Eicosanoids in carcinogenesis

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Abstract – Inflammation is the body’s reaction to pathogenic (biological or chemical) stimuli and covers a burgeoning list of compounds and pathways that act in concert to maintain the health of the organism. Eicosanoids and related fatty acid derivatives can be formed from arachidonic acid and other polyenoic fatty acids via the cyclooxygenase and lipoxygenase pathways generating a variety of pro- and anti-inflammatory mediators, such as prostaglandins, leukotrienes, lipoxins, resolvins and others. The cytochrome P450 pathway leads to the formation of hydroxy fatty acids, such as 20-hydroxyeicosatetraenoic acid, and epoxy eicosanoids. Free radical reactions induced by reactive oxygen and/or nitrogen free radical species lead to oxygenated lipids such as isoprostanes or isolevuglandins which also exhibit pro-inflammatory activities. Eicosanoids and their metabolites play fundamental endocrine, autocrine and paracrine roles in both physiological and pathological signaling in various diseases. These molecules induce various unsaturated fatty acid dependent signaling pathways that influence crosstalk, alter cell–cell interactions, and result in a wide spectrum of cellular dysfunctions including those of the tissue microenvironment. Although the complete role of eicosanoids, including that of the recently elucidated anti-inflammatory specialized pro-resolving lipid mediators (SPMs), e.g. lipoxins, resolvins, protectins and maresins, is not completely understood, the result of unrelenting chronic inflammation is fostering early stages of carcinogenesis. Chronic inflammation facilitates the transition from a normal cell to a cancerous one. The disruption of homeostasis across a wide, but identifiable, swath of diverse molecular pathways creates a microclimate which constitutes an early and necessary step in the 6-step sequence of carcinogenesis for the vast majority of cancers, termed “sporadic cancers”.

Keywords: 20-HETE, Cancer, Carcinogenesis, Cell transition, Chronic inflammation, Cyclooxygenase, Cox, EET, Eicosanoids, Epidemiology, Epigenetics, Fibrosis, Genomics, Leukotrienes, microRNA, Mutation, Pathogenesis, Precancerous niche, Proteomics, Reactive oxygen species, ROS, Somatic mutation

Introduction

The term eicosanoids comes from the Ancient Greek term ‘*εἴκοσι*’ (*eikosi*) meaning twenty. A chain of 20 polyunsaturated fatty acids (PUFA) is found in every mammalian cell with 20 carbon atoms and 4 double bonds in the cis-position also known as arachidonic acids (AA) and named all-cis-5,8,11,14-eicosatetraenoic acid [1]. C₂₀H₃₂O₂, 20:4(ω-6) is the chemical formula for omega-6 (ω-6) PUFA in which 20:4 refers to its 20 carbon atom chain with four double bonds and ω-6 refers to the position of the first double bond from the last, omega carbon atom. AA are found in animal and human tissue, in plants, and in food [1–6]. AA are esterified to membrane phospholipids. We now recognize their

importance “for normal cellular membrane fluidity, but also as a substrate for numerous enzymatic transformations that form biologically active lipid mediators, such as prostaglandins, leukotrienes, epoxyeicosatetraenoic acids, and endocannabinoids” [5].

Although scientists investigated neutral fats, such as glycerins and phospholipids, as far back as in the 19th century [7–10 reviewed in 11–13], significant progress began in the early days of X-ray crystallography [14 reviewed in 5]. Fish oil studies took place between 1899 and 1906 [15–17], and the Japanese chemist, Mitsunaru Tsujimoto (1877–1940), described how the addition of bromine could result in products of PUFA which could then be crystallized [17]. The British physiologist, Sir Percival Hartley (1881–1957), was the first to isolate and purify AA and understood that these fatty acids had four double bonds [18 reviewed in 5,19].

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Fig. 1. Cyclooxygenase (Cox) pathway of eicosanoid metabolism and its relevance in inflammation. *Nomenclature:* Simplified scheme of the cyclooxygenase pathway (COX) leading to the formation of pro-inflammatory prostaglandins. The nomenclature common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **ω -6-PUFAs** N-6 polyunsaturated fatty acid; **LA** linoleic acid, cis, cis-9,12-octadecadienoic acid; LA is not a direct substrate of prostaglandins – this occurs after metabolism to γ -LA; therefore LA here is in brackets; **γ -LA** gamma linolenic acid; **DGLA** dihomogamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-Icosatrienoic acid; **AA** archidonic acid, (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoic acid; **DTA** docosatetraenoic acid, (7Z,10Z,13Z,16Z)-7,10,13,16-docosatetraenoic acid; **BDPA** osbond acid, (All-Z)-4,7,10,13,16-docosapentaenoic acid; **Cox-1** cyclooxygenase 1; **Cox-2** cyclooxygenase 2; **Cox-3** splice variant and isoform of Cox-2, (therefore in brackets); **PGG₂** prostaglandin G₂, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGI₂** prostaglandin I₂, prostacyclin I₂, (5Z)-5-

The German chemical engineer, Julius Isidor Lewkowitsch (1857–1913), moved to England in 1887 and in 1913 coined the term “*arachidonic acid*” for those fatty acids which had been described earlier by Sir Hartley [20].

It was observed that the application of human seminal fluid induced uterine contractions [21 reviewed in 22], which later was identified as due to lipophilic compounds [23]. Von Euler thought that such compounds were produced by the prostate and therefore named these as prostaglandins (PGs) [24]. There is an alternative reason for the name of PGs, which is the 5-membered prostane ring in its structure. It was Karl Sune Detlof Bergström (1916–2004) and Jan Sjövall who showed that PGs come from seminal vesicles and isolated PG E (PGE) and PG F₂α (PGF₂α) [25]. Two independent groups showed that PGs are derived from essential fatty acids [26,27]. Sir John Robert Vane (1927–2004) showed that PG synthesis could be inhibited by aspirin and aspirin-like drugs [28]. In 1982, Vane and Bergström received the Nobel Prize for the discoveries of PGs, and Samuelsson for the discoveries of leukotrienes.

Due to their complexity, the following discussion of eicosanoids contains their pathways of cyclooxygenases (Cox), lipoxygenase (ALOX), cytochrome P450 (CYP) and reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), followed by unsaturated fatty acids and the recently discovered specialized anti-inflammatory lipid mediators (SPMs).

Eicosanoids

Eicosanoids contain signal-mediating molecules such as PGs, prostacyclins, thromboxanes (TXAs), leukotrienes (LTs), and related fatty acid derivatives which are integrated into the phospholipids of the cellular membranes formed from PUFA, especially the AA and other polyenoic fatty acids through four pathways [1,6] namely:

- the Cox pathway (Cox) (Fig. 1) leads to the formation of pro- and anti-inflammatory PGs [29–33],
- the LOX (ALOX) pathway (Fig. 2) leads to the formation of pro- and anti-inflammatory mediators, [34–38],
- the CYP pathway (Fig. 3) leads to the formation of hydroxy fatty acids (20-HETE) and epoxy eicosanoids [39–44] and

- free radical reactions induced by ROS and/or RNS lead to oxygenated lipids such as isoprostanes or isolevuglandins which exhibit pro-inflammatory activities [45–51].

For some time, eicosanoids have been known to be associated with diarrhea [52] and inflammation [53], and it was known that exogenous AA resulted in PGE synthesis [54]. Furthermore, that PGE was produced by mast cells [55,56], polymorphonuclear leukocytes [57], and macrophages [58]. Once the inflammatory effect of PGs were identified [59,60], contradictory findings were reported which suggested that PGs act as a turn-on/off mediator relevant for homeostasis [61,62] and that PGs were not accumulated but instead were newly synthesized [56].

One key checkpoint of AA metabolism is phospholipase A₂ (PLA₂); this enzyme was first isolated and purified from the venom of *Vipera berus* in 1971 [63]. Later the purification, sequencing and cloning of the first human non-pancreatic form obtained from synovial arthritic knee fluid (a point of inflammation) was identified [64,65]. A PLA₂ superfamily has since been recognized [66].

The substrate for Cox, ALOX and CYP to generate eicosanoids are the AA. PLA₂ in the cytosol is a key control checkpoint for inflammation and acts by hydrolyzing AA from membrane phospholipids [67]. The crystalline structure of human pancreatic PLA₂ was determined [68] including its anti-bacterial and anti-viral functions [69,70]. PLA₂s are expressed by macrophages, monocytes, T cells, mast cells, and neutrophils [71] and we know that the PLA₂ in the cytoplasm responsible for the production of lipid mediators in human macrophages is cytosolic PLA₂-α [72 reviewed in 66]. PLA₂ knock-down in mice results in less PG synthesis, decreased inflammation, and decreased cancer development [73]. The anti-inflammatory effect of zinc is thought to be mediated by inhibition of PLA₂ [74].

RAF proto-oncogene serine/mitogen-activated protein kinase kinase 1,2/threonine-protein kinase/extracellular signal-regulated kinase (Raf1/MEK1,2/Erk1,2) is activated by protein kinase C (PKC) activators such as phorbol esters but after stimulation of Erk2 phosphorylation, e.g., endotoxin. This pathway is only partially inhibited showing that there is a PKC independent pathway involved in Erk2 phosphorylation. The authors showed that using the selective inhibitor bis-indolylmaleimide (BIM) inhibited arachidonate metabolites from activated macrophages and that PKC-dependent

[(3aR,4R,5R,6aS)-5-hydroxy-4-[(E,3S)-3-hydroxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-2-ylidene]pentanoic acid; **6-keto-PGF₁α** 6-keto-prostaglandin F₁α, 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]-6-oxoheptanoic acid; **PGH₂** prostaglandin H₂, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGFF₂α** prostaglandine F₂ α, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PGD₂** prostaglandin D₂, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **PGE₂** prostaglandin E₂, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; **TXA₂** thromboxane A₂, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid; **MDA** malondialdehyde, propanedial.

