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 lipooxygenase 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 unremitting 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 micromilieu 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 'eíkosi' (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 formluar 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, eicosanoids, 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, Mitsumaru Tsujimoto (1877–1940), described how the addition of bromine could result in products of PUFA which could then be crystalized [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** dihomo gamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-eicosatrienoic 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; **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 prostan 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 F2alpha (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), lipooxygenase (ALOX), cytochrome P450 (CYP) and reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), followed by unsaturated fatty acids and the newly discovered specialized anti-inflammatory lipid mediators (SPMs).

Eicosanoids

Eicosanoids contain signal-mediating molecules such as PGs, prostaoyclines, 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 polyenioic 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 homoestasis [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-alpha [72 reviewed in 66]. PLA2 knockdown 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 (Rafl/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 E2k2 phosphorylation. The authors showed that using the selective inhibitor bis-indolylmaleimide (BIM) inhibited arachidonate metabolites from activated macrophages and that PKC-dependent
Fig. 2. Lipoxygenase (ALOX) pathway of eicosanoid metabolism and its relevance in inflammation. Nomenclature: Simplified scheme of polyenioic fatty acid metabolism via the lipoxygenase (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-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 dihomo gamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-linoleoctaenoic 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 lipoxygenase, arachidonate lipoxygenase; ALOX15 15-lipoxygenase, 15-LOX, 15-LOX-1, arachidonate 15-lipoxygenase; ALOX15B 15-lipoxygenase type II, 15-LOX-2, arachidonate 15-lipoxygenase type B; ALOX12 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; ALOX5 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; 17-HpDHA 17S-hydroperoxo-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid; 17-HDHA 17S-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid; RvD1 resolvin D1, (4Z,7Z,8R,9E,11E,13Z,15E,17Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; RvD2 resolvin D2, (4Z,7Z,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,17Z,19Z)-5,7,9,13-trihydroxydocosa-4,7,9,11,13,15,19-hexaenoic acid; RvD5 resolvin D5, (5Z,7S,8E,10Z,13Z,15E,17S,19Z)-4,7,10,13,15,19-hexaenoic acid; NPD1 neuroprotectin D1, (4Z,7Z,10R,11E,13E,15Z,17S,19Z)-4,7,10,13,15,19-hexaenoic acid; 14-HpDHA 14-hydroperoxo-docosahexaenoic acid 4-[(1E,3E,5E,7E,9E)-nonadeca-1,3,5,7,9-pentaenyl]dioxy-4-carboxylic acid; MaR1 maresin 1, (4Z,7R,8E,10E,12Z,14S,16Z,19Z)-4,11,17-trihydroxydocosa-5,7,9,11,13,15,19-hexaenoic acid.
Erk2-phosphorylation by the benzamide derivative JM34, which inhibits tumor necrosis factor alpha (TNFα) 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 oncovirus 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). PGE2α 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. PGE1α and PGE2α 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 prostanooids. 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 1α,25(OH)2-cholecalciferol (equivalent to 1α,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 catabolyzing 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 oxygen atoms 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), prosta-cyclin, 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), TNFα, interleukin-1-alpha (IL-1α), and...


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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-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** dihomo gamma-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; **AT-Cox2** aspirin-triggered cyclooxygenase 2; **CYP** cytochrome P450 isoforms; **18-HpEPE** 18-hydroxyeicosapentaenoic acid; **18-HEPE** (5Z,8Z,11Z,14Z,16E)-18-hydroxyicosa-5,8,11,14,16-pentaenoic acid; **RvE1** resolvin E1, (5S,7Z,10Z,12Z,14Z,16E,18R)-5,7,10,12,14,18-hexahydroxyicosapentaeic acid; **RvE2** resolvin E2, (5S,7Z,10Z,12Z,14Z,16E,18R)-5,7,10,12,14,18-hexahydroxyicosapentaenoic acid; **RvE3** resolvin E3, (5S,7Z,10Z,13Z,15E,18S)-17,18-dihydroxy-eicosapentaenoic acid; **Cox** cyclooxygenase; **20-HEPE** 20-hydroxyicosa-5,8,11,14,16-pentaenoic acid; **20-OH-PGE2** 20-hydroxy prostaglandin E2; **20-COOH-HETE** 20-carboxyhydroxyeicosatetraenoic 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, PGF2α, 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-β1) 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, antipyrene, and dipyrone, 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 directly in

Aspirin affects the PG pathway by suppressing the production of PGs and TXAs through acetylation of a serine-rest of Cox-1 through prostaglandine-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-κB) 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 adenomatosis 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-β1 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-β1-induced actin remodeling [174] and PGE-2 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 TNFα 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, PG2, PG12, prostaglandin D2 (PGD2) and PGF2α, 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-lipooxygenase (5-LOX, ALOX5), 12-lipooxygenase (12-LOX, ALOX12, 12S-LOX), 15-LOXα, and 15-LOXβ, respectively [79].

