriene B5 and the double lipoxygenase product. *Journal of Biology and Chemistry*, Vol.259, No.4 (February 1984), pp. 2383-2389, ISSN 0021-9258

Lee, T.H., Sethi, T., Crea, A.E., Peters, W., Arm, J.P. & Horton, C.E. (1988). Characterization of leukotriene B3: comparison of its biological activities with leukotriene B4 and leukotriene B5 in complement receptor enhancement, lysozyme release and chemotaxis of human neutrophils. *Clinical Science (London)*, Vol.74, No.5 (May 1988), pp. 467-475, ISSN 0143-5221

Levy, B.D. (2010). Resolvins and protectins: Natural pharmacophores for resolution biology. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Vol.82, No.4-6 (April-June 2010), pp. 327-332, ISSN 0952-3278

Levy, B.D., Clish, C.B., Schmidt, B., Gronert, K. & Serhan, C.N. (2001). Lipid mediator class switching during acute inflammation: signals in resolution. *Nature Immunology*, Vol.2, No.7 (July 2001), pp. 612-619, ISSN 1529-2908

Lingwood, D. & Simons, K. (2010). Lipid rafts as a membrane-organizing principle. *Science*, Vol.327, No.5961 (January 2010), pp. 46-50, ISSN 0036-8075

Löffler, G., Petrides, P.E. & Heinrich, P.C. (2007). *Biochemie & Pathobiochemie*, Springer Medizin Verlag, ISBN 3-540-32680-4, Heidelberg

Miles, E.A. & Calder, P.C. (1998). Modulation of immune function by dietary fatty acids. *Proceedings of the Nutrition Society*, Vol.57, No.2 (May 1998), pp. 277-292, ISSN 0029-6651

Milaud, T., Hammerling, G.J. & Garbi, N. (2010). Review of murine dendritic cells: types, location, and development. *Methods in Molecular Biology*, Vol.595, No.1 (February 2010), pp. 21-42, ISSN 1940-6029

Mogensen, T.H. (2009). Pathogen recognition and inflammatory signaling in innate immune defenses. *Clinical Microbiology Reviews*, Vol.22, No.2 (April 2009), pp. 240-273, ISSN 0893-8512

Murphy, K., Travers, P. & Walport, M. (2008). *Janeway`s Immunology*, Garland Science, Taylor and Francis Group, LLC, ISBN 0-8153-4123-7, New York

Norling, L.V. & Serhan, C.N. (2010). Profiling in resolving inflammatory exudates identifies novel anti-inflammatory and pro-resolving mediators and signals for termination. *Journal of Internal Medicine*, Vol.268, No.1 (July 2010), pp. 15-24, ISSN 0954-6820

Oh, D.Y., Talukdar, S., Bar, E.J., Imamura, T., Morinaga, H., Fan, W.Q., Li, P., Lu, W.J., Watkins, S.M. & Olefsky J.M. (2010). GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell, Vol.142, No.5 (September 2010), pp. 687-698, ISSN 0092-8674

Pesci, E.C., Milbank, J.B., Pearson, J.P., McKnight, S., Kende, A.S., Greenberg, E.P. & Iglewski, B.H. (1999). Quinolone signaling in the cell-to-cell communication system of Pseudomonas aeruginosa, *Proceedings of the National Academy of Science United States of America*, Vol.96, No.20 (September 1999), pp. 11229-11234, ISSN 0027-8424

Pike, L.J. (2003). Lipid rafts: bringing order to chaos. *Journal of Lipid Research*, Vol.44, No.4 (April 2003), pp. 655-667, ISSN 0022-2275

Pike, L.J. (2006). Rafts defined: a report on the Keystone symposium on lipid rafts and cell function. *Journal of Lipid Research*, Vol.47, No.7 (July 2006), pp. 1597-1598, ISSN 0022-2275

Pourova, J., Kottova, M., Voprsalova, M. & Pour, M. (2010). Reactive oxygen and nitrogen species in normal physiological processes. *Acta Physiologica*, Vol.198, No.1 (January 2010), pp. 15-35, ISSN 1748-1708

Prescott, J.F. (1991). Rhodococcus equi: an animal and human pathogen. *Clinical Microbiological Reviews*, Vol.4, No.1 (January 1991), pp. 20-34, ISSN 0893-8512

