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Emerging targets in lipid-based therapy☆

Stephanie C. Tucker[a,1] and **Kenneth V. Honn**[a,b,*]

[a]Department of Pathology, Wayne State University School of Medicine, and Karmanos Cancer Institute, Detroit, MI 48202, USA

[b]Department of Chemistry, Wayne State University School of Medicine, and Karmanos Cancer Institute, Detroit, MI 48202, USA

Abstract

The use of prostaglandins and NSAIDS in the clinic has proven that lipid mediators and their associated pathways make attractive therapeutic targets. When contemplating therapies involving lipid pathways, several basic agents come to mind. There are the enzymes and accessory proteins that lead to the metabolism of lipid substrates, provided through diet or through actions of lipases, the subsequent lipid products, and finally the lipid sensors or receptors. There is abundant evidence that molecules along this lipid continuum can serve as prognostic and diagnostic indicators and are in fact viable therapeutic targets. Furthermore, lipids themselves can be used as therapeutics. Despite this, the vernacular dialog pertaining to “biomarkers” does not routinely include mention of lipids, though this is rapidly changing. Collectively these agents are becoming more appreciated for their respective roles in diverse disease processes from cancer to preterm labor and are receiving their due appreciation after decades of ground work in the lipid field. By relating examples of disease processes that result from dysfunction along the lipid continuum, as well as examples of lipid therapies and emerging technologies, this review is meant to inspire further reading and discovery.

Keywords

Cancer; Bioactive lipids; Raman; Therapeutics; Biomarkers; Drug synergism

1. Introduction

The imbalance between lipid mediators that regulate inflammation or resolution, leads to a number of diseases, many of which are only now being appreciated for their underlying lipid origins. “Physiological” inflammation has its place. In the gastrointestinal tract it is necessary for proper development of the mucosal immune system, and is a tempered response that does not manifest in disease [1]. Ovulation can be considered another example of regulated physiological inflammation [2–4]. However, dysregulated lipid signaling can

☆Dysfunctional cell signaling dynamics in oncology-diagnostic, prognostic and treatment opportunities.

*Corresponding author at: Department of Pathology, 431 Chemistry Bldg., Wayne State University, Detroit, MI 48202, USA. Tel.: +1 313577 1018; fax: +1 313 577 0798. stucker@med.wayne.edu (S.C. Tucker), k.v.honn@wayne.edu (K.V. Honn).
[1]Present address: Department of Pathology, 433 Chemistry Bldg., Wayne State University, Detroit, MI 48202, USA.

lead to a host of ailments including fibrosis, cancer, and neurological disorders to name a few. The term *rheostat* has been used frequently in the lipids field to refer to the yin and yan, or balance of activities along the continuum depicted in Fig. 1. A case can be made for nearly every direction suggested by the figure and for nearly all lipid pathways. There are volumes written on lipid mediators or *bioactive lipids* and their associated pathways, these include the leukotrienes, lysophospholipids, prostaglandins, platelet activating factor, endocannabinoids, and prostanoids. Collectively the pathways with their receptors, enzymes, accessory proteins and associated lipid products are the subject of intense development for their usefulness as diagnostic and prognostic biomarkers as well as therapeutic targets, particularly in cancer. While this cast of players is better known for the roles they play in many diseases as a result of environment (e.g., diet) or genetics, it is the context of the activity along lipid pathways that determines outcome with regard to disease development, prevention or healing. New characters continue to emerge including novel receptors that are providing additional therapeutic targets, and lipids themselves are being used therapeutically.

Instead of a class by class comparison, which would again require volumes, the purpose of this review is to relate some loosely associated new and revisited ideas from the overall field by using pointed examples as they relate to the theme of this issue, and to highlight some exciting technologies being adapted to lipidomics from our colleagues in bioengineering/physics. It is hoped that for the veterans of the field as well as the uninitiated and curious, this review will encourage exploration into new ways to use lipids and their pathways to our advantage.

2. Lipids used as therapeutic pharmacologic agents

The omega-6 polyunsaturated fatty acid arachidonic acid (AA) is an eicosanoid precursor that can be acquired in cells by metabolism of linoleic acid or can be taken up by cells directly through dietary intake, which is the most common source. Once in the cell, this precursor of many lipid mediators is mobilized to lipid pools that are actively remodeled, such as the nuclear membrane. From there it is subsequently reassigned back to other cellular membranes that are the presumed sites of synthesis [5]. Arachidonic acid becomes anchored to membrane phospholipids like phosphatidylethanolamine, but primarily phosphatidylcholine and phosphatidylinositol, by esterification catalyzed by a fatty-acylCoA synthetase. The release of AA from the phospholipids is the signaling cascade lynchpin. The most common release mechanism is through the action of a Ca^{2+}-dependent cytosolic phospholipase A2 (cPLA2), particularly cPLA2α (group IVA), (also referred to as GIVA PLA2), in response to a cell stimulus [6–8]. The cPLA2 apparently evolved simultaneously with eicosanoid receptors, and more than 30 genes for phospholipase are encoded in mammalian genomes, including the secreted (sPLA2), the Ca^{2+}-independent (iPLA2), and Ca^{2+}-dependent (cPLA2) enzymes. These three classes have been the most studied to date [9,10]. Similarly the omega 3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be released from the membrane stores as well. The stimuli that lead down the signaling pathway are obviously diverse and include those that are "*complete activators*" such as calcium ionophores, microorganisms, and oxidants, as well as agonists that potentiate the cascade by "*priming*" the response in preparation for a more complete

stimulus [11]. Furthermore, the regulatory mechanisms for biosynthesis and secretion of lipid mediators are highly varied and depend on factors such as the expression levels and functional state of the metabolic enzymes, compartmentalization of the enzymes and finally expression levels and functional state of accessory proteins such as the transport proteins [11]. The cyclooxygenase (COX), lipoxygenase (LOX) and P450 epoxygenase enzymatic pathways can metabolize AA after its release from the cell membrane to generate numerous lipid effector molecules.