Various hydroxyeicosatetraenoic acid (HETE) metabolites are formed via the lipooxygenase 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, LTC4, 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 prediagnostic 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 neutrophile stimulation and chemotacticity.

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 (Δ468) 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 TNFα 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-β1 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 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 chemo-sensory 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, enteroenodocrine, 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-methyl-
trosamin-1-(3-pyridyl)-1-butane 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 Bye 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 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-κB [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-κB, TGF-β1/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 “more endometrial fibrosis by stimulating the production of anti-fibrotic PGE2 and inhibiting pro-fibrotic PGF2 α” [260]. 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-[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-1β, IL-8, TNF-α, sP-selectin, and S-selectin together with decreased NF-xB p65 activation and degradation of IkBα which may be mediated though peroxisome proliferator-activated receptor gamma (PPARγ) 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 endogeneous nitro-fatty acids (NFAs) were identified as potential future new well tolerated chemo-therapeutic 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 dismutate activity; they reported superoxide dismutase (SOD) catalyzing “the dismutation or disproportionation of superoxide free radical anions” of the superoxide (O2−) radical into both molecular oxygen (O2) and hydrogen peroxide (H2O2): O2− + O2− + 2H+ → O2 + H2O2 [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: (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 singulet oxygen (1O2), H2O2 and ozone (O3), and oxygen radicals such as hydroxyl radical (OH), and superoxide (O2− —). 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 seems 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 peroxyynitrite (ONOO−), nitrogen dioxide (NO2−), dinitrogen trioxide (N2O3), nitrous acid (HNO2), 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 (O2−) [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-kB 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 receptor, cholecystokinin B receptor (CCK(B)-R), Cox-2, and prostaglandin [330]. The continuous stimulation of Cox-2 and NF-kB signaling results in a persistent increase of inflammatory cytokines such as TNFs 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/1/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 (T1/2) of ROS are short contain in between < nanoseconds to seconds [335 reviewed in 336]: the very reactive OH radical has a T1/2 of approximately 10−9 s [337] compared to O2− and H2O2 in between 10−6 s and 10−2 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 6Δ desaturase, elongase, 5Δ desaturase, and 4Δ desaturase; those deriving from α-linolenic acid (ALA) 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 F3alpha (PGF3α), prostaglandin I3 (PGI3), thromboxane A3 (TXA3), and LTs such as leukotriene A5 (LTA5), leukotriene B5 (LTB5), leukotriene C5 (LTC5) and di 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 F2alpha (PGF2α), PGE2, TXA2, and LTs LTBD4, 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 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 LTC4, 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 denates 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 resolin E1, resolvin E2, and resolvin E3 with [412]. DHA-derived resolvins are counted among the D-series of resolvins, such as resolin 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 aspirin-triggered cyclooxygenase 2 (AT-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 (ATRvDs) 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), lipoxygenase (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): α-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)-eicosapentaenoic acid; DHA docosahexaenoic acid, (4Z,7Z,10Z,13Z,15Z,17S,19Z)-4,7,10,13,16,19-docosapentaenoic acid; RvE1 resolvin E1, (5Z,8Z,11Z,14Z,15S,18S)-15-hydroxyicosa-5,8,11,14,15-pentaenoic acid; RvE2 resolvin E2, (5Z,8Z,11Z,14Z,15S,18S)-17,18-dihydroxyicosa-5,8,11,14,15-pentaenoic acid; RvE3 resolvin E3, (5Z,8Z,11Z,13E,15E,18S)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid; Cox cyclooxygenase; ALOX lipoxygenase, arachidonate lipoxygenase; ALOX12 lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase; ALOX15B 15-lipoxygenase type II, 15-LOX-2, arachidonate 15-lipoxygenase type B; ALOX12 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; ALOX5 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; ALOX15 15-lipoxygenase, 15-LOX, 15-LOX-1, arachidonate 15-lipoxygenase type II; ALOX15B 15-lipoxygenase type II, 15-LOX-2, arachidonate 15-lipoxygenase type B; ALOX12 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; ALOX5 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; 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 resolvin E1, (5Z,8Z,11Z,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid; RvE2 resolvin E2, (5Z,8Z,11Z,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid; RvE3 resolvin E3, (5Z,8Z,11Z,13E,15E,18S)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid; Cox cyclooxygenase; ALOX lipoxygenase, arachidonate lipoxygenase; ALOX15B 15-lipoxygenase type II, 15-LOX-2, arachidonate 15-lipoxygenase type B; ALOX15B 15-lipoxygenase type II, 15-LOX-2, arachidonate 15-lipoxygenase type B; ALOX12 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; ALOX5 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; 17-HpDHA 17S-hydroperoxy-docosahexaenoic acid, all-cis-8,11,14,17-docosahexaenoic acid; 15-HpDHA 15S-hydroperoxy-docosahexaenoic acid, all-cis-8,11,14,17-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,14R,16R,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; RvD3 resolvin D3, (4Z,8E,9Z,10E,12Z,16R,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; RvD4 resolvin D4, (4Z,8E,9Z,10E,12Z,16R,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; RvD5 resolvin D5, (5Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid; 14-HpDHA 14-hydro(peroxy)-docosahexaenoic acid, 4-[(1E,4Z,7E,9E,11E,13E)-9-hydroxyoctadeca-1,3,5,7,9-pentaenyl]dioxetane-3-carboxylic acid; MaR1 marines 1, (4Z,7R,8E,10E,12Z,14S,16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid; 15-HpEPE 15-hydroperoxy-eicosatetraenoic acid, (5Z,8Z,11Z,13E)-15-hydroperoxyeicosapentaenoic acid, 5,8,11,13-tetraenoic acid; 15S/R-HETE 15S-HETE (5Z,8Z,11Z,13E,15S)-15-hydroxyeicosapentaenoic acid, 5,8,11,13-tetraenoic acid; 15S-epoxy-tetraene 5,6,15S-HETE, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-9-hydroxytetradeca-1,3,5,7,9-pentaeny]dioxetane-3-carboxylic acid; LTA4 leukotriene A4, (5Z,8Z,11Z,13E)-9-hydroxyoctadeca-1,3,5,7,9-pentaeny]dioxetane-3-carboxybutanoyl[amino]-3-(carboxymethylamino)-3-oxopropyl][sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; LTD4 leuko-
(ATRvD3) appear in the late phase of inflammation regulating neutrophils, mediators and enhancing phagocytosis and effectorcytosis, 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 BclXL 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-1β) induced Cox-2 expression and it is thought that PLA2 releases a DHA metabolite 