Prescott, S.M. (1984). The effect of eicosapentaenoic acid on leukotriene B production by human neutrophils. *Journal of Biological Chemistry*, Vol.259, No.12 (June 1984), pp. 7615-7621, ISSN 0021-9258

Quinn, P.J. & Wolf, C. (2009). The liquid-ordered phase in membranes. *Biochimica et Biophysica Acta*, Vol.1788, No.1 (January 2009), pp. 33-46, ISSN 0005-2736

Ricote, M., Li, A.C., Wilson, T.M., Kelly, C.J. & Glass, C.K. (1998). The peroxisome proliferator-activated receptor-gamma ia a negative regulator of macrophage activation. *Nature*, Vol.391, No.6662 (January 1998), pp. 79-82, ISSN 0028-0836

Robinson, J.M. (2009). Phagocytic leukocytes and reactive oxygen species. *Histochemistry and Cell Biology*, Vol.131, No.4 (April 2009), pp. 465-469, ISSN 0948-6143

Russell, D.G., Vanderven, B.C., Glennie, S., Mwandumba, H. & Heyderman, R.S. (2009). The macrophage marches on ist phagosome: dynamic assays of phagosome function. *Nature Reviews Immunology*, Vol.9, No.8 (August 2009), pp. 594-600, ISSN 1474-1733

Schmitz, G. & Ecker, J. (2008). The opposing effects of n-3 and n-6 fatty acids. *Progress in Lipid Research*, Vol.47, No.2 (March 2008), pp. 147-155, ISSN 0163-7827

Schmutzler, S., Bachmann, L., Fuhrmann, H. & Schumann, J. (2010). PUFA-dependent alteration of oxidative parameters of a canine mastocytoma cell line. *Acta Veterinaria Hungarica*, Vol.58, No.4 (June 2010), pp. 453-464, ISSN 0236-6290

Schumann, J. & Fuhrmann, H. (2010). Impairment of NFκB activity by unsaturated fatty acids. *International Immunopharmacology*, Vol.10, No.8 (August 2010), pp. 978-984, ISSN 1567-5769

Serhan, C.N., guest ed. (2005). Special issue on lipoxins and aspirin-triggered lipoxins. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Vol.73, No.3-4 (September-October 2005), pp. 139-321, ISSN 0952-3278

Serhan, C.N., Chiang, N., & Van Dyke, T.E. (2008). Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nature Reviews Immunology*, Vol.8, No.5 (May 2008), pp. 349-361, ISSN 1474-1733

Serhan, C.N., Gotlinger, K., Hong, S., Lu, Y., Siegelman, J., Baer, T., Yang, R., Colgan, S.P. & Petasis, N.A. (2006). Anti-inflammatory actions of neuroprotectin D1/protectin D1 and its natural stereoisomers: assignements of dihydroxy-containing docosatrienes. *Journal of Immunology*, Vol.176, No.6 (March 2006), pp. 1848-1859, ISSN 0022-1767

Silva, M.T. (2010). When two is better than one: macrophages and neutrophils work in concert in innate immunity as complementary and cooperative partners of a myeloid phagocyte system. *Journal of Leukocyte Biology*, Vol.87, No.1 (January 2010), pp. 93-106, ISSN 0741-5400

Simons, K. & Toomre, D. (2000). Lipid rafts and signal transduction. *Nature Reviews Molecular Cell Biology*, Vol.1, No.1 (October 2000), pp. 31-39, ISSN 1471-0072

Spite, M., Norling, L.V., Summers, L., Yang, R., Cooper, D., Petasis, N.A., Flower, M., Perretti, C.N. & Serhan, C.N. (2009). Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature*, Vol.461, No. 7268 (October 2009), pp. 1287-1291, ISSN 0028-0836

Stillwell, W. & Wassall, S.R. (2003). Docosahexaenoic acid: membrane properties of a unique fatty acid. *Chemistry and Physic of Lipids*, Vol.126, No.1 (November 2003), pp. 1-27, ISSN 0009-3084

Strateva, T. & Yordanov, D. (2009). Pseudomonas aeruginosa – a phenomenon of bacterial resistance. *Journal of Medical Microbiology*, Vol.58, No.9 (September 2009), pp. 1133-1148, ISSN 0022-2615

