Lipids as Main Constitutes of Biological Cells

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***Abstract*—Fatty acids (FAs) are mainly energy sources along with being membrane constituents. They consist of a carboxyl group at one end and a methyl group at the other. Their biological activities contribute to cell and tissue metabolism, function, and responsiveness to hormonal and other signals. Their biological activities consist of regulation of membrane structure and function; regulation of intracellular signaling pathways, transcription factor activity, and gene expression; and regulation of the production of bioactive lipid mediators. As a result of these effects, fatty acids influence health, well-being, and disease risk. Fatty acids influence a range of diseases such as cardiovascular disease, type 2 diabetes, inflammatory diseases, and cancer. The current paper sheds light on the role of lipids and fatty acids in biological systems. This involve their role in modulating the immune response and biological metabolic pathways in the body.**

***Keywords*— fatty acids; immune response; lipids; disease**

I. Introduction

Mammalian cells express a wide range of lipid species and use proteins to synthesis, metabolize and transport them. Lipids may have structural or signaling roles. Most lipids contain hydrophobic side chains and polar head groups which add to lipid diversity. Modification of lipid head groups are crucial to for some lipid functions for example, phosphorylation of phosphatidylinositol 4, 5-bisphosphate [PI (4, 5) P2, or P1P2] into phosphatidylinositol 3,4,5-trisphosphate [P1(3,4,5)P3, or P1P3]). Until recently, it has become clear that the identity of the hydrophobic side chains is also important.

To understand the roles of lipids in biological processes, it is important to identify which lipid families and species participate in a process, visualize these lipids in relevant cellular compartments or structures, measure physical and mechanical properties of relevant lipids and membranes and perturb lipid levels for phenotypic and functional analyses (Muro et al., 2014).

II. Role of Fatty Acids and Lipids in Cell Biology

Dietary recommendations are made to reduce the intake of saturated and trans-fatty acids due to their negative cardiovascular effects, whereas mono- and polyunsaturated fatty acids are recommended for their cardio-protective benefits. For example, oleic acid (OA) has proved beneficial in the reduction of blood pressure and low hypertension. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been associated with the prevention of cardiovascular diseases and cancer, while omega-6 polyunsaturated fatty acid (PUFA), gamma linolenic acid (γ-LNA) have anti-inflammatory properties. Altered levels of free fatty acids (FFAs) are associated with pathological states such as diseases like obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimers's disease (AD), atherosclerosis and cancer.

The effects of these fatty acids on membrane structure have been studied using a variety of techniques such as differential scanning calorimetry (DSC), fluorescence spectroscopy, electron spin resonance, light scattering electrophoresis, nuclear magnetic resonance and differential thermal analysis to name some (Ibarguren et al., 2014).

Lipids basically form the building blocks of cells. They constitute the key components of the plasma membrane and other cellular compartments such as the nuclear membrane, the endoplasmic reticulum, the golgi apparatus, and trafficking vesicles such as endosomes and lysosomes. The lipid composition of different organelles, cell types and tissues vary; therefore different lipids are required for different functions.

III. The Immune system and Fatty Acids

The immune system helps in identifying threatening and non-threatening antigens; in protection against pathogens like bacteria, viruses, fungi and parasites. Additionally, it aids in identifying and eliminating tumor cells and response to injury, surgery, burns and irradiation. It is highly complex and thus involves a wide range of specialized cells present throughout the body. Cells of the immune system interact with one another along with other cells (e.g. epithelial cells, endothelial cells, platelets etc.) so as to produce a response which may be local or systemic.

The immune response triggers the production of many chemical mediators; which help in the elimination of infectious organisms; some play a regulatory role in the activity of particular cells and some help in the termination of response.

The immune response is divided into the innate (or natural) immune response and the acquired (or specific) immune response. The former is activated on recognition of the structural features of pathogens for example, lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria, known as endotoxin is recognized by Toll-like receptor (TLR)-4 on the surface of innate immune cells whereas the latter, is specific for a single antigen and must be presented by an antigen-presenting cell to an antigen-specific T-cell.

Studies on the effect of fatty acids on immunity were started in the 1970s. The earliest study involved evaluating and

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comparing the effects of common short fatty acids (SFA) and the n-6 fatty acid, linolenic acid. The observations revealed modifications of the physical structure of plasma membrane of immune cells. They also discovered that eicosanoids such as PGE2, played a role in inflammation and regulation of the immune cell function. This find initiated studies on the common eicosanoid precursor arachidonic acid and also suggested that the effect of some fatty acids on immune cell responses may be due to modification of eicosanoid production.

Some in-vitro studies led to the discovery of the involvement of EPA and DHA on functional responses of immune cells to stimulation. Experimental studies and clinical trials of the use of fish oil for patients with rheumatoid arthritis showed significant anti-inflammatory activity with combination of EPA and DHA (Al-Khalaifah et al., 2022a, Al-Khalaifah et al., 2022b, Al-Surrayai and Al-Khalaifah, 2022, Amer et al., 2022, Attia et al., 2022, Kishawy et al., 2022).

Eicosanoids are active lipid mediators derived from PUFA, namely n-6 fatty acid arachidonic acid. The play an important role in inflammation and regulation of immune function. Eicosanoid produced from EPA are less biologically active than those produced from arachidonic acid, this may be because eicosanoid receptors have a much lower affinity for EPA-derived mediator than for the arachidonic acid-derived one. EPA acts as a substrate for COX, lipoxygenase and cytochrome P450 enzymes.