Fig. 2. Lipoxigenase (ALOX) pathway of eicosanoid metabolism and its relevance in inflammation. *Nomenclature:* Simplified scheme of polyenoic fatty acid metabolism via the lipoxigenase (ALOX) pathway, leading to the formation of anti- and pro-inflammatory mediators. Common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **ω-3-PUFAs** N-3 polyunsaturated fatty acid; **ALA** α-linolenic acid, (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid; **ETA** eicosatetraenoic acid, all-cis-8,11,14,17-eicosatetraenoic acid; **EPA** eicosapentaenoic acid, (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid; **DPA** docosapentaenoic acid, 7,10,13,16,19-docosapentaenoic acid; **DHA** docosahexaenoic acid, (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid; **ω-6-PUFAs** N-6 polyunsaturated fatty acid; **LA** linoleic acid, cis, cis-9,12-octadecadienoic acid; **DGLA** dihomogamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-Icosatrienoic acid; **AA** arachidonic acid, (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoic acid; **DTA** docosatetraenoic acid, (7Z,10Z,13Z,16Z)-7,10,13,16-docosatetraenoic acid; **BDPA** osbond acid, (All-Z)-4,7,10,13,16-docosapentaenoic acid; **ALOX** lipoxigenase, arachidonate lipoxigenase; **ALOX15** 15-lipoxigenase, 15-LOX, 15-LOX-1, arachidonate 15-lipoxigenase; **ALOX15B** 15-lipoxigenase type II, 15-LOX-2, arachidonate 15-lipoxigenase type B; **ALOX12** 12-lipoxigenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxigenase 12S type; **ALOX5** 5-lipoxigenase, 5-LOX, arachidonate 5-lipoxigenase; **17-HpDHA** 17S-hydroperoxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid; **17-HDHA** 17S-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid; **RvD1** resolvin D1, (4Z,7S,8R,9E,11E,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; **RvD2** resolvin D2, (4Z,7S,8E,10Z,12E,14E,16R,17S,19Z)-7,16,17-trihydroxydocosa-4,8,10,12,14,19-hexaenoic acid; **RvD3** resolvin D3, (4S,5E,7E,9E,13Z,15E,17R,19Z)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid; **RvD4** resolvin D4, (4S,6E,8E,10E,13E,15Z,17S,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15,19-hexaenoic acid; **RvD5** resolvin D5, (5Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-dihydroxydocosa-5,8,10,13,15,19-hexaenoic acid; **RvD6** resolvin D6, (4S,5E,7Z,10Z,13Z,15E,17S,19Z)-4,17-dihydroxydocosa-5,7,10,13,15,19-hexaenoic acid; **NPD1** neuroprotectin D1, protectin D1, (4Z,7Z,10R,11E,13E,15Z,17S,19Z)-10,17-dihydroxydocosa-4,7,11,13,15,19-hexaenoic acid; **14-HpDHA** 14-hydro(peroxy)-docosa-hexaenoic acid, 4-[(1E,3E,5E,7E,9E)-nonadeca-1,3,5,7,9-pentaenyl]dioxete-3-carboxylic acid; **MaR1** maresin 1, (4Z,7R,8E,10E,12Z,14S,16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid; **15-HpETE** 15-hydroperoxy-eicosatetraenoic acid, (5Z,8Z,11Z,13E)-15-hydroperoxyicoso-5,8,11,13-tetraenoic acid; **15S/R-HETE** 15S-HETE (5Z,8Z,11Z,13E,15S)-15-

Erk2-phosphorylation by the benzamide derivative JM34, which inhibits tumor necrosis factor alpha (TNF α) from macrophages, and is based on its inhibitory effect on PLA2 activation [75].

Cyclooxygenase (Cox) pathway and pro- and anti-inflammatory Prostaglandins (PGs) (Fig. 1)

Increased cyclooxygenase 2 (Cox-2) in human colorectal adenomas and adenocarcinomas was first reported in 1994 [76] followed by the association of Cox-2 with chronic inflammation and colorectal cancer (CRC) [77–79]. The degree of malignancy in lung cancer is directly correlated with Cox-2 expression [80]. Co-localization of HBx with the inner mitochondrial cytochrome c oxidase protein COXIII in liver cancer cells upregulates Cox-2 with consecutive ROS-induced cell growth [81].

It is known that PGs have multiple effects and are involved in inflammatory diseases such as rheumatoid arthritis, asthma, cardiovascular diseases, and cancer [22,82–89].

There is an association of cyclic adenosine 3',5'-monophosphate (cAMP) and PGs. cAMP was shown to be activated or abnormally regulated in neoplasia [90,91] but its impact in cancer is controversial as it was suggested cAMP has an inverse correlation with tumor growth [92] or is involved in hormone-induced tumor growth arrest [93], compared to the interrelationship between cAMP and 3',5'-cyclic guanosine monophosphate (cGMP) [94].

Mouse-derived fibroblasts transformed by the oncogenic polyomavirus, simian virus (SV40), resulted in constant cAMP activity. On the other hand, SV40-transformed rat fibroblasts show decreased cAMP levels. Stimulating cAMP with PGs revealed that this phenomenon depends on prostaglandin E2 (PGE2). PGF2 α and prostaglandin B1 (PGB1) were more effective as compared to prostaglandin A2 (PGA2) [95]. These experiments are important in that they reveal that PGs have different effects and that the same experiment in different species may produce different results.

PGs can be produced by tumors [96,97] and it was shown that PGs activate cAMP [98]. It has long been suspected that PGs and cAMP are involved in cell growth and cancer development [99] but this seems to be dependent on which specific PG is involved. PGF1 α (PGF1a) and PGF2 α (PGF2a) do not increase cAMP but 2-acetylaminofluorene (AAF)-induced cancer is associated with increased prostaglandin E1 (PGE1) [100].

The two Cox isoforms, cyclooxygenase 1 (Cox-1) and Cox-2 utilize AA liberated from membrane phospholipids and catalyze the conversion of AA to prostanoids. A splice variant of Cox-1, is cyclooxygenase 3 (Cox-3; also called Cox-1b or Cox-1 variant) [101]. Inflammation-induced Cox-2 is regulated by cytokines through macrophage activation [102] while Cox-1 is expressed constitutively [103]. Cox-2 is repressed physiologically by 1 α ,25(OH)₂-cholecalciferol (equivalent to 1 α ,25(OH)₂ vitamin D₃, 1,25(OH)₂D₃, calcitriol), which is the active form of vitamin D [104] and by glucocorticosteroids [105].

Cox-2 mRNA and protein suppression by calcitriol leads to an increase of the PG catabolizing enzyme, 15-hydroxyprostaglandin dehydrogenase, which in turn decreases levels of PGs and inflammatory cytokines [106]. The bioxygenase activity of Cox catalyzes the addition of two oxygens to AA producing an unstable cyclic hydroperoxide, prostaglandin G₂ (PGG₂), which is then reduced by Cox peroxidase activity to an endoperoxide, prostaglandin H₂ (PGH₂). PGH₂ is converted by various routes to prostaglandins (e.g. PGE₂), prostacyclin, and thromboxane A₂ (TXA₂) [107,108 reviewed in 101].

In K562 human leukemia cells, PGE₂ activates Ca²⁺-permeable transient receptor potential cation 7 (TRPC7) channels which can trigger apoptosis [109]. NAD⁺ and NADP⁺ radicals triggered by Cox peroxidase activity generate superoxide (O₂^{•−}) [107 reviewed in 101]. Exogenous PGE₂ in human patellar tendon fibroblasts (HPTFs) induce cell death and autophagy in a dose-dependent manner and mechanical stretching stimulates PGE₂ resulting in cell death. In contrast, the Cox inhibitors, indomethacin and celecoxib, block PGE₂ and reduce stretching-induced autophagy [110]. Lipopolysaccharide (LPS), TNF α , interleukin-1-alpha (IL-1 α), and

hydroxyicosa-5,8,11,13-tetraenoic acid; **15(R)-HETE** lacks a bit of the activity attributed to their S stereoisomers of 15(S)-HETE; **15S-epoxy-tetraene** 5,6-15S-HETE, 4-[(2S,3S)-3-[(1E,3E,5Z,7E,9S)-9-hydroxytetradeca-1,3,5,7-tetraenyl]oxiran-2-yl]butanoic acid; **15R-epoxy-tetraene** lacks a bit of the activity attributed to their S stereoisomers of 15S-epoxy-tetraene; **LXA4** lipoxin A₄, (5S,6R,7E,9E,11Z,13E,15S)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid; **LXB4** lipoxin B₄, (5S,6E,8Z,10E,12E,14R,15S)-5,14,15-trihydroxyicosa-6,8,10,12-tetraenoic acid; **15-epi-LXA4** (5R,6R,7E,9E,11Z,13E,15R)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid; **12-HpETE** 12-hydroperoxyicosa-5,8,10,14-tetraenoic acid; **12-HETE** (5E,8Z,10Z,14Z)-12-hydroxyicosa-5,8,10,14-tetraenoic acid; **5-HpETE** (6E,8Z,11Z,14Z)-5-hydroperoxyicosa-6,8,11,14-tetraenoic acid; **15-HETE** (5Z,8Z,11Z,13E)-15-hydroxyicosa-5,8,11,13-tetraenoic acid; **5-oxo-EETE** (6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid; **LTA4** leukotriene A₄, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; **LTC4** leukotriene C₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTD4** leukotriene D₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTE4** leukotriene E₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTB4** leukotriene B₄, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid.

Fig. 3. Cytochrome P450 (CYP) pathway of eicosanoid metabolism and its relevance in inflammation. *Nomenclature:* Simplified scheme of polyenoic fatty acid metabolism via the cytochrome P450 (CYP) pathway leading to the formation of anti- and pro-inflammatory mediators. Common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **ω-3-PUFAs** N-3 polyunsaturated fatty acid; **ALA** α-linolenic acid, (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid; **ETA** eicosatetraenoic acid, all-cis-8,11,14,17-eicosatetraenoic acid; **EPA** eicosapentaenoic acid, (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid; **DPA** docosapentaenoic acid, 7,10,13,16,19-docosapentaenoic acid; **DHA** docosahexaenoic acid, (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid; **ω-6-PUFAs** N-6 polyunsaturated fatty acid; **LA** linoleic acid, cis, cis-9,12-octadecadienoic acid; **DGLA** dihomogamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-Icosatrienoic acid; **AA** archidonic acid, (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoic acid; **DTA** docosatetraenoic acid, (7Z,10Z,13Z,16Z)-7,10,13,16-docosatetraenoic acid; **BDPA** osbond acid, (All-Z)-4,7,10,13,16-docosapentaenoic acid; **AT-Cox2** aspirin-triggered cyclooxygenase 2; **CYP*** cytochrome P450 isoforms; **18-HpEPE** 18-hydroxyeicosapentaenoic acid, 18-hydroxyicosa-2,4,6,8,10-pentaenoic acid; **18-HEPE** (5Z,8Z,11Z,14Z,16E)-18-hydroxyicosa-5,8,11,14,16-pentaenoic acid; **RvE1** resolvins E1, (5S,6Z,8E,10E,12R,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid; **RvE2** resolvins E2, (5S,6E,8Z,11Z,14Z,16E,18R)-5,18-dihydroxyicosa-6,8,11,14,16-pentaenoic acid; **RvE3** resolvins E3, (5Z,8Z,11Z,13E,15E,18S)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid; **Cox** cyclooxygenase; **20-HETE** 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid; **20-OH-PGE2** 20-hydroxy prostaglandin E2; **20-COOH-HETE** 20-carboxy-hydroxyeicosatetraenoic acid; **EETs** epoxyeicosatrienoic acid; **sEH** soluble epoxide hydrolase; **DHETs** dihydroxyeicosatrienoic acids.

nitric oxide (NO) donor (NONOate) increases acute and or chronic inflammation in both in vivo and in vitro in bovines with enhanced PGE₂, PGF₂ α , leukotriene B₄ (LTB₄), and leukotriene C₄ (LTC₄) [111,112]. Cox-1 expressions is increased at the mRNA level with prostaglandin E synthase (PGES) and transforming growth factor beta 1 (TGF- β 1) in small bowel cancers [113].

Lysophosphatidic acid (LPA) stimulates PGE₂ production in stromal cells via the induction of prostaglandin-endoperoxide synthase 2 (PTGS2) and PGES mRNA expression in bovine endometrium [114] and through activating its G protein-coupled receptors (LPAR 1-6) directly influences aspects of endometriosis and reproductive tissue associated tumors [115]. PGE₂ generated by Cox-2 in mice can protect beta-cells from apoptosis [116].