6-keto-PGF1α; [(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; PGF2α; [(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]-6-oxoheptanoic acid; EETs; [(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, prostaglandine F2α; prostanoids derived from DHA through 12-LOX by macrophages involved in resolution of inflammation and coined Protectin (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 effectorcytosis 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 ± 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 LT4A 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

leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxymethylamino)-3-carboxyethyl]sulfanyl-5-hydroxyicos-7,9,11,14-tetraenoic acid; LTE4 leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicos-7,9,11,14-tetraenoic acid; LTB4 leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicos-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); PG2 prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxacyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; PGF2α prostaglandin F2α, prostacyclin I2, (5Z)-5-[(3aR,4R,5R,6aS)-5-hydroxy-4-[(E,3S)-3-hydroxyoct-1-enyl]-3a,4,5,6a,7a-hexahydrocyclopenta[a]furano-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-dioxacyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; PGF2α prostaglandin F2α, alpha, (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,3R,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,3S,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxacyclo[3.1.1]heptan-2-yl]hept-5-enoic acid; MDA malondialdehyde, prostatelecid, Cox cyclooxygenase; Cox cyclooxygenase; 20-HETE 20-hydroxyicosatetraenoic acid, (5S,8Z,11Z,14Z)-20-hydroxyicos-5,8,11,14-tetraenoic acid; 20-OH-PGE2 20-hydroxy prostaglandin E2; ADH alcohol dehydrogenase; 20-COOH-HETE 20-carboxy-hydroxyicosatetraenoic acid; EETs epoxeyicosatetraenoic acid; sEH soluble epoxide hydrase; 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-κB pathway in a mouse colitis model decreasing IL-1β, TNF-α, IL-6, and INF-γ production [447]. Aggressive periodontitis leukocytes are effectively inhibited by MaR1 [448]. MaR1 administration inhibits TGF-β1 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 TNFα, IL-1β, 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 glycyrrhizin synthase kinase 3β (GSK3β) 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, 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-κB” [456].