One of the most exciting recent advances in lipid research involves the discovery of a subset of eicosanoid lipid mediators that are actively involved in mitigating inflammatory responses. The first hint that recovery from inflammation was not just a waning of proinflammatory signals, but in fact an active recovery process came from studies of "*spontaneously resolving inflammatory exudates*" [12]. Through cooperative interactions of cells within the inflammatory microenvironment, transcellular synthesis of the pro-resolving lipoxins occurs by two routes [13]. As part of this functional redundancy, leukocytes can provide LTA_4, a leukotriene intermediate from 5-LOX metabolism of AA, to neighboring cells such as platelets that in turn use this substrate to produce lipoxins LXA_4 and LXB_4 through the action of their own 12-LOX. Alternatively, LXA_4 and LXB_4 can be synthesized by cells through the uptake of a 15-LOX intermediate, and subsequent 5-LOX activity. Aspirin-triggered lipoxins also exist, but production of these occurs either through the COX-2 or P450 pathway [14]. The yin and yan transition of pro-inflammatory lipid production to that which resolves inflammation is modulated by still other lipid mediators such as a subset of prostaglandins.

The resolvins include the E-series (RvE1–E2) and D-series (RvD1–D6) lipid metabolites that originate from the omega 3 fatty acids, EPA and DHA respectively. DHA is also the source of maresins (MaR1) and neuro/protectins (NPD1/PD1). These newly characterized lipid mediators are thought to drive the benefits attributed to omega 3 up take [14].

Lipoxins, resolvins, maresins, and protectins (not to be confused with the membrane complement attack complex inhibitor protein (CD59) with the same name [15]) all target specific cell populations through defined surface receptors such as GPR32, FPRL1 (ALX/FPR2), cysLT1, ChemR23 (also activated by the protein chemerin), and BLT1 and have various immunoregulatory functions so as to regulate acute inflammation (reviewed in [16–18]).

This "resolution pharmacology" has already had a major impact on treatment modalities of, for example, periodontal disease [19,20]. In a lapine periodontitis model, leukocyte-mediated bone loss was prevented by RvE1, and it was demonstrated further that osteoclast differentiation was also abolished with resolvin treatment ([21] and references therein). These exciting preliminary studies on the effects of the pro-resolving arm of lipid mediators portend a blow to the resistance mechanisms of many diseases. The therapeutic effects of lipids in general, as well as from targeting their pathways, are heralding major advances in diverse disciplines.

2.1. Types of therapeutic lipids

Highly or polyunsaturated fatty acids (HUFA, PUFA) are the predominant source of lipid mediators, with both the eicosanoid (C20) and docosanoid (C22) fatty acid metabolites driving many phenotypes targeted for therapy including apoptotic pathways [22,23]. The direct consumption of preformed DHA and EPA has been demonstrated to have many therapeutic effects, particularly when derived from marine sources, as these substrates tend to skew the lipid continuum toward a healthy balance [24,25]. However, defined lipid mediators are being singled out of numerous lipid reaction pathways to treat specific diseases.

2.2. Specific examples of disease/pathobiology studies that suggest beneficial impact of lipids

Gynecological applications—Numerous studies on prostaglandins and their receptors in pregnancy have been reported [26]. Cervical ripening and the onset of labor are induced through the E and F series prostaglandins with a concomitant reduction of progesterone [27,28]. In a recent study that garnered national attention, midtrimester administration of progesterone was shown to decrease preterm delivery [29], an effect that is likely due to antagonistic effects on the lipid mediators.

Oral use of the prostaglandin E1 analog, misoprostol, was indicated for treating peptic ulcers and then adopted in the 1990s for use as a uterotonic (contracts the womb after child birth) in management of postpartum hemorrhage [30]. Oxytocin and ergometrine are two uterotonic drugs that are conventionally used to manage postpartum hemorrhage. While considered the gold standard, there are some drawbacks when considering their application in areas of the world where standard medical care may not be readily available. They are heat labile, require injection, and can elevate blood pressure. A recent Cochrane review of 72 randomized trials (52,678 women) reported that misoprostol was effective in reducing severe hemorrhage and reduced the need for blood transfusion. Given the lower cost, ease of administration, and its temperature stability, in addition to the fact that it can be used in hypertensives, oral administration of misoprostol was determined to be a viable treatment option particularly in low or middle-income countries despite some of the side effects such as fever and nausea that could impact maternal-infant bonding [31].

Misoprostol is now being used prophylactically to maintain uterine tone during C-section under anesthesia and to reduce blood loss during myomectomy for fibroids [32,33]. In 1995, and again in 2012, misoprostol was evaluated for its ability to reduce oral mucositis in response to chemotherapy and radiation [34,35]. Unfortunately the radiation study was cut short due to funding cuts and the chemotherapy pilot was never expanded to greater patient numbers. Therefore, the efficacy of prostaglandin treatments on oral mucositis in response to cancer treatments awaits further evaluation.

Diabetes studies—Gurgul-Convey et al. have proposed a new mechanism that involves prostacyclin or PGI2 to improve the treatment of type II diabetes. Rat islet cells have low levels of the enzyme prostacyclin synthase (PGIS). However, they ramp-up production in response to glucose stimulation. While the parental version of the beta-cell line, INS1E, did

not have the same response to glucose, they were made to artificially overproduce PGIS, which then significantly increased insulin production and secretion in response to nutritional cues. The prostacyclin analog iloprost, also used in other studies to mitigate pulmonary fibrosis [36], induced insulin secretion in parental INS1E cells, and the IP (prostacyclin) receptor antagonist CAY10441 attenuated the response in the PGIS over expressing transfectants. In addition to the IP receptor, it was determined that Epac2, a protein responsive to cAMP and present in exocytic machinery as a guanine nucleotide exchange factor (GEF), was also required for the observed effects [37]. Interestingly, in another study, palmitate was shown to induce autophagy and cell death in the same INS1E cell line as well as in isolated rat and human islet cells [38].

In a meta-analysis to determine the association of Omega-3 fatty acids and type II diabetes, Wu et al. concluded that regular intake levels were neither harmful nor helpful and that alphalinoleic acid was associated with “nonsignificant trends toward lower risk” [39]. A group looking at the cardioprotective effects of pioglitazone in diabetic patients, found that, like aspirin, it elevated the pro-resolving lipoxin metabolite of the omega 6 arachidonic acid, 15-epi-lipoxin A(4) (15-epi-LXA(4)) [40,41]. Clearly more research into specific effects of lipid mediators in diabetes phenotypes is warranted.