Another Cox isoform, Cox-3, is under investigation and not completely elucidated. It was first discovered in 1989 and found primarily to be expressed in the cerebral cortex and the heart [117]. We now know that Cox-3 is also found in the kidney and aorta [118]. Cox-3 is encoded by the same gene as Cox-1 with a difference of one intron and is under investigation [119]: Cox-3 derives from Cox-1 and is a smaller protein which is why it is also named partial Cox-1 (pCox-1), pCox-1 protein or Cox variant Cox-1V1. It is selectively inhibited by acetaminophen, phenacetin, antipyrine, and dipyrrone, as well as by some non-steroidal anti-inflammatory drugs (NSAIDs) and useful in treating pain and fever. It shares all the catalytic features and important structural features of Cox-1 and -2 and its inhibition results in decreases of PGE₂. Cox-3 may be involved in the regulation of body temperature [120–122]. Cox-3 assays using an anti-Cox-3 polyclonal sera pCox-1a was shown to have a little lower weight compared to Cox-3 (65kD) [Fig. 1 of 123]. NSAIDs inhibit PG synthesis and thereby function as anti-inflammatories and analgesics [124].

Acetaminophen (Paracetamol[®]) was synthesized 1878 [125] and is included as a NSAID. It is interesting that it was reported not to reduce inflammation or inhibit platelet aggregation and does not prolong bleeding time nor does it induce bleeding or ulceration [126] but it inhibits Cox-3 with a decrease in body temperature [122]. Cox-3 is highly expressed in cerebral endothelial cells and decreases PGE₂ [127]. Cox-3 inhibition in rats increases PGE₂, prostaglandin I₂ (PGI₂, prostacyclin), and TXA₂ levels in rats in both inflamed and non-inflamed tissues suggesting that Cox-1 and Cox-2 are more specific and effective in terms of prostanoid synthesis of PGE₂, PGI₂, and TXA₂ as compared to Cox-3. Furthermore, Cox-3 results in the augmentation of the vasodilatory activity of bradykinin by modifying Cox-1 and Cox-2 [128].

Dipyrrone (Metamizole[®]) inhibits Cox-3 more effectively than Cox-1 and Cox-2 and this effect is concentration dependent in that high levels (IC₅₀ >1000 μ M) inhibit all three isoforms, moderate levels (IC₅₀: 350 μ M) inhibit Cox-1 and Cox-3 and low levels (IC₅₀: 52 μ M) inhibit only Cox-3 [120 reviewed in 129,130]. It was suggested “that Cox inhibition achieved with dipyrrone may

be responsible for the augmentation of the smooth-muscle relaxing effects of the angiotensin-converting enzymes (ACEs) inhibitor losartan or lisinopril” while the combination of dipyrrone with losartan inhibited phenylephrine (Phe), potassium chloride (KCl), and angiotensin II (Ang II) induced contractions compared to combined dipyrrone with lisinopril inhibiting Phe and Ang II-induced contractions [130].

All Cox enzymes (Cox-1, Cox-2 and Cox-3) have been found to be expressed in glioblastoma and normal brain tissues but Cox-3 expression was significant higher in cancerous versus normal tissues [131]. Inhibiting Cox-3 with acetaminophen decreased glioblastoma tumor size by 71% in a rat model and by 43% using indomethacin. The exact molecular mechanisms still are unresolved. However, evidence such as epidemiology, molecular, genetic, polymorphisms, epigenetics, or proteomic Cox-3 research is warranted as information about its catalytic activity and signaling influence and crosstalk remains largely unknown.

Aspirin has long been known to be anti-inflammatory, anti-pyretic, and analgesic but this goes back to the knowledge of the salicytes as the medicine of the early ages used in a powder from the bark of the willow tree to treat fevers and pain [132]. Aspirin was produced in 1853 by the French chemist, Charles Frédéric Gerhardt (1816–1856) [133] and the isolation of acetylsalicylic acid (ASA) in pure form occurred in 1897 by Felix Hoffmann (1868–1946). The laboratory manager, Arthur Eichengrün (1867–1949), claimed that he had advised his co-worker Hoffmann to produce esters of salicylic acid [134], but Eichengrün was a German Jew and was arrested by the Nazis in 1943 and imprisoned in the Konzentrationslager Theresienstadt; after Eichengrün survived the KZ, he was confident enough to publish his claim in 1949 which was at first ignored. The British chemist, Walter Sneader, investigated the case during the 90s and came to the conclusion that attributing the discovery and first isolation of aspirin to the German chemist Felix Hoffmann (1868–1946) in 1897 had been wrong which was denied by Bayer [132,135–137].

Aspirin affects the PG pathway by suppressing the production of PGs and TXAs through acetylation of a serine-rest of Cox-1 through prostaglandin-H₂-synthase-1 (PTGS1) and Cox-2 through PTGS2, discovered by British pharmacologist, Sir John Robert Vane (1927–2004) in 1971 [28]. For this he was awarded the Nobel Prize in 1982.

Salicylic acid (SA) has different effects in animal models and in the human body: (1) PG pathway, (2) formation of NO- radicals with decrease of leucocyte adhesion [138] (3) thrombocyte adhesion, (4) signaling through nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway [139], and (5) uncoupling of phosphorylation in mitochondria [140].

Because of the inflammation-carcinogenesis association, aspirin data show an anticancer effect on overall cancer reduction [141–145]. Aspirin is effective in CRC [146–150] and may explain why it has an effect as a

neoadjuvant to radiochemotherapy in rectal cancer [151]. Aspirin was shown to be effective in the precancerous adenomatous polyposis coli or APC [152] and in terms of adenoma prior to CRC [153]. Effective aspirin use against cancers had been shown in ovarian [154,155], stomach [156–158], pancreas [159,160], hepatocellular carcinoma (HCC) [161], breast [162,163], prostate [164–166], melanoma [167] and mesothelioma [168]. Furthermore, aspirin seems to be effective in inflammatory diseases such as Alzheimer's [169] as well as in obesity, as morbid obesity increased cancer risk was reduced in those patients taking aspirin [170].

However, the mechanistic signaling pathways of aspirin are still under investigation [171]. Aspirin is absorbed in high-pH environments (pH of proximal colon 5–8.0) [172,173].

A meta-analysis of 5648 patients from 29 studies revealed that an overexpression of Cox-2 correlated with recurrence and survival in CRC. The analysis was judged to have contradictory findings in terms of survival and recurrence and, therefore, it was not recommended until recently to use Cox-2 as a prognostic biomarker for CRC patients [149]. For completeness, some authors advise caution with regard to bleeding complications [159].

Additional insights on the role of Cox pathways in cancer come from the following findings: (1) when TGF- β 1 was applied to human lung cancer A549 cells, it induced a downregulation of Cox-2 which resulted in a decrease of PGE₂; (2) the researchers administered PGE₂ or PGE₂ receptor agonists, and found that it suppressed TGF- β 1-induced actin remodeling [174] and PGE₂ inhibited the transition of a normal cell to a cancerous cell [175]. On the other hand, the continuous activation of macrophages led to interleukin 6 (IL-6)-induced increases in Cox-2 expression and serum PGE₂ levels (Cox-2/PGE₂ pathway), thus facilitating cell transition and metastasis in lung cancer [176]. The fact that increased levels of TNF α and IL-6 in patients in various stages of chronic kidney disease reflects an ongoing chronic inflammatory state [177] and highlights the importance of maintaining Cox homeostasis. This observation may explain why a continuous activation of T-cells with triggering of neutrophils, macrophages, and their cytokine release may be of greater consequence than previously thought. Excellent reviews about the different opinions on Cox isoenzymes, in vivo PGs, PGE₂, PGI₂, prostaglandin D₂ (PGD₂) and PGF₂ α , and the diversity of receptor subtypes (EP1-EP4) are available [178,179].

Lipoxygenase (ALOX) pathway (Fig. 2)

The ALOX enzymes are another important class within AA metabolism. The abbreviation LOX here should not be mistaken for the 2nd available abbreviation of lysyl oxidase which constitutes a completely different enzyme. The various LOXs convert “*arachidonic, linoleic, and other polyunsaturated fatty acids into biologically active metabolites that influence cell signaling, structure, and metabolism*” [180 reviewed in 181]. The following

LOXs are known such as arachidonate 5-lipoxygenase (5-LOX, ALOX5), 12-lipoxygenase (12-LOX, ALOX12, 12S-LOX), 15-LOXa, and 15-LOXb, respectively [79].

Various hydroxyeicosatetraenoic acid (HETE) metabolites are formed via the lipoxygenase pathway, such as 5-hydroxyeicosatetraenoic acid (5-HETE), the reaction intermediate 5-hydroperoxy eicosatetraenoic acid (5-HpETE), 5-oxo-eicosatetraenoic acid (5-oxo-ETE), 8-hydroxyeicosatetraenoic acid (8-HETE), 12-hydroxyeicosatetraenoic acid (12-HETE), 15-hydroxyeicosatetraenoic acid (15-HETE) as well as the LTs, such as LTC₄, LTD₄, leukotriene D₄ (LTD₄) and leukotriene E₄ (LTE₄) [182]. The prostate, lung, colorectal, and ovarian cancer (PLCO) screening trial was a nested case-control study (157 cases/156 matched controls) that analyzed the pre-diagnostic serum levels of 31 AA/linoleic acid/alpha-linoleic acid metabolites with risk of developing ovarian cancer and found the following results to be positively associated with ovarian cancer: the identification risk-related fatty acid metabolites such as 8-HETE, 12,13-Dihydroxyoctadec-9-enoic acid (12,13-DHOME), 13-hydroxyoctadecadienoic acid (13-HODE) and 9-hydroxyoctadecadienoic acid (9-HODE) [154].

Leukotrienes

Under the influence of mast cells, the expression of ALOX in immune cells such as leukocytes, eosinophils, basophils, neutrophils, macrophages, and platelets is activated resulting into the release of leukotrienes (LTs) from these cell types [183]. LTs are brokers of the inflammatory immune response and are found in body fluids. Cysteinyl LTs (CysLTs) that involve the amino acid cysteine in their structure include LTC₄, LTD₄, LTE₄ and LTF₄, LTB₄, LTG₄ and leukotriene 5 (LTB₅) [184]. LTB₅ is the LTB₄ equivalent formed from eicosapentaenoic acid and its chemotactic activity is several orders of magnitude lower than that of LTB₄ [185].

The LT receptor slow reacting substance (SRS) of anaphylaxis antagonist FPL-55712 was found to be much more effective in inhibiting LTE₄ and LTF₄ compared to LTC₄ and LTD₄ [186] which raises the question if there are different bioactivities and if the concentrations in biological samples as well as bioactivity might be poorly understood.

As part of the immune response, LTs chemically attract T-cells [187,188]. Consequently, LTs have been linked to conditions associated with an inflammatory response such as asthma and allergy [189,190], neurological diseases including dementia [191], stroke, and ischemic events [192,193], multiple sclerosis [194,195] and cancer [196–198].

The association of various leukotrienes and cancers such as lung, esophageal and prostate cancer had been reported in detail [reviewed in 182]. However, the cysteinyl leukotrienes LTC₄, LTD₄ and LTE₄ induce various effects, such as cell recruitment, muscle contraction and vessel dilatation and permeability, and 5-LO signaling can

induce increased LTs synthesis especially by leukocyte recruitment. The released exosomes with LTB₄ can even create a gradient with additional para- and autocrine neutrophil stimulation and chemoattractivity.