EPA and DHA have the ability to generate distinct effects on membrane order in immune cells owing to their highly unsaturated nature. The use of EPA and DHA for cells involved in inflammation and immunity occurs at the expense of arachidonic acid, this leads to a decline in the amount of substrate available to produce inflammatory and regulatory eicosanoids. They also inhibit T-cell proliferation and production of key T-helper 1 type cytokine IL-2 in cell cultures. In animals, studies have reported that high amounts of fish oil or individual n-3 fatty acids reduced T-cell proliferative responses and alterations in t-helper 1 cytokine gene expression and production. However, studies in human subjects are limited , though some studies revealed that an increased intake of EPA along with DHA decreased human T-cell proliferation and IL-2 production.

These effects of n-3 fatty acids on T-cells are associated with changes in membrane order, altered patterns of eicosanoid production and modification of early signal transduction events in the plasma membrane (Al-Khalaifah, 2020, Al-Khalaifah, 2018, Al-Khalaifah and Al-Nasser, 2020, Al-Khalaifah and Al-Nasser, 2021, Al-Khalaifah et al., 2017, Al-Khalaifah et al., 2020a, Al-Khalaifah et al., 2020b, Amer et al., 2021, El-Maaty et al., 2021, Omar et al., 2021).

Lipid rafts are membranes with distinct structural compositions. They are enriched with sphingolipids and cholesterol and their side chains are rich in short fatty acids (SFAs). Proteins involved in signal transduction like Src family kinases, G proteins, growth factor receptors, mitogen-activated protein kinases and protein kinase C are found in lipid rafts (Calder, 2013, Al-Khalifa, 2016a, Al-Khalifa, 2015, Al-Khalifa, 2016b, Al-Khalifa et al., 2016, Al-Khalifa et al., 2012).

IV. Implications and Effects of Fatty Acids on Human Health

There have been rising questions on disease association with relation to interactions between diet, gut and microbiome components, particularly in autoimmunity. Evidences point in the direction that nutrition and bacterial metabolites may have an impact on the immune response with relation to disease and autoimmunity.

Fatty acids form an essential component of our daily diet and are now become an area of concern with special focus on SFAs. These SFAs are primarily metabolized by gut bacteria obtained from indigestible carbohydrates which in turn may prove benficial for diseases in model of inflammatory bowel disease (IBD) and allergic asthma. Long-chain Fas (LCFAs) are suspected of being a trigger for many diseases. However, researches of these saturated fatty acids on the innate immune system are limited to the cardiovascular disease and their impact on adaptive immune system is not studied comprehensively.

The gut microbiome has recently been established as a contributor to pathogenesis or multiple sclerosis (MS), a T-cell mediated autoimmune disease of the central nervous system (CNS) with neurodegenerative effects. A study was undertaken to show dietary-induced changes in the gut shaped Th cell responses as a result of the effect of dietary SFAs and the lesser-studied medium-chain (MC) FAs or LCFAs. The results showed that LCFAs enhanced the differentiation and proliferation of T helper 1 (Th1) and/or Th17 cells impaired intestinal sequestration via p38-MAPK pathway. On the other hand, SFAs expanded gut T regulatory (Treg) cells by the suppression of the JNK1 and p38 pathway.

Experimental autoimmune encephalomyelitis (EAE) was used a a model for T-cell mediated autoimmunity to depict that LCFAs decreased SFAs in the gut and aggravated the diseases by expanding pathogenic Th1 and Th17 cell populations in the small intestine.

Treatments with SFAs helped reform EAE and reduce axonal damage by means of long-lasting imprinting ion lamina-propria-derived Treg cells. Thus, the study exhibited a direct dietary impact on intestinal-specific and central nervous system-specific, Th cell response in autoimmunity (Haghikia et al., 2015).

The two families of PUFA are classified as omega-3 (n-3) and omega-6 (n-6) fatty acids. The human body is capable of producing all; except for two fatty acids, linoleic acid (LA) and alpha-linolenic acid (ALA) also known as essential fatty acids.

PUFAs regulate a range of biological functions such as blood pressure and blood clotting up till the development and functioning of the brain and nervous system. LA is derived from sources such as plant oils of sunflower, safflower and corn oils. ALA is obtained from green leafy vegetables, flaxseed and rapeseed oils.

FAs form 28-42% of the total energy consumed by European populations. Due to an increased consumption of LA-rich vegetable oils, n-6 PUFA consumption has increased and is higher than n-3 PUFA. The optimal dietary intake of n-6:n-3 ratio is around 1-4:1.

PUFAs play an important role in the composition of cell membranes by maintaining homeostasis for correct membrane protein function and influence membrane fluidity. Thus, helping in the regulation if cell signaling processes cellular functions and gene expression.

The n-6 PUFAs contribute to the chronic inflammatory conditions in humans such as nonalcoholic fatty liver disease (NAFLD), ID and neurodegenerative diseases such AD.

NAFLD is a hepatic component of the Metabolic Syndrome and is becoming a serious public health problem. It results in severe liver damage beginning with steatosis and leads to steatohepatitis (NASH), advanced fibrosis and cirrhosis. Both, nutritional factors and alterations in lipid metabolism of the liver are the primary metabolic abnormalities which lead to hepatic steatosis.

n-3 LC PUFA acts as a therapeutic target in the pathogenesis of NAFLD. In the liver, these PUFAs possess the ability to direct FAs away from triacylglycerol storage and to enhance their oxidation. However, these PUFAs are low in patients with NAFLD. A higher n-6:n-3 LC-PUFA ratio may lead to the development of fatty liver due to irregularity in liver lipid metabolism. Recently, fish oil has proved beneficial in the alleviation of NAFLD by decreasing plasma nonesterified fatty acids (NEFA) concentrations; decreasing de novo lipogenesis, very low-density lipoprotein (VLDL) export, and plasma triglyceride concentrations and decreased adipocyte size and visceral fat content (Patterson et al., 2012).

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