

Oxylipins in Inflammatory-Related Diseases NAFLD, Obesity, and T2D

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Contributor: Mariya Misheva , Jethro Johnson , James McCullagh

Oxygenated polyunsaturated fatty acids (oxylipins) are bioactive molecules established as important mediators during inflammation. Different classes of oxylipins have been found to have opposite effects, e.g., pro-inflammatory prostaglandins and anti-inflammatory resolvins. Production of the different classes of oxylipins occurs during distinct stages of development and resolution of inflammation. Chronic inflammation is involved in the progression of many pathophysiological conditions and diseases such as non-alcoholic fatty liver disease, insulin resistance, diabetes, and obesity. Determining oxylipin profiles before, during, and after inflammatory-related diseases could provide clues to the onset, development, and prevention of detrimental conditions.

eicosanoid

inflammation

diagnosis

progression

mass spectrometry

1. Introduction

Oxylipins are bioactive lipid mediators derived from the enzymatic or non-enzymatic oxidation of polyunsaturated fatty acids (PUFAs). The enzymatic oxidation of PUFAs is carried out by cyclooxygenases (COX), lipoxygenases (LOX) ^{[1][2][3][4]} or cytochrome P450s (CYP) ^{[5][6][7][8][9][10]}. PUFAs are those fatty acids that have more than one double bond in their backbone. When the final double bond is at the carbon–carbon double bond in the n-6 position (the sixth bond counting from the methyl end), they are referred to as omega-6 fatty acids. When that bond is in the n-3 position, these are known as omega-3 fatty acids ^[11]. There are two PUFAs in the human body that cannot be produced endogenously, linoleic and alpha-linolenic acid (LA and ALA), and accordingly they are defined as essential fatty acids. LA is an omega-6 fatty acid that is metabolised to arachidonic acid (AA) and dihomo-gamma-linolenic acid (DGLA). ALA is an omega-3 fatty acid which is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Therefore, based on research discoveries so far AA, DGLA, EPA and DHA are the non-essential fatty acids which give rise to numerous oxylipin families (**Figure 1**). Importantly, mammals including humans cannot convert omega-6 to omega-3 PUFAs. Hence, the levels of these oxylipins reflect the consumption of omega-3 or omega-6 PUFAs. Specific omega-3 and omega-6 metabolites have been implicated to have opposing beneficial or detrimental effects in human health and disease, with omega-3-derived compounds found to be generally anti-inflammatory while oxylipins originating from omega-6 fatty acids have predominantly pro-inflammatory effect ^{[12][13]}. The pleiotropic effects of these compounds are increasingly appreciated with different oxylipins having dissimilar roles in physiological and pathophysiological processes ^{[14][15][16][17][18]}. Importantly, the superclass of oxylipins includes hundreds of structurally and stereochemically distinct species ^[14]. Thus, profiling of oxylipins can be an important tool in investigating their role in pathophysiological processes.