The disruption of homeostatic mechanisms by LTs alters the tumor microenvironment and facilitates the progression of cancer [182] but it is important to note that immune cells can play dual roles both producing immunosuppressive and inflammatory regulatory mediators [199]. Especially the interaction of the immune systems with its various cell types needs to be further elucidated as Cox-2 inhibition can result into LTB₄ increase [reviewed in 182]. The homeostasis of Cox-2 versus 5-LO seems to be of importance if cell proliferation is effectively or ineffectively inhibited. For this, the various ALOX enzymes are likely to be important.

Various LOX enzymes

Until now, our knowledge about the detailed biological functions of LOXs isoforms is limited [37], and known arachidonate LOXs contain arachidonate 5-lipoxygenase (5-LOX, ALOX5, 15-LO-1, 15-LOX-1), 12-LOX, arachidonate 12-lipoxygenase type II (ALOX12B, 12R-LOX), arachidonate 15-lipoxygenase (ALOX15), and ALOX15 type II (ALOX15B) [200].

5-LOX is upregulated in cancers of the lung [201], esophagus [202], colon [203], pancreas [204–206] prostate [207,208], breast [209], brain and promyelitic leukemic HL-60 cells [210], and in osteosarcoma [211] and mesothelioma [212]. 5-LOX is also found to be down-regulated in colon adenoma of familial adenomatous polyposis (FAP) patients versus non-cancer colorectal mucosa [213]. 5-LOX derived from mast cells promote in the APC ($\Delta 468$) murine model of colon polyposis triggers polyposis [214]. The inhibition of 5-LOX in a mouse breast cancer model revealed the opposite: abrogation of neutrophil pro-metastatic activity resulted in reduced metastasis [215]. We assume that these contradictory data may be a result of differences in expressed metabolites such as e.g. 5-HpETE and 5-HETE.

Increased expression of Cox-2 and ALOX5 are reported in lung cancer and knocking-out 5-LOX resulted into progression [216]. In this regard 5-LOX blockade resulted in an increase of apoptosis [200]. 5-LOX was shown to be higher expressed in HCC versus normal liver tissues and inhibiting 5-LOX induces apoptosis and blocks cancer progression [217]. A 22-fold elevated expression of 15-lipoxygenase-2 in ovarian cancer compared to normal ovarian tissue was observed and 15-lipoxygenase-2 was augmented [218]. Increased 5-LOX metabolites enhanced TNF α and heparin-binding epidermal growth factor-like growth factor (HB-EGF) through upregulation of matrix-metalloproteinase 7 (MMP-7) which was associated with increased tumor-associated macrophages infiltration [219]. 5-LOX was also increased in brain cancer [210], thyroid cancer together with promotion of metalloproteinase 9 (MMP-9) [220].

Procarcinogenic LOXs include 5-, 8-lipoxygenase (8-LOX), and 12-LOX while 15-lipoxygenase-1 (15-LOX-1) and possibly 15-lipoxygenase-2 (15-LOX-2) which was previously thought to be anticarcinogenic [221]. 15-LOX-1 is decreased in esophageal cancer but applying the Cox-2 inhibitor SC-236 to gastric cancer cells induced apoptosis without affecting Cox-1, Cox-2, 5-LOX and 12-LOX. Thus, the upregulation of 15-LOX-1 may be developed as a therapeutic target in the future [222]. NSAIDs can induce apoptosis in colon cancer cells through 15-LOX-1 upregulation in the absence of Cox-2 [181,221]. TGF- β 1 induces SMAD4/4 with consequent increase of the 5-LOX promoter activity followed with upregulated 5-LOX expression [223] building yet another bridge to chronic inflammation during carcinogenesis via the lipoxygenase signaling pathways.

Chronic cystitis showed slight increases of 5-LOX and 12-LOX versus marked increase in bladder cancer tissues and inhibition of lipoxygenase resulted into “*chromatin condensation, cellular shrinkage, small membrane bound bodies (apoptotic bodies) and cytoplasmic condensation*” [224]. This effect was also shown in bladder cancer cells in vitro [225]. In canine osteosarcoma cells 5-LOX was upregulated in about 65% in the cytoplasm, cell culture and xenograft model and application of the canine 5-lipoxygenase inhibitor tepoxalin diminished xenograft tumor growth together with cell proliferation in mice [226].

Applying the thromboxane synthetase and 5-lipoxygenase inhibitor ketoconazole versus placebo into melanoma cell incubated mice showed significantly reduced incidence of metastasis and tumor mass with better survival in the ketoconazole-treated mice compared to placebo [227]. Recently CarbORev-5901 as a new carborane-based inhibitor of the 5-LOX was reported to be more stable and effective in melanoma and colon cancer cell lines was reported [228], but investigations in various cancers so far missing. It seems that 5-LOX is also constitutively highly expressed in patients with idiopathic pulmonary fibrosis [229].

It was suggested that Cox-2 is responsible for the regulation of the lipid metabolism [230]. This goes in line with the findings that inhibiting 5-LOX and Cox-2 blocks colon cancer proliferation, migration, as well as invasion in vitro [231]. This may explain why NSAID intake might result in some 50% reduction of the relative CRC risk [232,233] as the combined Cox-1 and Cox-2 activity is increased in CRC [234]. The non-enteroendocrine “*tuft cells*” which are referred to chemosensory cells showed mainly Cox-1 overexpression while Cox-2 was primarily found in absorptive cells and are “*rather constitute a distinct entity with transcription factor requirements for differentiation that differ from those of enterocytes, enteroendocrine, Paneth, and goblet cells*” [supplemental material Fig. S1A not shown here by 235 and reviewed by 234]. Tuft cells first were reported in 1956 in rat trachea and mouse gastrointestinal tract [236,237 reviewed in 235].

Inhibiting 5-LOX and the 5-lipoxygenase-activating protein (FLAP) by the tobacco carcinogen, 4-methylni-

trosamino-1-(3-pyridyl)-1-butanone suppresses carcinogenesis [238] and modulating LOX by clearly defining pro- and anti-carcinogenic effects depend on which metabolite is used and may be an option in anticancer treatment [181]. Receptors for LTB₄ are upregulated in gastric cancer but 5-LOX does not appear to be involved in gastric [239] or in colon carcinogenesis in rodents [240] which may explain why 5-LOX is not widely observed in carcinogenesis or it may well be that 5-LOX itself may have its own homeostasis maintenance pathway. Furthermore, anti-*Helicobacter* therapy by Tanshinone IIA from *Salvia miltiorrhiza* Bge resulted in lower chronic inflammation and 5-LOX [241]. 15-LOX suppresses colitis associated colon cancer by inhibiting IL-6/signal transducers and activators of transcription (STAT3) signaling [242]. Therefore antagonizing 5-LOX and/or promoting 15-LOX is thought being effective as a future anti-cancer therapy. However, recent experiments with 15-LOX1 knockout mice suggested that this enzyme exhibits a pro-inflammatory role in the dextrane sodium sulfate induced mouse colitis model. In fact, these knockout mice were strongly protected from inflammatory symptoms [243].

Cytochrome P450 pathway (CYP) and hydroxy fatty acids (20-HETE) (Fig. 3)

The CYP signaling pathway in AA metabolism involves the ω -hydroxylases and epoxygenases: “ *ω -hydroxylases convert AA into hydroxyeicosatetraenoic acids (HETEs) and epoxygenases which converts it to epoxyeicosatrienoic acids (EETs)*” [79].

20-hydroxyeicosatetraenoic acid (20-HETE)

Another underappreciated product of PUFA metabolism in the context of eicosanoids is the (CYP) metabolite, 20-HETE [244], which has been in cardiovascular diseases [245] and cancers [246,247]. Down-regulation of 20-HETE decreases proliferation in renal cancer cells [248], and enzymes that catalyze the formation of 20-HETE, such as cytochrome P450 4A/F (CYP4A/F) are found in higher concentrations in ovarian cancer than in normal tissues [249]. Cytochrome P450 2J2 (CYP2J2) is highly expressed in hematologic malignant diseases and promotes tumor cell growth [250]. Future research on the metabolism of 20-HETE and its biosynthesizing cytochromes might demonstrate specifically how 20-HETE contributes to carcinogenesis. 20-HETE increases ACE mRNA, protein through NF- κ B [251].

Epoxyeicosatrienoic acids (EETs)

Another group of products of eicosanoid metabolism are the cytochrome P-450 metabolites, the EETs [252]. Cytochrome P450 2C (CYP2C) and cytochrome P450 2J (CYP2J) are CYPs epoxygenases that metabolize AA to biologically active EETs (5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET), which in turn, are further “*metabolized to*

less active dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH)” [253].

The idea of using EETs in anticancer therapy emerged in the late 1980s [254,255]. An elevated CYP2J2 expression has been reported in esophageal, liver, breast, lung, and colorectal organs [250,256 reviewed in 253]. Markers such as these eicosanoids could serve as targets in cancer therapy [257]. The potential for such a use was demonstrated by the inhibition of sEH, which decreased NF- κ B, TGF- β 1/Smad3, and inflammatory signaling pathways, together with activating peroxisome proliferator-activated receptor (PPAR) isoforms with consequent treating effectively renal interstitial fibrogenesis in obstructive nephropathy in mice [258].

Cytochrome P450 3A4 (CYP3A4) expression promotes STAT3-mediated breast cancer cell growth via 14,15-EET [259]. EET analogs and sEH inhibitors are thought to have application in multiple diseases [260], such as Parkinson’s [261], renal interstitial fibrosis in obstructive nephropathy [258], marrow or cord blood transplantation [262], inflammatory bowel disease-associated cancer [263], and other cancers [264,265].

Elastase (ELA) is known to be induced by bacteria and regulates fibrosis and PG output; ELA-inhibition is assumed to reduce “*mare endometrial fibrosis by stimulating the production of anti-fibrotic PGE2 and inhibiting pro-fibrotic PGF2 α* ” [266]. In the rabbit, 5,6-EET stimulates endogenous PGE2 synthesis [267].

11,12-EET triggers hematopoietic stem and progenitor cells (HSPCs) in zebra fish via the activator protein 1 (AP-1) and runt-related transcription factor 1 (RUNX1) transcription, independent of any hemogenic endothelium need for phosphatidylinositol 3-kinase (PI3K) pathway activation [262]. Dual inhibition with RAF-1 and sEH with trans-4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexyloxy}-pyridine-2-carboxylic acid methylamide (t-CUPM) was reported to be of potential use in preventing chronic pancreatitis and in ameliorating pancreatic cancer [268]. Greater 14,15-epoxyeicosatrienoic acid levels were reported in breast cancer tissue than in noncancerous tissue [265].

EETs are rapidly metabolized, short-lived signaling molecules produced by various cell types and investigated and reported as potential targets for treating inflammation and cancer [269]. Lipid hydroperoxides (LOOHs), with Vitamin C as a regulator, seem to be necessary for EET formation [270]. On the other hand, EETs have been seen as a double-edged sword in cardiovascular diseases and cancer concerning the use of anti-EET drugs [253]. The anti-inflammatory effects of soluble sEH inhibitors appear to be independent of leukocyte recruitment [271].

The CYP allele CYP3A7*1C is associated with adverse outcomes in chronic lymphocytic leukemia (CLL), breast cancer, and lung cancer [272]. CYP3A4, found mainly in liver and intestine, binds to N1-hexyl-N5-benzyl-biguanide (HBB) inhibiting the CYP3A4 AA epoxygenase activity that suppress intra-tumoral mechanistic target of rapamycin (mTOR) [273]. CYP2J2 metabolizes AA to anti-inflammatory, -fibrotic and

—oxidant 5,6-, 8,9-, 11,12-, and 14,15-EETs [274–279] resulting in a decrease of IL-1 β , IL-8, TNF- α , sP- and sE-selectin together with decreased NF- κ B p65 activation and degradation of I κ B α which may be mediated through peroxisome proliferator-activated receptor gamma (PPAR γ) activation [280,281].