Stulnig, T.M. (2003). Immunomodulation by polyunsaturated fatty acids: Mechanisms and effects. *International Archives of Allergy and Immunology*, Vol.132, No.4 (December 2003), pp. 310-321, ISSN 1018-2438

Trautmann, M., Lepper, P.M. & Haller, M. (2005). Ecology of Pseudomonas aeruginosa in the intensive care unit and the evolving role of water outlets as a reservoir of the organism. *American Journal of Infection Control*, Vol.33, No.5 (June 2005), pp. S41-S49, ISSN 0196-6553

Tresset, G. (2009). The multiple faces of self-assembled lipidic systems. *PMC Biophysics*, Vol.2, No.1 (April 2009), pp.3, ISSN 1757-5036

Van, L.F. & Leo, O. (2002). Membrane lipid rafts: new targets for immunoregulation. *Current Molecular Medicine*, Vol.2, No.6 (September 2002), pp. 557-570, ISSN 1566-5240

Varol, C., Yona, S. & Jung, S. (2009). Origins and tissue-context-dependent fates of blood monocytes. *Immunology and Cell Biology*, Vol.87, No.1 (January 2009), pp. 30-38, ISSN 0818-9641

Veesenmeyer, J.L., Hauser, A.R., Lisboa, T. & Rello, J. (2009). Pseudomonas aeruginosa virulence and therapy: evolving translational strategies. *Critical Care Medicine*, Vol.37, No.5 (May 2009), pp. 1777-1786, ISSN 0090-3493

Walloschke, B., Fuhrmann, H. & Schumann, J. (2010). Enrichment of RAW264.7 macrophages with essential 18-carbon fatty acids affects both respiratory burst and production of immune modulating cytokines. *Journal of Nutritional Biochemistry*, Vol.21, No.6 (June 2010), pp. 556-560, ISSN 0955-2863

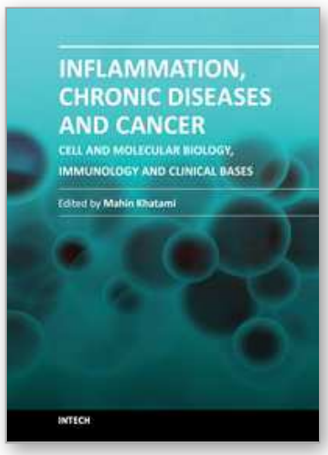
Wassall, S.R. & Stillwell, W. (2008). Docosahexaenoic acid domains: the ultimate non-raft membrane domain. *Chemistry and Physic of Lipids*, Vol.153, No.1 (May 2008), pp. 57-63, ISSN 0009-3084

Yang, X.Y., Wang, L.H., Chen, T., Hodge, D.R., Resau, J.H., DaSilva, L. & Farrar, W.L. (2000). Activation of human T lymphocytes is inhibited by peroxisome proliferator-activated receptor gamma (PPARgamma) agonists - PPARgamma co-association with transcription factor NFAT. *Journal of Biological Chemistry*, Vol.275, No.7 (February 2000), pp. 4541-4544, ISSN 0021-9258

Yaqoob, P. (2003). Lipids and the immune response: from molecular mechanisms to clinical applications. *Current Opinion in Clinical Nutrition and Metabolic Care*, Vol.6, No.2 (March 2003), pp. 133-150, ISSN 1363-1950

Ye, S., Tan, L., Ma, J., Shi, Q. & Li, J. (2010). Polyunsaturated docosahexaenoic acid suppresses oxidative stress induced endothelial cell calcium influx by altering lipid composition in membrane caveolar rafts. *Prostaglandins, Leukotrienes and essential fatty acids*, Vol.33, No.1 (July 2010), pp. 37-43, ISSN 0952-3278

Zeyda, M., Saemann, M.D., Stuhlmeier, K.M., Mascher, D.G., Nowotny, P.N. & Zlabinger, G.J. (2005). Polyunsaturated fatty acids block dendritic cell activation and function independently of NF-kappaB activation. *Journal of Biological Chemisry*, Vol.280, No.14 (April 2005), pp. 14293-14301, ISSN 0021-9258



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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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