Influencing the disruption of homeostasis depends, amongst other things, on the local balance of eicosanoid pro- and anti-inflammatory 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 morbidity 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 micromilieu 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**

1O2 Singlet oxygen
5,6-EET 5,6-Epoxyeicosatrienoic acid
5-HETE 5-Hydroxyeicosatetraenoic acid
5-HpETE 5-Hydroperoxide intermediate
arachidonic acid
LTB5  Leukotriene B5  PD1  Protectin D1 (neuroprotectin D1, NPD1)
LTC4  Leukotriene C4  PDX  NPD1 isomer (10(S),17(S)-dihydroxy-docosahexa-4Z,7Z,11E,13Z,15E,19Z-
esa/enoic acid)
LTC5  Leukotriene C5  PGE  Prostaglandin E
LTC4S Leukotriene C4 synthase
LTD4  Leukotriene D4  PGD2  Prostaglandin D2
LTD5  Leukotriene D5  PGB1  Prostaglandin B1
LTE4  Leukotriene E4  LG  Prostaglandin G
PG  Prostaglandin
LXA4  Lipoxin A4, 5S,6R,15S-trihydroxy-7E,9E,13E-eicosatetraenoic acid  PGD3  Prostaglandin D3
LXB4  Lipoxin B4, 5S,14R,15S-trihydroxy-6E,8Z,10E,12E-eicosatetraenoic acid  PGE1  Prostaglandin E1
MAPK  Mitogen-activated protein kinase  PGES  Prostaglandin E synthase
MaR  Maresin  PGF1a  Prostaglandin F1alpha
MaR1 Maresin 1  PGF2a  Prostaglandin F2alpha
MaR2 Maresin 2  PGG2  Prostaglandin G2
MCTR1 Maresin conjugates in tissue regeneration 1  PGH2  Prostaglandin H2
MCTR2 Maresin conjugates in tissue regeneration 2  PGD2  Prostaglandin D2
MCTR3 Maresin conjugates in tissue regeneration 3  PGI3  Prostaglandin I3
MEK1,2 Mitogen-activated protein kinase 1,2  PLA2  Phospholipase A2
MMP-7 Matrixmetalloproteinase 7  PLC-NO Prostaglandin I2, prostacyclin
MMP-9 Matrixmetalloproteinase 9  PGI2  Prostaglandin I2, prostacyclin
Mn-SOD Manganese-superoxide dismutase (SOD)  PPAR  Peroxisome proliferator-activated receptor
NADPH Nicotinamide adenine dinucleotide phosphate  PMN  Polymorphonuclear neutrophil
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells  PPARγ  Peroxisome proliferator-activated receptor gamma
N2O3 Dinitrogen trioxide  PGF1a  Prostaglandin F1alpha
NADPH Nicotinamide adenine dinucleotide phosphate  PTGS2  Prostaglandin-endoperoxide synthase 2
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells  PPAR  Peroxisome proliferator-activated receptor
NFA Nitro-fatty acid  RNS  Reactive nitrogen species
Ni-SOD Nickel-superoxide dismutase (SOD)  ROS  Reactive oxygen species
NO Nitric oxide  RUNX1  Runt-related transcription factor 1
NO2 Nitrogen dioxide  RV  Resolvins
NOC Nitric oxide (NO) donor  SA  Salicylic acid
NOX Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase  sEH  Soluble epoxyde hydrolase
NPD1 Neuroprotectin D1 (PD1,protectin D1)  SGK1  Serine/threonine-protein kinase 1
NSAID Non-steroidal anti-inflammatory drug  SOD  Superoxide dismutase
ω-3 PUFA Omega-3 (n-3) polyunsaturated fatty acid  SOD1  Superoxide dismutase 1
ω-6 PUFA Omega-6 (n-6) polyunsaturated fatty acid  SOD2  Superoxide dismutase 2
ω-9 PUFA Omega-9 (n-9) polyunsaturated fatty acid  SPM  Specialized pro-resolving lipid mediator
O2 Oxygen  STAT3  Signal transducers and activators of transcription
O2- Superoxide  SV40  Polyomavirus simian virus
O3  TAK1  Transforming growth factor beta-activated kinase 1
ONOO- Peroxynitrite  t-CUPM  Trans-1-{4-[4-chloro-3-trifluoromethyl-phenyl]-ureido[ cyclohexyl-\loxy]-pyridine-2-carboxylic acid
O2 Oxygen  methyamide
O3  TGF-B1  Transforming growth factor beta 1
ONOO- Peroxynitrite  TNFa  Tumor necrosis factor alpha
OA  TRPC7  Transient receptor potential cation 7 channel
pCox- Partial Cox-1, pCox-1 protein or Cox variant Cox-1V1
PD Protectin
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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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