Furthermore, the epoxygenase-dependent metabolite, 11,12-EET, inhibits epithelial Na channels (ENaC) in the rat renal cortical region [282] (renal tubular epithelial cells) which is dependent on Cox activity and cell polarity [283].

Another bridge to chronic inflammation was recently shown. sEH plays a significant role in neurological diseases such as Parkinson or dementia [284] but also triggers obesity induced chronic colonic inflammation [285]. The importance of the research of LOXs may be recognized as most recently endogenous nitro-fatty acids (NFAs) were identified as potential future new well tolerated chemotherapeutic drug candidates [286].

Reactive oxygen and nitrogen species induced formation of EETs and oxygenated lipids

The free radical story [287,288] started by the Swedish student John Rhodin in 1954 who reported in his doctorate microbodies [289], which afterwards were “*mistakenly suggested ...that they were precursors to mitochondria*” [290 reviewed in 291–293]. In 1966, these microbodies were described as peroxysomes by the British born Belgian biochemist Christian de Duve (1917–2013) [294]. At that time De Duve already had discovered new organelles and had termed lysosomes and endosomes; he also discovered important processes, such as autophagy, endocytosis and exocytosis [293].

McCord and Fridovich created an inactive metal-free apoenzyme and adding copper resulted into some 80% recovery from dismutase activity; they reported superoxide dismutase (SOD) catalyzing “*the dismutation or disproportionation of superoxide free radical anions*” of the superoxide ($O_2^{\cdot -}$) radical into both molecular oxygen (O_2) and hydrogen peroxide (H_2O_2): $O_2^{\cdot -} + O_2^{\cdot -} + 2H^+ \rightarrow O_2 + H_2O_2$ [295,296]. Saito et al. investigated SOD in erythrocytes without finding a difference between young and elderly subjects [297]. Peroxisomes from fungi and plants contain antibiotics [298], toxins [299], and signaling molecules [300 reviewed in 292], and liver peroxisomes are involved in beta-oxidation of rare fatty acids [301–304].

Today, three SOD families are known in regard to the metal cofactor and protein: (1) copper-zinc-SOD (Cu-Zn-SOD) in eukaryotes (animals/humans, plants, fungus) found in cytosol, peroxisomes, or chloroplast, (2) iron-SOD (Fe-SOD) or manganese-SOD (Mn-SOD) which are found in peroxisomes and mitochondria in prokaryotes (archaea and bacteria) and plants (Fe-SOD) or in humans (Mn-SOD) and (3) nickel-SOD (Ni-SOD) in prokaryotes [305]. There are not just intra- and

intersubunit motions within the different subdomains of SOD known but there also seems to be an intersubunit information exchange [306].

Reactive oxygen (ROS) and reactive nitrogen species (RNS)

Reactive oxygen species (ROS) “*are a family of molecules that are continuously generated, transformed and consumed in all living organisms as a consequence of aerobic life*” [101,307,308] meaning ROS are naturally a metabolism product relevant for homeostasis, physiology as well as for so-called *oxidative stress*, a term coined by Sies in 1985 [309 reviewed in 310,311]. ROS include nonradical derivatives of singlet oxygen (1O_2), H_2O_2 and ozone (O_3), and oxygen radicals such as hydroxyl radical (OH $\cdot$), and superoxide ($O_2^{\cdot -}$). When ROS and RNS react with unsaturated lipids, lipid hydroperoxides are formed, which can damage biomembranes and or inactivate proteins. The major source of ROS in most mammalian cells is the respiratory chain of the mitochondria and about 1–2% of the daily oxygen consumption is converted to ROS (incomplete reduction of oxygen during cellular respiration). 1–2% does not really seem a lot but considering the fact that a normal human being consumes about 450 l of oxygen per day, a large number of ROS are normally produced. Luckily, most of these potentially damaging chemicals are readily detoxified by the antioxidative defense system. In addition, other ROS and RNS sources are the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) and xanthine oxidase (XO). Accumulation of ROS is prevented by SOD, which rapidly convert in the cytosol cytosolic and in the mitochondrial intermembrane space superoxide dismutase 1 (SOD1). Superoxide dismutase 2 (SOD2) is located in the mitochondrial matrix and contributes to detoxifying superoxide produced during cellular respiration [312–314]. As pointed out, “*accumulation of superoxide is more associated with oxidative stress than redox signaling*” [315].

Reactive nitrogen species (RNS) are antimicrobial molecules; they are mainly generated by phagocytic cells and involve nitric oxide (NO), with its derivative peroxynitrite ($ONOO^-$), nitrogen dioxide ($NO_2^{\cdot}$), dinitrogen trioxide (N_2O_3), nitrous acid (HNO_2), and others [316,317]. Both, ROS and RNS can modulate regulatory proteins and are linked to each other in plants and animals/humans inducing consequent signaling [316,318].

ROS is also involved in autophagy and the major source regulating ROS is superoxide ($O_2^{\cdot -}$) [319]. Mitochondrial ROS metabolism is needed for normal KRAS associated cancer cell proliferation [320]. AA metabolites such as 5-LOX and Cox can induce ROS through Nox stimulation [321 reviewed in 322].

ROS have various physiological and pathophysiological damaging properties next to evolution and are an essential consecutive part of signaling for various physiologies as cellular adhesion, signaling and migration, apoptosis, lipid metabolism, stem cell differentiation, immune response, and sport, and during aerobic and

anaerobic respiration as well as pathologies, such as e.g. acute and chronic inflammation, atherosclerosis, renal diseases, arthritis, cardiovascular and neurodegenerative diseases, ageing, cancer [reviewed in 315,323,324]. ROS levels are increased by ultraviolet (UV) radiation, cigarette smoking, and alcohol consumption. They are also elevated in infections and after an ischemia-reperfusion (I/R) injury. It has been suggested that the homeostasis of ROS production versus the capacity to detoxify rapidly is what determines the degree of oxidative stress at any given time in a tissue or organ [101]. In synovial fibroblasts, ROS promote the phosphorylation of mitogen-activated protein kinases (MAPKs) and NF- κ B through the activation of transforming growth factor beta-activated kinase 1 (TAK1), and lead to an increased expression of Cox-2 and PGE2 [325]. Further, even PGs induce Cox-2 expression [326].

Abnormal ROS levels can result in MAPK and PI3K signaling with STAT3 activation and phosphorylation of SNAIL with E-Cadherin suppression and a loss of cell polarity [327]. A chronic increase in ROS by macrophages increases levels of C-X-C chemokine receptor type 4 (CXCR4) and trigger the transition of a normal cell to a cancer cell [328]. It seems that under physiological conditions, a Cox- and -ROS homeostasis exists. Both Cox-1 and Cox-2 are expressed in normal human gastric mucosa and in gastric ulcers; they are increased by an *H. pylori* infection, but Cox-1 alone can increase gastric PGE2 production [329]. *H. pylori*-infected gastric epithelium co-express gastrin, its receptors, cholecystikinin B receptor (CCK(B)-R), Cox-2, and prostaglandin [330]. The continuous stimulation of Cox-2 and NF- κ B signaling results in a persistent increase of inflammatory cytokines such as TNF α and IL-6, as well as ROS and nitrogen-free radical species [331]. Skin samples from patients with chronologically aged and photoaged skin showed greater Cox-2 expression in keratinocytes and fibroblasts compared to that observed in younger individuals [332].

Since a multi-billion market grew promising the health effects of antioxidants and creating a global dietary supplements industry that is expected to grow in the U.S. alone to some \$220 billion by 2022 [333]. The detailed understanding of the ROS complexity may not be as easy as earning money through the sale of antioxidants.

Applying the cytochrome c peroxidase assay to measure the rates of free H₂O₂ with a cytosolic steady-state concentration and a rate of 90 nmol/l/min/wet weight of liver revealed that “some (40–80%) of the H₂O₂ generated in the peroxisomes is destroyed inside the organelle, and that the remaining 20–60% diffuses to the surrounding medium” [334]. Half-life times (T_{1/2}) of ROS are short contain in between < nanoseconds to seconds [335 reviewed in 336]: the very reactive OH radical has a T_{1/2} of approximately 10^{−9}s [337] compared to O₂[−] and H₂O₂ in between 10^{−6}s and 10^{−5}s [338] respectively [reviewed in 339]. There is hope using low level magnetic field to modulate cellular produced H₂O₂ [336].

Unsaturated fatty acids (PUFAs)

Unsaturated fatty acids are associated with the Cox and LOX pathways. PUFAs are essential and have to ingested by external sources (food). They are associated with inflammation and cancer; the main two PUFAs families are metabolized through 6 Δ desaturase, elongase, 5 Δ desaturase, and 4 Δ desaturase; those deriving from α -linolenic acid (ALA) result into eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) and are named family of omega-3 (n-3) PUFAs (ω -3 PUFAs) and are less inflammatory. In contrast, those deriving from linoleic acid (LA) result in gamma-linolenic acid (GLA), di-homo-gamma-linolenic acid (DGLA), AA, docosatetraenoic and docosapentaenoic acid and are part of the family of omega-6 (n-6) PUFAs (ω -6 PUFAs). The last (most far away from the carboxylic group) carbon-carbon double bond is found in the ω -6 position. ω -6 PUFAs are more pro-inflammatory while ω -3 PUFAs with the carbon-carbon double bond in the ω -3 position have more anti-inflammatory effects [340–344]. The third fatty acids family involves the non-essential monounsaturated fatty acid omega-9 (n-9), ω -9 MUFAs with the carbon-carbon double bond in the ω -9 position [345,346]. ω -9 MUFAs induce fatty acid oxidation and are associated with a greater anti-inflammatory effect in a sepsis model [347], but showed direct associations with mortality within the Cardiovascular Health Study [348]. Furthermore, “*high ω -9: ω -6 ratio and low ω -6: ω -3 ratio significantly reduced inflammatory response in rats submitted to dental extraction*” [349].

ω -3 PUFAs are anti-inflammatory. Their metabolism via the Cox / lipooxygenase pathway induce the formation of prostaglandin D₃ (PGD₃), prostaglandin F₃ α (PGF₃ α), prostaglandin I₃ (PGI₃), thromboxane A₃ (TXA₃), and LTs such as leukotriene A₅ (LTA₅), leukotriene B₅ (LTB₅), leukotriene C₅ (LTC₅) and leukotriene D₅ (LTD₅). ω -6 PUFAs induce more pro-inflammatory effects triggering the biosynthesis of the 2-series of prostaglandins which comprises prostaglandin E₂ (PGE₂), prostaglandin F₂ α (PGF₂ α), PGD₂, TXA₂, and LTs LTB₄, LTC₄, LTD₄ and LTE₄.

The association of PUFAs with AA metabolism and Cox metabolism and inflammatory/anti-inflammatory effects and cancer/anti-cancer effects provides in vitro and in vivo evidence, that ω -6 PUFAs stimulate cancers of the oral cavity [350], gastric [351,352], colon [353–355], liver [356,357], prostate [358,359], breast [360–364], endometrium [365], pancreas [366,367], bladder [368], urethral [369], lung [370], and melanoma cell growth [371–374] compared to ω -3 PUFAs suppressing it. This is in accordance with our understanding of precancerous lesions [375–379].