Cardiovascular studies—Similar questions have arisen with regard to efficacy of n-3 long chain polyunsaturated fatty acids (LCPUFA) in cardiovascular disease. However, the disparate study results on the beneficial effects of omega 3 on arrhythmia were recently reconciled by proposing that they serve as an “upstream therapy” by suppressing cell damage responses to inflammation, apoptosis, ischemia, *etc*., that is to say that they impart their benefits by preventing pathological structural remodeling of cardiac tissue particularly when applied during early stages of disease [42,43].

A recent study by Khairallah et al. has demonstrated that DHA supplementation increases overall mitochondrial n-3 PUFA content and dramatically alters mitochondrial cardiolipin, a tetraacyl phospholipid that is required to form the junctions between inner and outer mitochondrial membranes [44,45]. In general, depletion of total cardiac mitochondrial cardiolipin, and reduction of the tetralinoleoyl cardiolipin (L_4CL) that makes up 60–80% of the cardiac mitochondrial cardiolipin pool, is associated with cardiac pathologies. Moreover, mitochondrial dysfunction overall has diverse repercussions and is known to impact diabetes and neurodegeneration in addition to heart failure (reviewed in [45]).

The findings by Stanley et al. that fish oil supplementation could prevent cardiomyocyte apoptosis in a rat model of chronic aortic hypertension led the investigators to uncover a link between DHA and the *mitochondrial permeability transition pore* (*MPTP*) [46]. Specifically it was determined that moderate DHA supplementation delayed Ca^{2+}-induced opening of the pore, which is significant as opening of the MPTP leads to a permeability transition that results in depolarization and cell death [46]. Therefore, the contribution of mitochondrial dysfunction to cardiac pathologies may be mitigated by DHA-mediated membrane remodeling. In the clinic, administration of 0.9–3.6 g/d of DHA + EPA to heart failure patients lessened hospitalization and mortality as well as improved left ventricular function [46]. It is known that increased uptake of DHA and EPA decreases inflammatory mediators

in the lipid pathways, reduces pro-inflammatory cytokine gene expression, and elevates beneficial resolvins and eicosanoids such as PGE3 and LTB5, for example. An additional potential benefit stems from elevation of the less cytotoxic peroxidation products from the long chain n-3 PUFAs, such as 4-hydroxy-2-hexanal (HHE), in comparison to those generated from n-6 PUFAs, such as 4-hydroxy-2-nonenal (HNE), which has deleterious effects on mitochondria and is also associated with left ventricular function [46]. The complexity and impact of dietary ratios of beneficial fats to carbohydrates in relation to healthy versus unhealthy weight, and the role of these ratios in cardiovascular disease onset or progression is an area actively being investigated [46].

Nevertheless, despite the numerous benefits of targeting the eicosanoids in cardiovascular diseases, there are significant consequences to global disruption of the physiological yin and yan, and specific targeting of individual components on the lipid continuum such as the lipid receptors or lipid enzymes would be more desirable. This has been covered in an excellent review by Capra et al. [47].

Critical care—In critically ill patients, such as those with sepsis, elevated circulating PLA2 can predict the risk of acute respiratory distress syndrome (ARDS), and it has long been recognized that modulation of systemic inflammatory response syndrome (SIRS) by targeting the lipid continuum could benefit critical care medicine [48,49]. In clinical trials, enteral administration of EPA and gamma-linolenic acid (GLA) could prevent progression to sepsis [50]. However, others reported that this regimen did more harm and could not be recommended for treating the critically ill patient [51]. In the pediatric setting, as reported by Shimizu, alprostadil (PGE1) and dinosprostone (PGE2) are used to treat primary pulmonary hypertension as well as ductus-dependent congenital heart disease. Similarly, misoprostol has improved juvenile rheumatoid arthritis and has been used to stave-off NSAID and corticosteroid damage to the gut in children [52]. For premature infants with hypoxemic respiratory failure due to respiratory syncytial virus (RSV) pneumonia, it is the inhalation of PGI2 together with high frequency oscillatory ventilation that improves clinical outcome [53]. Thus lipids continue to be utilized in novel critical care treatments.

Fibrosis and kidney disease—Epithelial to mesenchymal transition (EMT) occurs in both normal biology, as in development and response to injury, and pathobiology, as in cancer and organ fibrosis and is classified according to context [54]. Tissue and organ fibrosis are currently being debated as a form of EMT (reviewed in [55]). EMT onset and regulation is governed by numerous factors such as growth factors, reactive oxygen species, epigenetic factors, and relay of mechanosensory information [56,57]. As an aside, the mechanosensory stimulation of PGE2 production by low-intensity pulsed ultrasound (LIPU) has been demonstrated to induce cell differentiation albeit in osteoblasts through osteocytes, which leaves open the possibility of modulating EMT phenotypes in the future [58]. Currently though, diseases such as systemic sclerosis (SSc) and idiopathic pulmonary fibrosis (IPF) are still an enigma and remain difficult to treat [59]. Interstitial fibrosis in end-stage renal failure has also been correlated with EMT phenotypes [57]. Increasingly, lipid mediators are being substantively implicated in fibrosis and are currently the targets of emerging therapies (reviewed in [59]). In a study out of Italy, EPA and DHA were

demonstrated to counter the kind of inflammation and extracellular matrix (ECM) accumulation seen in renal disease [60]. Meanwhile, several animal models have demonstrated that renal proximal tubule inflammation and dysfunction in diabetic nephropathy could be linked to altered levels of cannabinoid receptors, where for example AM251, a CB1 receptor agonist, ameliorated albuminuria and CB2 receptor agonists such as AM1241 could reduce monocyte chemoattractant protein MCP-1 as well as chemokine (C-C motif) receptor 2 (CCR2) (reviewed in [61]). In another report of the antifibrotic effects of lipid mediators, dihydrosphingosine-1-phosphate (dhS1P) was shown to affect scleroderma fibroblasts through its up regulation of phosphatase and tensin homolog (PTEN), and normalization of proteases and transcription factors [62].