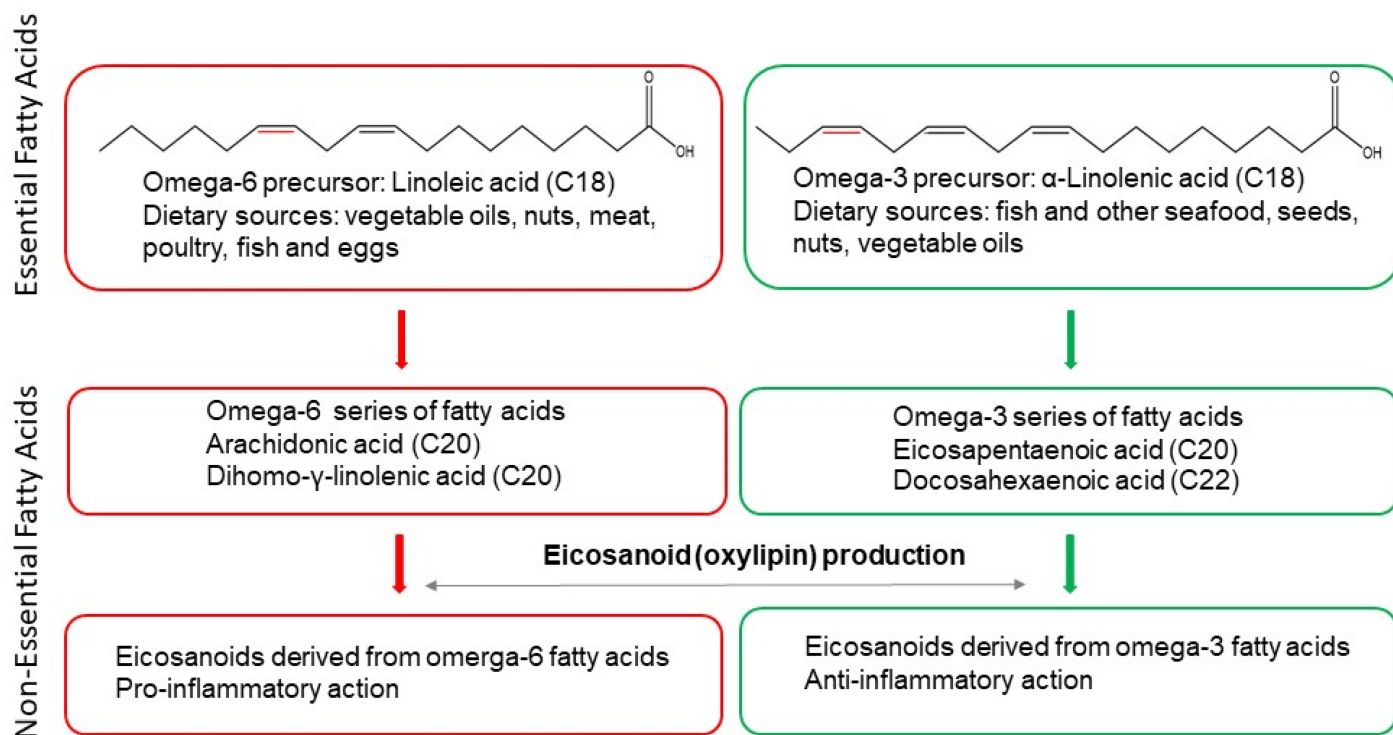


Figure 1. General overview of essential and non-essential polyunsaturated fatty acids. LA is a non-essential fatty acid and precursor of the omega-6 series of fatty acids and eicosanoids which have mostly pro-inflammatory action. ALA is a non-essential fatty acid and precursor of the omega-3 series of fatty acids and eicosanoids which have predominantly anti-inflammatory effect. Omega-6 and omega-3 double bonds are marked in red. Chemical formulas were created using ChemDraw®. More detailed description of the role of PUFAs in inflammatory processes, including exceptions, is outlined in the main text.

2. Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is a chronic liver disease that results in an excessive increase in fat (steatosis) in the liver without evidence of other causes of liver disease (such as alcohol). There are two progressive subtypes of NAFLD: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) which is progression of NAFLD beyond NAFL alone [19]. The main difference between the two types is the presence of inflammation. NAFL is characterised by little or no inflammation or liver damage. NAFL usually does not cause complications, though it can lead to pain from liver enlargement [20][21]. In comparison, NASH is categorised by inflammation and liver damage in addition to the build-up of fat. NASH can result in the development of cirrhosis which in turn can lead to liver cancer [22][23][24][25].