As PUFAs are directly associated with various signaling pathways and crosstalk in chronic inflammation, obesity, and the microbiome, these topics are reviewed separately within this Special Issue.

Due to the above studies, the involvement of PGE₂, and LTB₄ involvement through Cox-1, Cox-2 and 5-LOX

are thought to have a pro-carcinogenesis effects via inflammation [341,366,380]. Cox-2, PGE2 and EP2 and EP4 receptors stimulating pancreatic cancer cell growth while ω -3 PUFAs e.g. ω -3 PUFAs downregulates MMP-9 [381] and PGE2 by competitive effect in the AA metabolism [382], and has anti-inflammatory effects [383]. Granulocyte-macrophage CSF colony stimulating factor (CSF) (gm-CSF) induce PLA2 activity with PLA2 protein and consequent trigger rat alveolar macrophages (but not peritoneal macrophages or peripheral blood monocytes) to generate LTB4 as well as the 5-lipoxygenase products LTC, and 5-HETE [384 reviewed in 385].

Specialized pro-resolving lipid mediators (SPMs) (Figs. 2–4)

A new class of lipid mediators derived from AA and other polyenoic fatty acids are the family of specialized pro-resolving mediators (SPM). These signaling molecules are biosynthesized from AA and other frequently occurring polyenoic fatty acids (DHA, EPA) and function as counterregulators of pro-inflammatory stimuli inducing the resolution of inflammation [386–397]. This class of mediators involves lipoxins (LXs), resolvins (RVs), protectins (PDs) and maresins (MaRs); SPMs have distinct cellular and sometimes transcellular pathways of biosynthesis and they have been suggested to be quick at the resolution of inflammation. LXs derive from ω -6 PUFAs and Rvs, PDs and MaRs from ω -3 PUFAs [387–391,393,395,396,398–400 reviewed in 397–405].

Although not entirely clear at the present, the newly discovered anti-inflammatory and pro-resolving eicosanoids, such as lipoxins, resolvins, maresins and protectins could be one reason why multiple inflammatory changes in the tumor microenvironment directly results in a remodeled ECM. Furthermore, it could explain why the disruption of the homeostasis between anti- and pro-inflammatory mediators is needed, although there are additional pieces of missing information such as the period of time how long the disruption has to occur with regard to various pathogenic stimuli until a normal to cancer cell transition can occur.

Lipoxins (LXs)

LXs are metabolites of ω -6 PUFAs. They are formed from AA, which are converted to its 14,15-epoxide and this reaction might be catalyzed by an arachidonic acid 15-lipoxygenating enzyme – such as ALOX12, ALOX15, aspirin-treated Cox-2, and CYPs – to di-hydroxy-eicosatetraenoates. This dihydroxy derivative may then be oxidized by an arachidonic acid 5-lipoxygenating enzyme (ALOX5) to a trihydroxy compound, which is called lipoxin B4 (LXB4) [*5S,14R,15S-trihydroxy-6E,8Z,10E,12E-eicosatetraenoic acid*]. This compound carries three hydroxyl residues and four double bonds. An alternative of lipoxin formation is when an arachidonic acid 5-lipoxygenating enzyme converts arachidonic acid

to its 5,6-epoxide. This intermediate is subsequently hydrolyzed to the 5,6-diol and finally oxygenated at C15 by an arachidonic acid 15-lipoxygenating enzyme. In this case LXA4 (5S,6R,15S-trihydroxy-7E,9E,11Z,13E-eicosatetraenoic acid) is formed. Both lipoxin isomers have a 15-epi-equivalent which differs from the structure of LXA4 and LXB4 by having adverse chirality at C15 (15R). These 15-epi-LX-isomers are formed via the catalytic activity of aspirin treated Cox-2 (instead of a 15-lipoxygenating LOX) and thus, they are sometimes called aspirin-triggered lipoxins. LXs are rapidly inactivated e.g. in monocytes by dehydrogenases [406,407]. The 15-LOX derived precursor molecule for LX biosynthesis, 15-S-hydroperoxyeicosatetraenoic acid (15-(S)-HpETE) is an active form of 15-HETE having 15(S)-configuration; it also functions as LTs antagonists [408]. Anti-inflammatory lipids such as LXA4 [408], RVs, PDs and MaRs [409], may function as a sentinel against a pathogenic stimulus and cytokine-triggered inflammatory overreaction. LXA4 together with LXB4 can inhibit LT-triggered polymorphonuclear neutrophils (PMN) [410]. It had been suggested that “*PGs, LXA4, resolvins, protectins, maresins, and LTs modulate macrophage phenotype and function*” [385].

Resolvins (RVs)

The name Resolvins denotes from “*resolution phase interaction products*” which limit neutrophil infiltration as well as chemokines and cytokines effects [411]. These metabolites are formed from ω -3 PUFAs. EPA derived resolvins are E-series resolvins such as resolvin E1, resolvin E2, and resolvin E3 with [412]. DHA-derived resolvins are counted among the D-series of resolvins, such as resolvin D1 (RvD1) [413–416], resolvin D2 (RvD2) [415–418], and resolvin D5 (RvD5) [419].

Resolvins carry various chiral centers and thus this family of proresolving mediators also involves epimers. An important signaling pathway from aspirin was discovered in 1995: aspirin, a Cox-isofoms inhibitor that acetylates Cox-2, induces the synthesis of “*aspirin-triggered*” pro-resolving mediators in humans, including 15-epi-lipoxin A4. This metabolite stimulates phagocytosis of apoptotic inflammatory cells, which is required for cleaning up the battlefield of inflammation [386,420–423]. The formation of 15R-hydroxy products by acetylated Cox-2, which is named “*aspirin-triggered cyclooxygenase 2*” (AT-Cox-2) can also be catalyzed by microsomal, mitochondrial, or bacterial enzymes CYPs with the following products: aspirin-induced epimers of resolving D3, 17R-D series resolvins (RVs) and docosatriene (DTs) which are denoted aspirin-triggered resolvins (ATRVs) and aspirin-triggered DTs (ATDTs) [396,411,424,425].

RvD1 is anti-inflammatory and regulates human polymorphonuclear leukocyte transendothelial migration and its epimer, aspirin-triggered form (ATRVd1) 17-oxo-RvD1, is much more resistant against rapid inactivation [414]. RvD2 downregulates leukocyte-endothelial interactions in vivo via adhesion receptor expression modulation [417]. RvD3 and its aspirin-triggered 17R-epimer

Fig. 4. Eicosanoid metabolism and its relevance in inflammation. *Nomenclature:* Simplified scheme of the eicosanoid metabolism with formation from polyunsaturated fatty acids, including cyclooxygenase (Cox), lipoxigenase (ALOX), and cytochrome p450 (CYP) pathways with the formation of anti- and pro-inflammatory regulatory mediators. Common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **ω-3-PUFAs** N-3 polyunsaturated fatty acid; **ALA** α-linolenic acid, (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid; **ETA** eicosatetraenoic acid, all-cis-8,11,14,17-eicosatetraenoic acid; **EPA** eicosapentaenoic acid, (5Z,8Z,11Z,14Z,17Z)-eicos-5,8,11,14,17-pentaenoic acid; **DPA** docosapentaenoic acid, 7,10,13,16,19-docosapentaenoic acid; **DHA** docosahexaenoic acid, (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid; **ω-6-PUFAs** N-6 polyunsaturated fatty acid; **LA** linoleic acid, cis, cis-9,12-octadecadienoic acid; **DGLA** dihomogamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-Icosatrienoic acid; **AA** archidonic acid, (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoic acid; **DTA** docosatetraenoic acid, (7Z,10Z,13Z,16Z)-7,10,13,16-docosatetraenoic acid; **BDPA** osbond acid, (All-Z)-4,7,10,13,16-docosapentaenoic acid; **AT-Cox2** aspirin-triggered cyclooxygenase 2; **CYP*** cytochrome P450 isoforms; **18-HpEPE** 18-hydroxyeicosapentaenoic acid, 18-hydroxyicosa-2,4,6,8,10-pentaenoic acid; **18-HEPE** (5Z,8Z,11Z,14Z,16E)-18-hydroxyicosa-5,8,11,14,16-pentaenoic acid; **RvE1** resolvins E1, (5S,6Z,8E,10E,12R,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid; **RvE2** resolvins E2, (5S,6E,8Z,11Z,14Z,16E,18R)-5,18-dihydroxyicosa-6,8,11,14,16-pentaenoic acid; **RvE3** resolvins E3, (5Z,8Z,11Z,13E,15E,18S)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid; **Cox** cyclooxygenase; **ALOX** lipoxigenase, arachidonate lipoxigenase; **ALOX15** 15-lipoxigenase, 15-LOX, 15-LOX-1, arachidonate 15-lipoxigenase; **ALOX15B** 15-lipoxigenase type II, 15-LOX-2, arachidonate 15-lipoxigenase type B; **ALOX12** 12-lipoxigenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxigenase 12S type; **ALOX5** 5-lipoxigenase, 5-LOX, arachidonate 5-lipoxigenase; **17-HpDHA** 17S-hydroperoxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid; **17-HDHA** 17S-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid; **RvD1** resolvins D1, (4Z,7S,8R,9E,11E,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; **RvD2** resolvins D2, (4Z,7S,8E,10Z,12E,14E,16R,17S,19Z)-7,16,17-trihydroxydocosa-4,8,10,12,14,19-hexaenoic acid; **RvD3** resolvins D3, (4S,5E,7E,9E,13Z,15E,17R,19Z)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid; **RvD4** resolvins D4, (4S,6E,8E,10E,13E,15Z,17S,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15,19-hexaenoic acid; **RvD5** resolvins D5, (5Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-dihydroxydocosa-5,8,10,13,15,19-hexaenoic acid; **RvD6** resolvins D6, (4S,5E,7Z,10Z,13Z,15E,17S,19Z)-4,17-dihydroxydocosa-5,7,10,13,15,19-hexaenoic acid; **NPD1** neuroprotectin D1, protectin D1, (4Z,7Z,10R,11E,13E,15Z,17S,19Z)-10,17-dihydroxydocosa-4,7,11,13,15,19-hexaenoic acid; **14-HpDHA** 14-hydro(peroxy)-docosahexaenoic acid, 4-[(1E,3E,5E,7E,9E)-nonadeca-1,3,5,7,9-pentaenyl]dioxete-3-carboxylic acid; **MaR1** maresin 1, (4Z,7R,8E,10E,12Z,14S,16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid; **15-HpETE** 15-hydroperoxy-eicosatetraenoic acid, (5Z,8Z,11Z,13E)-15-hydroperoxyicosa-5,8,11,13-tetraenoic acid; **15S/R-HETE** 15S-HETE (5Z,8Z,11Z,13E,15S)-15-hydroxyicosa-5,8,11,13-tetraenoic acid; **15S-epoxy-tetraene** 5,6-15S-HETE, 4-[(2S,3S)-3-[(1E,3E,5Z,7E,9S)-9-hydroxytetradeca-1,3,5,7-tetraenyl]oxiran-2-yl]butanoic acid; **15R-epoxy-tetraene** lacks a bit of the activity attributed to their S stereoisomers of 15S-epoxy-tetraene; **15R-epoxy-tetraene** lacks a bit of the activity attributed to their S stereoisomers of 15S-epoxy-tetraene; **LXA4** lipoxin A4, (5S,6R,7E,9E,11Z,13E,15S)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid; **LXB4** lipoxin B4, (5S,6E,8Z,10E,12E,14R,15S)-5,14,15-trihydroxyicosa-6,8,10,12-tetraenoic acid; **15-epi-LXA4** (5R,6R,7E,9E,11Z,13E,15R)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid; **12-HpETE** 12-hydroperoxyicosa-5,8,10,14-tetraenoic acid; **12-HETE** (5E,8Z,10Z,14Z)-12-hydroxyicosa-5,8,10,14-tetraenoic acid; **5-HpETE** (6E,8Z,11Z,14Z)-5-hydroperoxyicosa-6,8,11,14-tetraenoic acid; **15-HETE** (5Z,8Z,11Z,13E)-15-hydroxyicosa-5,8,11,13-tetraenoic acid; **5-oxo-ETE** (6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid; **LTA4** leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; **LTC4** leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropylsulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTD4** leuko-

(ATrD3) appear in the late phase of inflammation regulating neutrophils, mediators and enhancing phagocytosis and efferocytosis, which contain the removal of dying apoptotic cells by phagocytosis [389,396,405].