Neurobiology—Lipid mediators are associated with traumatic brain injury, cerebral ischemia, subarachnoid hemorrhage, and exicitotoxic injury. Numerous diseases including epilepsy, Alzheimer's, amyotrophic lateral sclerosis, Parkinson, and Creutzfeldt-Jakob disease have some form of underlying component along the lipid continuum [63,64]. Arachidonic acid metabolites are implicated in affective disorders, where studies have shown a clear benefit associated with omega 3 fatty acid consumption [65,66], and neuroprotectin D1 (NPD1; 10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15E,19Z hexaenoic acid), the 15-LOX product of DHA, effectively improves lipid bilayer properties, reduces apoptosis, and down regulates inflammation to positively impact many neurological diseases [67]. Furthermore, omega 3 fatty acids also protect against long term injury from neonatal hypoxicischemic brain injury [68], perhaps also through the actions of resolvins. A competitive inhibitor of the COX enzymes and 5-LOX called licofelone is able to abate symptoms of Huntington's disease in a mouse model, and may prove useful in the treatment of Alzheimer's disease as well, as a recent study has demonstrated that transfer of the 5-LOX gene to mice worsened their Alzheimer's phenotypes [69,70]. Simultaneous inhibition of the COX enzymes and 5-LOX with licofelone appears to improve drug delivery of riluzole in spinal cord injuries by lowering the efflux drug transporter P-glycoprotein (abcb1), which is upregulated in many cancers as well [71]. However, in Alzheimer's β-amyloid itself can down regulate Abcb1 at the blood brain barrier to exacerbate the condition [72], which again speaks to the balance that pharmaceutical targeting of lipid mediators must achieve.

Arthritis—Proresolving lipid mediators have been steadily developed alongside synthetic anti-rheumatic drugs to target rheumatic diseases with success, though side effects have sidelined some prominent drugs [73–77]. A new lipidomics study has begun to identify and profile those natural products within synovial fluids of rheumatoid arthritis patients that could be targeted for further development in treatment including the maresins, the D-series resolvins, and lipoxins [78]. Conceptually the high density lipoproteins (HDL), like resolvins, are protective and anti-inflammatory, and part of their function is to prevent the oxidation of low density lipoprotein (LDL). However, in an acute phase response, they become pro-inflammatory (pi-HDL), and should the acute phase become chronic then diseases associated with chronic inflammation such as arthritis develop [79]. As oxidized LDL has also been found in synovial fluid, and LDL are seeded with metabolites of linoleic

and arachidonic acids, it will be interesting to see what crosstalk occurs between the pro-resolving fatty acid derivatives and the pi-HDL or oxidized LDL [40].

Cancer—Studies to modulate the lipid continuum have been most concentrated in an effort to impact cancer in all its forms and permutations. The use of natural lipids has many benefits not the least of which is patient acceptability. The usefulness of nutritional agents and their derivatives has repeatedly been borne out in their impact on a diverse array of cancers including colorectal cancers as well as breast cancer [80,81]. In a newly published breast cancer study, it was determined that colony stimulating factor 1 (CSF1) could be suppressed by the effects of fish oil induced elevation of PTEN levels mediated by the reduced expression of the microRNA miR21 [82]. Another study has suggested that omega 3 consumption would counter the potential for breast cancer invasion by progestin hormone replacement therapy [83]. On the flip side where estrogen depletion is desired, there are a host of issues associated with antiestrogen therapy with agents such as Tamoxifen and Raloxifene. Aside from the fact that they do not prevent the expansion of estrogen receptor negative breast cancer, they can also cause thromboembolism [84]. Therefore studies are underway to determine if Raloxifene in combination with an omega 3 regimen, like Lovaza could be of some benefit. More promise for the benefit of omega 3 in skewing the lipid continuum comes from a recent study that suggested it may ameliorate the debilitating side-effects of peripheral neuropathy associated with paclitaxel therapy [85].

Just as has been reported in animal models of prostate cancer, the administration of EPA and DHA can also attenuate the growth of pancreatic cells in a xenograft model of MIA-PaCa-2 and is even more effective in combination with inhibitors of autophagy [86]. In the same study, growth of both Capan 2 and MIA-PaCa-2 cells were attenuated by EPA and DHA through the activation of caspase-8 and production of reactive oxygen species (ROS).

Unfortunately, cancer cells are always evolving mechanisms to outsmart our best efforts, and a fatty acid binding protein (FABP) has just been described in triple negative breast cancer that is associated with poor prognosis. When bound to DHA, FABP7 can stimulate the retinoid-activated nuclear receptor, RXRbeta, to promote transcription and cell survival [87]. Therefore, despite the growing arsenal of lipid mediators used to attack cancer, there is still a need to evaluate combinatorial therapies and to explore new sources of therapeutic molecules. Ultimately though, such strategies together with the anti-inflammatory, or pro-resolving, lipid mediators may soon finally force recalcitrant cancers, such as those of the pancreas and colon, to meet their match [88,89].

3. Targeting lipid pathways

The therapeutic use of lipids is coming into its own. However, there are plenty of examples along the lipid continuum where lipids and their signaling pathways are the culprits of disease, and often these lipid systems are inter-related by means of shared regulatory nodes [90,91]. The ceramide pathway is involved in many patho/biological functions including cancer and metabolic syndrome to name a few [92,93]. The eicosanoids are culprits in asthma and allergic inflammation [94]. Likewise, they are intimately associated with carcinogenesis and metastasis and have been shown to regulate nearly every phenotype

associated with cancer and its progression, from angiogenesis to integrin modulation for adhesion, and endothelial cell retraction to tumor cell invasion [95]. Lipoxygenases have been the targets for development of many cancer chemopreventive inhibitors [96,97]. However, many additional enzymes along the lipid continuum can be targeted for pharmaceutical intervention, including those in the ceramide/sphingolipid as well as the endocannabinoid pathways [98,99].

Most lipid mediators initiate cell signals through either paracrine or autocrine mechanisms by binding to Rhodopsin-like seven-transmembrane G-protein coupled receptors (GPCR), and these too have been the focus of targeted therapeutic development [100]. As of 2010 there were five prostanoid receptors with an additional four subtypes, four leukotriene receptors, and eleven lysophospholipid receptors that include six lysophosphatidic acid and 5 sphingosine 1-phosphate receptors [101]. Additionally there are two cannabinoid receptors and the platelet activating receptor. The classic and currently accepted International Union of Pharmacology (IUPHAR) receptor names, according to class of lipid as well as the historical context of their discovery, as well as a phylogenetic study are summarized in succinct reviews by Howlett and Mizutani [101,102]. A number of receptors whose ligands were previously undefined, the so-called “orphan” receptors, have been paired with bioactive lipids [103,104]. Historically, thromboxane and the prostaglandins, which are both products of arachidonic acid metabolism by the COX enzyme, were the first bioactive lipids to have their receptors characterized, followed a decade later by the receptors for leukotrienes and lipoxins, which are arachidonic acid metabolites of the 5-LOX and 15-LOX enzymes respectively. Recently receptors for 12(S)-HETE and several autacoids, small molecules with short half lives similar to hormones that act near the site of synthesis, such as maresins, resolvins, protectins and lipoxins have been identified [16,103]. The receptor for 12(S)-HETE was identified as the orphan receptor GPR31 and christened 12-HETER1 [103]. Its expression and signaling activity was associated with prostate cancer progression and was demonstrated to be essential for cancer cell invasion in vitro.