Although the pathogenesis of NAFLD is still not completely understood, its connection to fat build-up is clear. Bodyweight reduction among NAFLD patients showed lower levels of triglycerides, cholesterol, and the eicosanoids 5-Oxo-eicosatetraenoic acid (5-oxo-ETE) and lipoxinA4 (LXA4), and was linked to a significant improvement in steatosis [26]. Analysis of liver tissue samples from obese patients has indicated a complicated relationship between eicosanoid levels and paediatric NAFLD. CYP-produced eicosanoids have been shown to be downregulated during fibrosis, but increased in the steatosis stage, while the levels of precursor PUFAs and the

production of hydroxyeicosatetraenoic acids (HETEs), hydroxyeicosapentaenoic acids (HEPEs), and hydroxydocosahexaenoic acids (HDHAs) remained unchanged [27]. Although the pathogenesis of NAFLD is still not completely understood, its connection to fat build-up is clear. Bodyweight reduction among NAFLD patients showed lower levels of triglycerides, cholesterol, and the eicosanoids 5-Oxo-eicosatetraenoic acid (5-oxo-ETE) and lipoxinA4 (LXA4), and was linked to a significant improvement in steatosis [26]. Analysis of liver tissue samples from obese patients has indicated a complicated relationship between eicosanoid levels and paediatric NAFLD. CYP-produced eicosanoids have been shown to be downregulated during fibrosis, but increased in the steatosis stage, while the levels of precursor PUFAs and the production of hydroxyeicosatetraenoic acids (HETEs), hydroxyeicosapentaenoic acids (HEPEs), and hydroxydocosahexaenoic acids (HDHAs) remained unchanged [27].

NAFLD is usually asymptomatic and diagnosed after the incidental finding of abnormal liver disease or steatosis during liver imaging, and after other causes of liver disease have been excluded [28]. Liver biopsy is the gold standard for diagnosing and staging NAFLD [29][30]. Therefore, there is significant interest in developing non-invasive and accurate methods for NAFLD diagnosis and assessing its progression. Measuring oxylipin levels presents one possible approach. Evaluation of the levels of eicosanoid concentration in serum and liver tissue in rats during steatosis indicated a strong positive correlation between 9-HODE and 13-HODE and NAFLD progression.

3. Obesity and Diabetes

Apart from NAFLD, chronic inflammation is associated with obesity which in turn contributes to the development of insulin resistance and type 2 diabetes (T2D). The plasma level of three eicosanoids (unknown eicosanoid (EIC 62), 8-iso-prostaglandin A1 (8-iso-PGA1), and 12-hydroxy-5,8,10-heptadecatrienoic acid (12-HHTrE) was shown to predict incident T2D [31] and the resolvin D2/LTB4 ratio, and may serve as a biomarker of prognosis for ischemic stroke [32]. An analysis of clinical samples revealed significant differences in the levels of four oxylipins (PGF2 α , PGE2, 15-keto-PGE2, and 13,14-dihydro-15-keto-PGE2) between T2D patients and the corresponding lean and obese control subjects, with the combination of PGF2 α and 15-keto-PGE2 having the most predictive value [33]. Targeted lipidomics analysis of human urine samples indicated that metabolite products of PGD and PGE are associated with low-grade chronic inflammation in obesity [34]. Upregulated PGE2 production by β -cells may have a role in the β -cells' adaptation response to obesity and insulin resistance in T2D when PGE2 and its receptor EP3 are highly expressed [35].

However, the levels of other oxylipins such as the SPMs and hydroxy-DHA metabolites were shown to be lower in obesity and white adipose tissue inflammation [36]. Animal studies revealed that increasing the bioavailability of SPMs such as Maresin-1 minimises inflammation and mediates therapeutic actions [37]. It is not surprising therefore that eicosanoids are seen as potential targets to combat obesity. One such approach suggests seeking ways to increase the energy expenditure of thermogenic tissues such as brown and brite adipose tissue. Both 5-HETE and 5,6-EET have been reported to be consistently associated with the abundance of those tissues, though further studies are needed to determine whether those eicosanoids are candidates that affect thermogenic capacity [38].

4. Technological Advancements

The importance of oxylipins in physiological and pathophysiological processes is underscored by their role in the ability of cells to acquire different functional phenotypes depending on the microenvironment. Omega-3 and omega-6 PUFA-derived oxylipins can modulate the inflammatory phenotype of cells [39] by acting as ligands for receptors such as the peroxisome proliferator-activated receptor PPAR [40] and prostaglandin E2 (PGE2) receptor PTGER4 [41].