Protectins (PDs)

Protectin D1 (PD1) is termed neuroprotection D1 (NPD1) when described in the central nerve system and will be here named NPD1 to avoid confusion; NPD1 derives from DHA lipooxygenation through 15-LOX metabolism and reported to be neuroprotective [426,427]. Bcl-2 proteins such as Bcl-2 and Bcl-xL are increased by NPD1 with a decrease of pro-apoptotic bcl-2-associated X protein (Bax, bcl-2-like protein) and Bcl-2-associated death promoter (BAD) expression together with inhibition of interleukin 1-beta (IL-1 β) induced Cox-2 expression and it is thought that PLA2 releases a DHA precursor [426]. NPD1 was found to be generated by LOX-dependent T helper type 2-skewed peripheral blood mononuclear cells, and inhibits secretion of TNF α , interferon gamma (IFN γ), promotes apoptosis and blocks even T cell migration [428]. NPD1 “reduces infiltrating leukocytes and blocked TLR-mediated activation of macrophages” and alleviates kidney injury [429].

NPD1 protects against inflammation promoting wound healing [430] and is also found in neutrophils [413,431], and decreases inflammation and hyperresponsiveness in asthma [432]. The dihydroxy-containing DHA derivative NPD1 decreases proapoptotic protein and stimulates antiapoptotic Bcl-2 protein, protects against oxidative stress and inhibits mitochondrial cytochrome c activated caspase-3 and by this it's induced cleavage and inhibits inflammatory IL-1 β -induced Cox-2 expression [427]. NPD1 selectively “enhances neuronal differentiation, an action not shared by eicosanoids, such as LTB₄ or leukotriene C₄” [433] and suppresses “Abeta42-triggered activation of proinflammatory genes while upregulating the antiapoptotic

genes encoding Bcl-2, Bcl-xL, and Bfl-1(A1)” and is suggested to be effective in neurodegenerative diseases and spinal cord injuries [434].

Aspirin-triggered NPD1 (AT-NPD1) reduced neutrophil infiltration in an inflammatory bowel mouse model [395,435] and aspirin-triggered LXA4 (ATLXA4) suppressed proinflammatory cytokines and chemokines [393]. The NPD1 isomer PDX inhibits blood platelets aggregation [436].

Maresins (MaRs)

Maresin 1 (MaR1) was reported as a new 7,14-dihydroxydocosa-4Z,8,10,12,16Z,19Z-hexaenoic acid SMPs derived from DHA through 12-LOX by macrophages involved in resolution of inflammation and coined Maresin (macrophage mediator in resolving inflammation) [437]. MaR1 is produced by macrophages, leukocytes and platelets [438] and has anti-inflammatory effects [439].

Two synthesized diastereomers blocked neutrophil infiltration in an acute peritonitis model [440]. MaR1 reduces neutrophil infiltration in peritonitis, reduces chemotaxis and enhances efferocytosis of apoptotic neutrophils with increased effectiveness compared to RvD. Investigating planaria flatworm infections (of the class *Turbellaria*) reported that MaR1 increased stimulation of tissue regeneration including shortening the regeneration time interval. MaR1 showed potent inflammatory analgesic effects with an IC₅₀ of 0.49 $\pm$ 0.2 nM and by this reduced chemotherapy induced (vincristine-initiated) neuropathic pain [441]; an anti-neuropathic pain amelioration was recently reproduced [442]. Further, 13S,14S-epoxy-maresin was reported as precursor of MaR1 converted by macrophages inhibiting LTA4 and 12-LOX promoting phenotype change of M1 into M2 macrophages [443].

Leukotriene C₄ synthase (LTC₄S) and glutathione S-transferase Mu 4 (GSTM4) catalyze the formation of the synthesized epoxide intermediate maresin conjugates in

triene D₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTE₄** leukotriene E₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTB₄** leukotriene B₄, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid; **LA** linoleic acid, cis, cis-9,12-octadecadienoic acid; LA is not a direct substrate of prostaglandins – this occurs after metabolism to γ -LA; therefore LA here is in brackets; γ -**LA** gamma linolenic acid; **Cox-1** cyclooxygenase 1; **Cox-2** cyclooxygenase 2; **Cox-3** splice variant and isoform of Cox-2; (therefore in brackets); **PGG₂** prostaglandin G₂, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGI₂** prostaglandin I₂, prostacyclin I₂, (5Z)-5-[(3aR,4R,5R,6aS)-5-hydroxy-4-[(E,3S)-3-hydroxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-2-ylidene]pentanoic acid; **6-keto-PGF₁ α** 6-keto-prostaglandin F₁ α , 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]-6-oxoheptanoic acid; **PGH₂** prostaglandin H₂, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGFF₂ α** prostaglandin F₂ α , (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PGD₂** prostaglandin D₂, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **PGE₂** prostaglandin E₂, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; **TXA₂** thromboxane A₂, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid; **MDA** malondialdehyde, propanedial; **Cox** cyclooxygenase; **Cox** cyclooxygenase; **20-HETE** 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid; **20-OH-PGE₂** 20-hydroxy prostaglandin E₂; **ADH** alcohol dehydrogenase; **20-COOH-HETE** 20-carboxy-hydroxyeicosatetraenoic acid; **EETs** epoxyeicosatrienoic acid; **seH** soluble epoxide hydrolase; **DHETs** dihydroxyeicosatrienoic acids.

tissue regeneration 1 (MCTR1), which is converted by gamma-glutamyltransferase (GGT) to MaR conjugates in tissue regeneration 2 (MCTR2), followed by conversion to MaR conjugates in tissue regeneration 3 (MCTR3) by a dipeptidase which increases our understanding of tissue repair and regeneration [444]. This may provide a deeper understanding why carbon tetrachloride-induced liver injury can be alleviated by MaR1 [445]. Furthermore, MaR1 reduces inflammation response of bronchial epithelial cells to organic dust [446], and inhibits the NF- κ B pathway in a mouse colitis model decreasing IL-1 β , TNF- α , IL-6, and INF- γ production [447]. Aggressive periodontitis leukocytes are effectively inhibited by MaR1 [448]. MaR1 administration inhibits TGF- β 1 in fibroblasts [449] and consequent epithelial-to-mesenchymal cell transition in vitro, and attenuates bleomycin-induced pulmonary fibrosis [450]. Vascular endothelial hyperplasia in mice was attenuated by RvD2 and MaR1 [451].

Maresin 2 (MaR2, 13R,14S-diHDHA) also has anti-inflammatory effects but this is less potent compared to MaR1 [452]. RVD1, RVD2 and MaR1 each decrease TNF α , IL-1 β , IL-8 together with upregulated phosphorylation and activation of protein kinase B (Akt, PKB), serine/threonine-protein kinase 1 (SGK1) and cAMP response element binding protein (CREB, CREB-1) and the anti-inflammatory glycogen synthase kinase 3 β (GSK3 β) but not MAPK-related molecules [453].

Summary (Fig. 4)

Eicosanoids “like PGs, lipoxins and leukotrienes play essential roles in maintenance of mucosal integrity” and “can become major drivers of inflammatory processes” [454]. Otherwise the inevitable ageing process may be delayed by changing the homeostasis by calorie restriction, exercise, and parabiosis through growth differentiation factor-11 (GDF-11) and AA anti-inflammatory metabolites such as LXA4, RvDs, PvDs and MaRs increase NO, hydrogen sulfide (H₂S), and carbon monoxide (CO) with suppressing NF- κ B and alter mTOR [385].

Kaposi’s sarcoma-associated herpesvirus (KSHV) decreased anti-inflammatory LXA4 in host cells; using de novo KSHV-infected endothelial cells in vitro Kaposi’s sarcoma and primary effusion lymphoma models with lipoxin and epilipoxin decreased NF- κ B, AKT, ERK1/2, Cox-2, and 5-LOX [455]. Otherwise, Cox-2 is also “constitutively expressed, in the absence of overt inflammation, with a specific tissue distribution that includes the kidney, gastrointestinal tract, brain, and thymus” and this is “independent of commensal microorganisms and not associated with activity of the inflammatory transcription factor NF- κ B” [456].

Influencing the disruption of homeostasis depends, amongst other things, on the local balance of eicosanoid pro- and anti-inflammation mediators: ionophore stimulated lymphocytes, monocytes, and basophils together with synthetic LTB4 induced in vitro chemotaxis of fibroblasts but applied LTB4 10⁻⁸ concentrations result

into optical migration while higher concentrations have an inhibitory effect [457]. Triggering a fibrotic tissue process by the sulfidopeptide LT stimulated fibroblasts only when simultaneously PG synthesis was suppressed by indomethacin [458]. Detailed knowledge of various pathways with its functional implications is needed and “...metabolic network by using systems biology approaches, should be strongly encouraged” [459]. Furthermore, this needs to include reaction specificity information of regulatory mediators impacting the biological activity of various enzymes and proteins including its dynamic changes [460–463].

Furthermore, important consequences of homeostasis disruption influencing the preparation of the precancerous niche (PCN) in this Special Issue “*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*” include undervalued ubiquitous proteins [464], various pathogenic stimulus evoking chronic inflammation [465], remodeled fibrosis by chronic inflammation [466], the microbiome and morbi obesity [467] and PCN induced chronic cell-matrix stress with normal to cancer cell transition [468].

Eicosanoids are hydrophobic hormone-like substances built from PUFAs that play important roles in maintaining physiological levels of inflammation and signaling pathways. Disruption of this delicate homeostasis can create not just persistent inflammation but, with ROS and RNS species, trigger fibrosis and cell transition leading to cancer. Where do we stand today? The available evidence in regard to eicosanoids has been provided. However, not everything is well understood. The data suggest that eicosanoids are not always deleterious as there are newly elucidated anti-inflammatory and pro-resolving eicosanoids (lipoxins, resolvins, maresins, and protectins) which counteract the inflammatory reaction that are important for homeostasis. Until now this mystery, especially with the detailed biological roles of such mediators in cancer and carcinogenesis and associated inflammation are not well understood [469–472].