In an unrelated study meant to determine the underlying mechanism of periventricular leukomalacia, linked to cerebral palsy in premature infants, 12-LOX enzymatic activity (leukocyte type) was determined to contribute to oligodendrocyte death in response to glutathione depletion [105]. This would suggest that attenuation of neuronal receptor isoforms of 12HETER1 identified in the prostate study would benefit oligodendrocytes by inhibiting cell death, whereas in prostate cancer, receptor inhibition would promote cell death. Furthermore, in a study of neuronal excitotoxicity from cerebral ischemia, several HETE isoforms, particularly 12(S)-HETE, could actually protect against AMPA receptor-mediated toxicity [106]. While the 15(S)-HETE and 5(S)-HETE isoforms also offered some protection, it is unlikely that they are acting through the same receptor. In diseases such as amyotrophic lateral sclerosis, epilepsy, and ischemia, direct targeting of the AMPA receptor function has not met with much success [107]. Therefore, in the future the novel 12(S)-HETE receptor may offer an attractive alternative target. These observations speak again to the lipid continuum where the yin and yan balance of lipid mediators and targeted therapy depends on context.

Endocannabinoid receptors

There are two known cannabinoid receptors, CB1 and CB2 [108]. However, suggestive evidence is accumulating in support of additional receptors such as in the endothelium as well as a novel isoform for analgesia [109]. GPR55 shares a mere 14–15% homology with either CB1 or CB2. However, it is responsive to cannabinoids as well as to lysophosphoinositol (LPI) and its crosstalk with CB1 and CB2 has been proposed based on pharmacological data. It is also upregulated in enteric epithelial cells and neurons in response to systemic inflammation and is being investigated for its role in the gastrointestinal tract, where it has also been associated with mechanoreceptors in the gut [110]. The CB1 antagonists SR141716A and AM251 have the opposite effect on, and apparently stimulate, GPR55, which may speak to the fact that the CB receptors are interacting with different downstream G-proteins than those interacting with GPR55, whose interaction with $G_{\alpha 13}$ predominates and activates RhoA and ROCK, leading ultimately to transcriptional activation. Additionally, it has been shown that GW405833, which is a CB2 ligand, can serve as an agonist of GPR55 and stimulate LPI signaling [111]. Because of the putative role of GPR55 in such diverse processes such as cancer, nociception, and insulin secretion, and its involvement in many organ systems, it is currently the focus of much attention in the lipid receptor field [110]. GPR55 clearly binds LPI, which has also been shown to be protective for cerebral ischemia and glutamate excitotoxicity in culture. Furthermore, GPR55 and its signaling pathway are involved in decidual tissue regression, angiogenesis, bone resorption (in addition to CB2 [112]), and cancer cell proliferation and migration, where elevated GPR55 has been correlated to poor prognosis in a number of cancers, and arachidonyl-LPI is elevated in the plasma and ascites of ovarian cancer patients compared to their healthy counterparts (reviewed in [113]). In light of the recent issues with the antagonists/inverse agonists of CB1, and their adverse effects such as nausea and psychiatric disturbances, such as were seen with rimonabant [114], GPR55 may offer an alternative or augmented route for therapies meant to target the endocannabinoid system.

Sphingosine 1-phosphate (S1P) receptors

S1P is the end product of a complex lipid pathway that originates at the plasma membrane with the release of sphingomyelin by sphingomyelinases followed by the action of ceramidases and ultimately the sphingosine kinase to produce the ligand for the S1P receptors [115]. The S1P receptors (S1P1-05, called previously Edg-1,3,5,6,8) represent another example of a lipid continuum that requires perfect balance. Their ligands are essential for endothelial health and vascular development. However, acute ligand excess can cause cardiac death (reviewed in [116]). S1P can also be found on HDL particles, and dependent on the receptor subtype present, can mediate numerous phenotypes including cancer-associated angiogenesis, proliferation and stem cell migration, as well as oligodendrocyte progenitor and immune cell migration [117–119]. The S1P3 receptor has been associated with a worsening of sepsis, and can potentiate epidermal growth factor receptor (EGFR)-mediated cancer phenotypes in lung cancer cells [116,120]. Reportedly, the first antagonizing antibody of a lipid-activated receptor was developed for S1P3 that shows therapeutic promise for treating sepsis and breast cancer progression [117]. S1P1 receptor antagonists have also been forthcoming,as the latest to be developed show promise

in treating autoimmune inflammation such as in multiple sclerosis (reviewed in [119]). Other lysophospholipid receptors have been reviewed nicely by Ishii et al. [121].

The S1P1 receptor structure has just been resolved [122]. Moreover, the recognition of lipid receptors as therapeutic targets has given rise to intensive comparative modeling of these challenging membrane bound receptors, where careful selection of the template on which to model can give insight into the development of antagonists [123]. Likewise, the exciting development of new infrared (IR) probes that are genetically encoded is enabling us to track receptor activation [124].

Others

The prostanoid and thromboxane receptors as druggable targets are the subject of nice reviews by Anderson and Kontogiorgis [125,126]. Likewise the cognate nuclear lipid GPCRs can be found described by Marrache et al. [127].

3.1. Natural products

Natural products have been interrogated for use in anti-cancer therapies as well as in cancer prevention [128]. It has been appreciated for some time that flavonoids modulate lipid mediators [129–131]. They continue to inspire drug design as new inhibitors of the lipid pathways as well as antimicrobials are discovered [132–135].