The eicosanoid class comprises hundreds of structurally and stereochemically distinct species derived either enzymatically or non-enzymatically from a handful of precursors. It is therefore not surprising that within the group of eicosanoids can be found isomers (e.g., PGE2 and PGF2 α) with different biological functions [14]. In addition to their diversity, eicosanoids occupy a small mass range and are found in low nanomolar concentrations in biological samples (e.g., human plasma and murine bone marrow-derived macrophages [42]). Thus, their detection and evaluation require methods that are sensitive, selective, and reproducible.

Mass spectrometry is a powerful technique for identifying and quantifying known and unknown analytes, and offers high specificity and selectivity. Technical advances have given mass spectrometry a range of tools to obtain information at the molecular level from samples, such as determining the molecular weight of an analyte, its separation from isomeric and isobaric species, its chemical formula, its molecular structure, and structural information [43][44][45]. Mass spectrometry can be used to investigate a wide range of classes of molecules, including those with small and large molecular weights, volatile and non-volatile, polar and non-polar [46][47][48].

Applications using mass spectrometry are either targeted or untargeted. Untargeted approaches attempt to measure as many compounds as possible in a sample, and can be used to discover unanticipated changes between experimental groups. This information can then be used to generate and test hypotheses, for example by applying targeted approaches which offer a selection of the best possible conditions for the detection, identification, and (absolute or relative) quantitation of particular analytes of choice, and is usually used in follow-up experiments. Targeted approaches may use multiple reaction monitoring (MRM) methods which use the knowledge of the mass of the ionised analyte and its corresponding fragments formed during the mass spectrometry analysis [49][50].

For lipidomics, liquid chromatography-mass spectrometry (LC-MS) is commonly used. LC separates molecules depending on their hydrophobicity, molecular size, and polarity, and covers a broad range of non-polar and weakly polar analytes [51][52]. Another separation method that is gaining popularity in metabolomics is ion mobility coupled with mass spectrometry (IMS-MS; IM-MS) (IMS) [42][53][54][55][56][57][58].

Recently, supercritical fluid chromatography (SFC) has gained traction as an alternative technique to LC in lipidomics due to its high efficiency [59][60]. Briefly, SFC uses supercritical fluid such as CO₂ as a mobile phase [61], which results in high separation efficiency and short separation time [62][63]. SFC-MS/MS methods have been reported to detect inflammation-related lipids including oxylipins in rats [64], as well as for the simultaneous

measurement of five AA-derived metabolites (PGD₂, PGE₂, PGF₂α, 6KetoPGF₁α and LTB₄) in biological samples [65]. Thus, SFC coupled to MS is a promising approach for the interrogation of the lipidome.

Novel ionisation approaches have appeared with the development of ambient mass spectrometry, characterised by direct sampling and ionisation of the analytes with no or minimal sample preparation [66]. Ambient ionisation MS has been successfully employed to rapidly differentiate bacterial species based on their lipid profiles [67]. Mass spectrometry imaging (MSI) developments allow more detailed investigations of biological questions such as the biochemical origin of lipid spatial distribution [68]. Examples of MSI techniques include secondary ion mass spectrometry (SIMS), Desorption electrospray ionisation (DESI) and matrix-assisted desorption/ionisation (MALDI). Lipid characterisation is now possible due to technological advances in SIMS [69]. DESI-MSI can record 2D distributions of polar lipids in tissue slices at ambient conditions (at atmospheric pressure) [70], and has been developed for the simultaneous imaging of polar and non-polar lipids in mouse brain tissue [71]. Improvements in MALDI resolution resulted in the identification and localisation of lipids within the kidney, as well as the localisation of lipid droplets with lesion-specific macrophages [72]. Thus, further method developments could provide the means to image eicosanoids in a variety of biological samples.

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