Eicosanoids are derived from fatty acids which explain the necessity to discuss the microbiome and morbid obesity for understanding the “*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*”. The disruption of homeostasis across a wide, but identifiable, swath of diverse molecular pathways creates a microclimate which constitutes an early and necessary step during the 6-step sequence of carcinogenesis for the vast majority of cancers, termed “sporadic cancers” because their etiology is not understood [473,474].

Nomenclature

1O ₂	Singlet oxygen
5,6-EET	5,6-Epoxyeicosatrienoic acid
5-HETE	5-Hydroxyeicosatetraenoic acid
5-HpETE	5-Hydroperoxide intermediate arachidonic acid

5-LOX	5-Lipoxygenase (ALOX5, 15-LO-1, 15-LOX-1)	Cox-1 variant COXIII	Cyclooxygenase 3, Cox-3, Cox-1b Inner mitochondrial cytochrome c oxidase protein
5-oxo-ETE	5-Oxo-eicosatetraenoic acid	CRC	Colorectal cancer
8,9-EET	8,9-Epoxyeicosatrienoic acid	CREB	cAMP response element binding protein (CREB-1)
8-HETE	8-Hydroxyeicosatetraenoic acid	Cu-Zn-SOD	Copper-zinc-superoxide dismutase (SOD)
8-LOX	8-Lipoxygenase	CYP	Cytochrome P450
9-HODE	9-Hydroxyoctadecadienoic acid	CYP2C	Cytochrome P450 2C
11,12-EET	11,12-Epoxyeicosatrienoic acid	CYP2J	Cytochrome P450 2J
12-HETE	12-Hydroxyeicosatetraenoic acid	CYP2J2	Cytochrome P450 2J2 epioxygenase
12-LOX	12-Lipoxygenase (ALOX12, 12S-LOX)	CYP3A4	Cytochrome P450 3A4
12,13-DHOME	12,13-Dihydroxyoctadec-9-enoic acid	CYP4A/F	Cytochrome P450 4A/F
12R-LOX	Arachidonate 12-lipoxygenase type II (ALOX12B)	CysLTs	Cysteinyl LTs
13-HODE	13-Hydroxyoctadecadienoic acid	DPA	Docosapentaenoic acid
14,15-EET	14,15-Epoxyeicosatrienoic acid	DHA	Docosahexaenoic acid
15-HETE	15-Hydroxyeicosatetraenoic acid	DHET	Dihydroxyeicosatrienoic acid
15-LOX	15-Lipoxygenase (ALOX15)	DT	Docosatriene
15-LOX-1	15-Lipoxygenase-1	EET	Epoxyeicosatrienoic acid
15-LOX-2	15-Lipoxygenase-2	ELA	Elastase
15-epi-LXA4	15-Epi-lipoxin A4 (aspirin triggered lipoxin A4, ATLXA4)	ENaC	Epithelial Na channel
15-epi-LXB4	15-Epi-lipoxin B4 (aspirin triggered lipoxin B4, ATLXB4)	EPA	Eicosapentaenoic acid
15(R)-HETE	15(R)-Hydroxyeicosatetraenoic acid	Erk1,2	Extracellular signal-regulated kinase 1, 2
15-(S)-HETE	15(S)-Hydroxyeicosatetraenoic acid (Icomucret)	FAP	Familial adenomatous polyposis
20-HETE	20-Hydroxyeicosatetraenoic acid	Fe-SOD	Iron-superoxide dismutase (SOD)
AA	Arachidonic acid	FLAP	5-Lipoxygenase-activating protein
AAF	2-Acetylaminofluorene	GDF-11	Growth differentiation factor-11
ACE	Angiotensin-converting enzyme	gm-CSF	Granulocyte-macrophage colony stimulating factor (CSF)
Akt	Protein kinase B (PBK)	GSK3 β	Glycogen synthase kinase 3 β
ALA	α -Linolenic acid	GSTM4	Glutathione S-transferase Mu 4
ALOX	Lipoxygenase (LOX)	H ₂ O ₂	Hydrogen peroxide
ALOX15B	Arachidonate 15-lipoxygenase type II	H ₂ S	Hydrogen sulfide
Ang II	Angiotensin II	HB-EGF	Heparin-binding epidermal growth factor-like growth factor
AP-1	Activator protein 1	HBB	N1-hexyl-N5-benzyl-biguanide
ATDT	Aspirin-triggered docosatriene	HCC	Hepatocellular carcinoma
ATLXA4	Aspirin-triggered LX4	HETE	Hydroxyeicosatetraenoic acid
ATRvD	Aspirin-triggered resolvin	HNO ₂	Nitrous acid
ATRvD1	Aspirin-triggered RvD1 epimer, 17-oxo-RvD1	HPTF	Human patellar tendon fibroblast
ATRvD3	Aspirin-triggered RvD3 epimer	HSPC	Hematopoietic stem and progenitor cell
AT-Cox2	Aspirin-triggered cyclooxygenase 2	IFN γ	Interferon gamma
AT-NPD1	Aspirin-triggered NPD1	IL-1 α	Interleukin-1-alpha
Bax	Bcl-2-associated X protein (bcl-2-like protein 4)	IL-1b	Interleukin-1-beta
BAD	Bcl-2-associated death promoter	IL-6	Interleukin 6
BIM	Bisindolylmaleimide	I/R	Ischemia-reperfusion
cAMP	Cyclic adenosine 3',5'-monophosphate	KCl	Potassium chloride
CCK(B)-R	Cholecystokinin B receptor	KSHV	Kaposi's sarcoma-associated herpesvirus
cGMP	3',5'-Cyclic guanosine monophosphate	LOOH	Lipid hydroperoxide
CLL	Chronic lymphocytic leukemia	LOX	Lipoxygenase (ALOX)
CO	Carbon monoxide	LPA	Lysophosphatidic acid
Cox	Cyclooxygenase	LPAR 1-6	G protein-coupled receptors
Cox-1	Cyclooxygenase 1	LPS	Lipopolysaccharid
Cox-2	Cyclooxygenase 2	LT	Leukotriene
Cox-3	Cyclooxygenase 3, Cox-1b, Cox-1 variant	LTA5	Leukotriene A5
Cox-1b	Cyclooxygenase 3, Cox-3, Cox-1 variant	LTB4	Leukotriene B4

LTB5	Leukotriene B5	PD1	Protectin D1 (neuroprotectin D1, NPD1)
LTC4	Leukotriene C4		
LTC5	Leukotriene C5	PDX	NPD1 isomer (10(S),17(S)-dihydroxy-docosa-hexa-4Z,7Z,11E,13Z,15E,19Z-enoic acid)
LTC4S	Leukotriene C4 synthase		
LTD4	Leukotriene D4		
LTD5	Leukotriene D5	PG	Prostaglandin
LTE4	Leukotriene E4	PGB1	Prostaglandin B1
LX	Lipoxin	PGD2	Prostaglandin D2
LXA4	Lipoxin A4, 5S,6R,15S-trihydroxy-7E,9E,11Z,13E-eicosatetraenoic acid	PDG3	Prostaglandin D3
LXB4	Lipoxin B4, 5S,14R,15S-trihydroxy-6E,8Z,10E,12E-eicosatetraenoic acid	PGE1	Prostaglandin E1
		PGE2	Prostaglandin E2
		PGES	Prostaglandin E synthase
MAPK	Mitogen-activated protein kinase	PGF1a	Prostaglandin F1alpha
MaR	Maresin	PGF2a	Prostaglandin F2alpha
MaR1	Maresin 1	PGF3a	Prostaglandin F3alpha
MaR2	Maresin 2	PGG2	Prostaglandin G2
MCTR1	Maresin conjugates in tissue regeneration 1	PGH2	Prostaglandin H2
MCTR2	Maresin conjugates in tissue regeneration 2	PGI2	Prostaglandin I2, prostacyclin
MCTR3	Maresin conjugates in tissue regeneration 3	PGI3	Prostaglandin I3
		Phe	Phenylephrine
MEK1,2	Mitogen-activated protein kinase kinase 1,2	PI3K	Phosphatidylinositol 3-kinase
		PKC	Protein kinase C
MMP-7	Matrixmetalloproteinase 7	PLA2	Phospholipase A2
MMP-9	Matrixmetalloproteinase 9	PLCO	Prostate, lung, colorectal, and ovarian cancer screening trial
Mn-SOD	Manganese-superoxide dismutase (SOD)	PMN	Polymorphonuclear neutrophil
mTOR	Rapamycin	PPAR	Peroxisome proliferator-activated receptor
N ₂ O ₃	Dinitrogen trioxide	PPAR γ	Peroxisome proliferator-activated receptor gamma
NADPH	Nicotinamide adenine dinucleotide phosphate	PTGS2	Prostaglandin-endoperoxide synthase 2
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells	PUFA	Polyunsaturated fatty acids
NFA	Nitro-fatty acid	Raf1	RAF proto-oncogene serine/threonine-protein kinase
Ni-SOD	Nickel-superoxide dismutase (SOD)	RNS	Reactive nitrogen species
NO	Nitric oxide	ROS	Reactive oxygen species
NO ₂ ⁻	Nitrogen dioxide	RUNX1	Runt-related transcription factor 1
NONOate	Nitric oxide (NO) donor	RV	Resolvin
Nox	Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase	SA	Salicylic acid
NPD1	Neuroprotectin D1 (PD1,protectin D1)	sEH	Soluble epoxide hydrolase
NSAID	Non-steroidal anti-inflammatory drug	SGK1	Serine/threonine-protein kinase 1
ω -3 PUFA	Omega-3 (n-3) polyunsaturated fatty acid	SOD	Superoxide dismutase
ω -6 PUFA	Omega-6 (n-6) polyunsaturated fatty acid	SOD1	Superoxide dismutase 1
ω -9 PUFA	Omega-9 (n-9) polyunsaturated fatty acid	SOD2	Superoxide dismutase 2
		SPM	Specialized pro-resolving lipid mediator
		STAT3	Signal transducers and activators of transcription
O ₂	Oxygen	SV40	Polyomavirus simian virus
O ₂ ⁻	Superoxide	t-CUPM	Trans-4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexyloxy}-pyridine-2-carboxylic acid methylamide
O ₃	Ozone		
ONOO ⁻	Peroxynitrite	TAK1	Transforming growth factor beta-activated kinase 1
PBK	Protein kinase B (Akt)	TGF- β 1	Transforming growth factor beta 1
pCox-	Partial Cox-1, pCox-1 protein or Cox variant Cox-1V1	TNFa	Tumor necrosis factor a
PD	Protectin	TRPC7	Transient receptor potential cation 7 channel

TXA	Thromboxane
TXA1	Thromboxane A1
TXA2	Thromboxane A2
TXA3	Thromboxane A3
UV	Ultraviolet
XO	Xanthine oxidase

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Conflict of interest

The author reports the following conflict of interest: Björn LDM Brücher is Editor-in-Chief in Life Sciences-Medicine of 4open by EDP Sciences. Ijaz S. Jamall is Senior Editorial Board member in Life Sciences-Medicine of 4open by EDP Sciences. The authors, of their own initiative, suggested to the Managing Editorial to perform a transparent peer-review of their submittals. Neither author took any action to influence the standard submission and peer-review process, and report no conflict of interest. The authors alone are responsible for the content and writing of the manuscript of this Special Issue. This manuscript contains original material that has not previously been published. Both authors contributed to the discussion on its contents and approved the manuscript.

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