3.1.1. Flavonoids—Baicalin, a glucuronide of Baicalein (12-LOX inhibitor), is a flavonoid out of Asian herbals that is known for its anti-inflammatory properties. It has been reported to prevent differentiation of Th17 cells, which are a $CD4^+$ T helper (Th) subset that is currently the subject of intense study for their role in immunity and inflammation [136–138]. Differentiation of Treg and Th17 cells is reciprocally regulated by TGFβ and accessory cytokines through differentially utilized transcriptional regulators such as the Forkhead family transcription factor (Foxp3), the Retinoic Acid-related Orphan Receptor (RORgammaT), as well as the Aryl Hydrocarbon Receptor (AHR), which is best known for regulating gene expression in response to environmental contaminants but is also stimulated by non-toxic endogenous ligands [137,139–141]. The latter receptor appears to harbor a promiscuous ligand binding site insomuch as it binds numerous synthetic and natural ligands including the flavonoids and lipid products. Both lipoxin A4 and prostaglandin G_2 are AHR ligands that lead to AHR-dependent gene expression including, CYP1A1 (Cytochrome P4501A1), prostaglandin endoperoxide H synthase 2 (COX2), murine epiregulin (EREG), and multidrug resistance genes such as MDR1 and BRCP (breast cancer resistance protein) [142,143].

Th17 cells are implicated in numerous pathological and physiological processes including rheumatoid arthritis, immune tolerance, mucosal infections and allergy, and tumor cell microenvironment (Reviewed in [140,144,145] and references therein). Th17 cells have also been invoked as a link between inflammatory bowel diseases and preterm birth [146], but their role in cancer is unclear [147]. A study of Th17 cells and their associated cytokines in pancreatic cancer by He et al., found that Th17 cells were in greater abundance in the circulation of cancer patients versus healthy individuals [148]. Likewise, Th17 cells were

positively correlated with microvessel density and were more abundant in lymph node metastases and cancer tissues, particularly Stage III and IV, than in neighboring normal tissue. While there was no apparent association of Th17 cells with histological grade, age or gender, specific cytokines from this Th subset were reportedly higher in patients with poorer prognosis [148]. Interestingly, although Th17 cells were associated more with breast cancer than with healthy tissue, the study by Yang et al. reported a negative association between Th17 numbers and stage, lymph node metastases, and blood vessel invasion, and suggested that the increased presence of Th17 cells in breast cancer was indicative of a favorable prognosis [149]. In the future it may be determined that the balance between Treg, the regulatory T cells, and Th17 cells in relation to lipid mediators is the reason for such disparate results.

As with Baicalin, the catechin of green tea, epigallocatechin-3-gallate (EGCG) also impedes Th17 differentiation, regardless of whether they are induced under normally polarizing stimuli such as TGF-β +IL-6, or through combinations of IL-6 or IL-23 with IL-1β [150]. EGCG down regulated phosphorylated STAT3, which resulted in reduced levels of RORgammaT, a transcription factor necessary for Th-17 development. In their model of autoimmune encephalomyelitis (EAE), Wang et al. likewise showed that EGCG could lower circulating IL6 as well as the soluble form of the IL6 receptor [150].

With regard to other cancers and cancer-related phenotypes, in HepG2 hepatocellular carcinoma cells EGCG suppresses PGE2 secretion as well as EP1 prostanoid receptor levels. Moreover, HepG2 viability and motility in response to either PGE2 or ONO-DI-004, an EP1 receptor agonist, was also inhibited by addition of EGCG [151]. It should be noted that PGE2 can promote Th17 differentiation through EP2 receptor activation, which suggests that additional targets of EGCG may be forthcoming (reviewed in [152]).

EGCG has anti-thrombotic activity in that it can inhibit release of AA as well as AA-induced platelet aggregation [151]. Coadministration of EGCG with photodynamic therapy (PDT) in a mouse mammary tumor model was determined to increase responsiveness to therapy by reducing PDT-induced PGE2 and promoting apoptosis through attenuation of both GRP-78 and survivin [153].

The soy isoflavones have also featured in recent prostate cancer studies where it was determined that they could be used to sensitize cancer cells to radiotherapy, and in a porcine model they were shown to affect lipid metabolism in adipose, liver, and skeletal muscle through their activity on adipokines and myokines [154,155]. The effect of lipid mediators on adipocyte function and metabolic syndrome is another area that is rapidly expanding in lipidomics [156].

3.1.2. Others—Scientific literature is rich with compelling examples, as presented by Wallace in 2002, of why lipid mediators should be at the forefront when considering complementary cancer therapies [157]. Nutritional pharmaceuticals or *nutraceuticals* continue to be developed as we collectively gain a greater appreciation for the wisdom of ancient ways. Curcumin, a compound derived from the spice turmeric, has been the subject of many studies and the source of emerging drugs that target bioactive lipid pathways. It is

an anti-inflammatory agent and can sensitize existing chemotherapies. This synergism is likely due to its concomitant effect on both COX and LOX enzymes as well as cPLA2 phosphorylation, which has been described [158–160]. While curcumin can be consumed in great quantity without adverse effect, its bioavailability is limited [161]. In a study meant to address the underlying mechanisms of colon cancer resistance to chemotherapy, a synthetic analogue of curcumin (known as 3, 4-difluorobenzo curcumin or CDF) in synergy with 5-fluorouracil and oxaliplatin (5-FU + Ox) dramatically inhibited the growth of chemo-resistant cells including CD44 positive stem cells [162]. In the latest effort to improve bioavailability, a curcumin-cyclodextrin conjugate was tested for its efficacy in reducing lung tumor burden in an orthotopic mouse model with some success [163]. Additionally, this conjugated form potentiated the effect of Gemcitabine, a nucleoside analog used for chemotherapy of a number of cancers. The IC_{50} of CDF in cultured cells was also improved with cyclodextrin. When tested in a mouse model this combination resulted in the pancreas having tenfold more CDF over serum concentrations [164]. While the relatedness of the following observations remains to be determined, it is noteworthy that CDF regulates the tumor suppressive microRNAs miR34a/miR34c, and that a regulatory binding site for these microRNAs, which are actually elevated in a model of hepatic fibrosis, was identified in the gene for acyl-CoA synthetase long-chain family member 1 (ACSL1) [165,166]. Furthermore, a study of palmitate-induced pancreatic β-cell dysfunction, found that miR34a modulated VAMP2, a protein on secretory vesicles involved in insulin secretion [167]. The apparent disparate functions of miR34 likely reflect tissue-based differences of gene expression perhaps related to bioactive lipid pathways. Curcumin and its derivatives appear to be viable therapeutics in the treatment of cancer, and have the additional benefit of serving as useful tools for studying several disease states that may fall under the regulation of curcumin-responsive microRNAs in relation to lipid mediators. Synthetic curcuminoids have been identified through protein modeling studies of known LOX enzyme structures in combination with biochemical assays [168]. Using this approach, two such inhibitors were identified (E22C, E26C) that successfully inhibited endothelial sprout formation, an early step in angiogenesis, in an in vitro assay with human umbilical vascular endothelial cells (HUVEC).

As a result of impaired AA mobilization, cPLA2α knockout mice are protected from metabolic syndrome, ischemic injury of the brain, and Alzheimer's, but have impairments with regard to implantation and parturition [9]. In an effort to knockout cPLA2 activity from a pharmacological standpoint, several curcumin analogs, identified as rosmarinic acid, tetrahydrocurcumin, dihydrocurcumin and hexahydrocurcumin, have been discovered that can inhibit the PLA2 hydrophobic binding pocket from binding substrate thereby preventing the release of AA and downstream metabolic events [169]. Extracts from the white oatmeal *Avena sativa* can also attenuate the stimulated mobilization of AA in keratinocytes, though not completely, through the reduction of PLA2 transcription and protein production [170]. Phlorotannins from the brown algae *Eisenia bicyclis* are also potent inhibitors of PLA2, albeit of the secretory type, and are even more effective in some instances at inhibiting LOX enzymes than EGCG [171].

3.2. Pharmaceuticals

In a search for additional drugs that could target lipoxygenases and protect against, for example, neurodegenerative diseases, an initial computer screen of compounds that could bind the 15-LOX active site was paired with a screen for inhibition of recombinant enzymatic activity. Then, using a cellular assay to screen 20 hits that were originally found from the virtual screen of 50,000 compounds, two novel lipoxygenase inhibitors were discovered, called LOXBlock-1, and −3, that could protect neuronal and oligodendroglial cells from oxidative stress-induced cell death [172].

The Cytochrome P450 enzymes add epoxides to arachidonic acid to generate epoxyeicosatrienoic acids or EETs, which are additional lipid mediators that have a role in inflammation and platelet aggregation, as well as cancer [173]. The soluble epoxide hydrolase, or sEH, in turn degrades the EETs into dihydroxyeicosatrienoic acids or DHETs, thereby attenuating EETs. Small molecule inhibitors of the sEH are currently in development for the treatment of chronic inflammation [174].

3.2.1. New agents—In 2012, several new, modified NSAIDs have been reported that have differing effects on the lipid pathways. Elkady et al. have developed membrane prostaglandin E synthase (mPGES1) and 5-LOX inhibitors that show no COX-1 inhibition [175]. This was done by modifying the carboxylic acid functional group to sulfonamide derivatives, where “lonazolac derivative 22” and “indomethacin derivative 17” were found to be the best at inhibiting mPGES1 and 5-LOX respectively.

Additionally, another class of modified NSAIDS in a new form of aspirin penned NOSH-aspirin for “nitric oxide- and hydrogen sulfide-releasing hybrid (compound NBS-1120) has been in the news for its extremely potent inhibition of mouse colon cancer xenografts in vivo, in addition to its attenuation of numerous other malignant cell types, including pancreatic, breast, lung, prostate and leukemic cells [176,177]. Derivatization such that nitric oxide and hydrogen sulfide are released, has the dual benefit of protecting against the gastric side-effects as well as potently killing cancer cells by apoptosis and attenuating cell cycle progression. Whereas the indomethacin and lonazolac derivatives of the former aspirin compound did not impact COX1, the NOSH aspirin did. The impact of these drugs on the lipid continuum with regard to other mediators such as the lipoxins will be of great interest.

3.2.2. Manufacturing of therapeutic lipids—The creative use of natural systems such as single cell green algae to successfully manufacture fully functional antibodies was described nearly a decade ago and pharmaceutical production of proteins in algae continues to expand [178,179]. Similarly, the study of lipid production in algae from the field of aquaculture has led to novel insight and the potential for scale-up production of therapeutic lipids in addition to alternative energy lipids [180– 182]. Cross-discipline studies have led to the identification of novel lipid enzymes such as elongases and destaturases in eukaryotic algae that can be directly exploited for DHA production [183,184]. Organic extracts of microalgae have potential antioxidant and antiproliferative effects, and contain antineoplastic lipids, including glyco- and phospholipids, from brown and red algae, which have been determined to impact Meth-A fibrosarcoma [185–189]. Endogenous lipids from

marine algae have proven to be useful antineoplastic agents as well. The EPA fraction of diethyl ether extracts of the diatom *Cocconeis scutellum* reportedly attenuated BT2 breast cancer cells, and marine derived EPA and DHA have been shown to sensitize animal tumor models to numerous cancer drugs, an observation that is being supported in various phase II and III clinical trials [190,191]. The commercial use of microalgae in the development of therapeutic lipids is a burgeoning area of development [192,193]. Additionally, and as an alternative to microalgae, the budding yeast *Saccharomyces cerevisiae* has the capacity to produce lipids of pharmaceutical interest whose production can be monitored at the single cell level by another technology coming into the lipidomics field; Coherent Anti-Stokes Raman Spectroscopy or CARS [194] (described in Section 4.2 of this review).

3.3. Applications (single and multi target)

The term rheostat has been used frequently in the lipidomics field to refer to the yin and yan of lipid activities along the continuum where the balance in the lipid signaling pathways may dictate health or disease progression. The diversity of lipid signaling pathways that can be targeted by lipids and novel drugs to impact diseases is offering a wealth of therapeutic possibilities that is increasingly recognized and being developed in both academia and by pharmaceutical companies alike, as both single and multi-targeted, synergistic therapies continue to be explored.

3.3.1. Single target (lipid centered)—Co-administration of the arachidonic acid metabolite 12-HETE with NSAIDs and opioids has been shown to reduce reperfusion injury. Recently the drug Fingolimod (FTY-720), which is an S1P1 antagonist that has been approved for treatment of multiple sclerosis, was shown to be effective as well [195,196]. While it did not afford protection against glutamate excitotoxicity, it did reduce infarct size. Incidentally, FTY-720 has also been used in animal models of fibrosis (reviewed in [59]).

Regardless of context be it sepsis or cancer, and regardless of where the lipid continuum is targeted either at the level of enzymes, lipid products, or receptors, clearly lipid mediators are leading us into new therapeutic avenues.

3.3.2. Multi-target (synergism of lipid therapy with existing chemotherapy)—A prime example of our knowledge gap with regard to the synergistic effects of targeting the lipid enzymes was revealed with the advent of COX inhibition [197]. As another recent study demonstrated, Celecoxib, a COX-2 inhibitor was found to cause off-target effects that led to increased amphiregulin (AREG) expression by myofibroblasts and subsequent stimulation of the EGFR. The study found that while Celecoxib was able to stave-off new adenomas, patients who were treated with the drug did not experience a reduced incidence of colon cancer, and in fact saw a greater incidence of adenomas which were more aggressive within 2 years [198]. While the desired benefit may be ultimately achieved by targeting the growth factor pathways in combination with COX-2, it nevertheless illustrates the need for alternate strategies. Using a different approach, Lim et al. demonstrated that administration of DHA in combination with Sulindac sulfide did suppress growth of human colon cancer xenografts, and this was through the death receptor (DR)5-dependent extrinsic apoptotic pathway [199]. DHA has also been shown to synergize with the effects of

clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) against tumor cells in a PPARalpha-dependent mechanism to affect a lower IC_{50} of clioquinol. The effect was attributed to the attenuation of NF-κB and prosurvival molecules such as Bcl-2, Akt and p65 [200]. Subsequently DHA was shown to target SOD1 in a PPARalpha dependent manner [201]. DHA also synergizes with and enhances curcumin activity against breast cancer cell proliferation [158].

Tumor cell-induced platelet aggregation (TCIPA) is a recognized process involving crosstalk between the two cell types in their microenvironment, whereby lipid metabolism of the platelets can induce integrin upregulation of tumor cells and promote tumor cell metastasis [202,203]. Rao et al. have demonstrated that DHA can inhibit platelet AA metabolism by COX into the bioactive thromboxane A2, resulting in less platelet aggregation [204]. After nearly three decades of research, thromboxane inhibitors are still actively being developed for a host of other diseases impacted by COX activity including lupus nephritis, asthma, and septic shock to name a few, and many are used in a combinatorial approach to restore the yin and yan along the lipid continuum [126,205].

As another example of the pleiotropic effects wrought by some of the lipid mediators, the enzyme 12-LOX from the lipoxygenase pathway produces a metabolic product from arachidonic acid called 12(S)-HETE that is clearly linked with much pathology (Table 1). It is known to stimulate angiogenesis in tumors as well as induce metastasis, and it can lead to TCIPA [202,206–209]. However, there is evidence that it could be therapeutic as well. In the context of wound healing, 12(S)-HETE is known to be a mitogen for endothelial cells and inhibition of the 12-LOX enzyme with BMD122 (formerly called BHPP; N-benzyl-N-hydroxy-5-phenylpentamide) prevents injured endothelial cell monolayers from responding to serum-induced repair [210]. Another potential benefit from 12(S)-HETE is implied by the results from a study meant to evaluate the cardioprotective effects of concomitant administration of NSAIDS with opioids [211]. Administration of 12(S)-HETE prior to reperfusion appeared to reduce infarct size. When 12(S)-HETE production was inhibited by the 12-LOX enzyme inhibitor baicalein, prior to the coadministration of ibuprofen and morphine, the protective effects of the NSAID-opioid combination were lost.

Synergism between lipid pathways and chemotherapies has been studied in other models too. In a model of acute lymphoblastic leukemia, manipulation of the sphingolipid pathway could overcome cell resistance to the retinoid 4HPR N-(4-hydroxyphenyl)retinamide (4-HPR, fenretinide) [212], and ceramide has been proposed to drive resistance to doxorubicin [213]. Decursin, which is a putative anti-cancer coumarin out of the roots of the Korean *Angelica gigas* was determined to induce cell death in myeloid leukemia cells through its inhibition of COX2-dependent expression of survivin protein [214]. These data suggest there could be additional targets in lipid pathways that could provide a beneficial synergism with existing pharmaceutical applications. For years studies have been reporting on lipid pathways being modulated in combination as a means to therapy and a sample of recent studies are listed in Table 2. While there are numerous reports on the efficacy of modulating lipid mediators in tandem with standard chemotherapy, there does not appear to be a standard that correlates the class of pharmaceutical, e.g. microtubule inhibitors, with the

lipid pathway most likely to impact it. Systems biology may eventually allow us to establish such correlations.

4. Lipidomic methodologies

With the advent of “omics” technologies, proteomics and genomics have advanced at breakneck speeds and are performed routinely at many institutions. However, after decades of ground-breaking lipid research, the field of lipidomics is also having a major impact on numerous basic and clinical disciplines. Therefore, a brief overview of methodologies to study lipids is presented here in the context of their applications.

The tools and techniques commonly applied to the study of proteins such as chemical probes or antibody-based assays are currently available and are actively being developed for lipidomics [215,216]. Likewise, molecular sensors have been described recently for in situ quantitative imaging of cellular lipids, where lipid binding motifs from lipid receptors are repurposed as they are engineered together with inducible fluorophores to yield reporters of spatio-temporal signals on binding of the lipid ligand [217]. The translation of this technology to interrogate lipid mediators in general will become possible as more lipid receptor binding sites are described. Other technologies are described below.

4.1. LC–MS

Liquid chromatography–mass spectrometry (LC–MS), coupled with electrospray ionization techniques, is most commonly used in lipidomics [218–220]. The basic principle couples liquid phase separation with spectroscopy, which allows for quick and precise separation, identification and quantitative analyses of lipid species by providing size, sequence, and structural information.

Lipids present in biological fluids such as urine have been analyzed by separation and spectroscopy methods to evaluate disease states such as essential hypertension and prostatic diseases including prostate cancer [221–223]. Further application of the method has been extended recently to an LC–MS/MS screen for lipids and lipid mediators of synovial fluid from rheumatoid arthritis patients where the profiles of various inflammatory mediators and resolvins have been reported [78]. While LC–MS is routinely used for discovery and/or quantitative lipidomics of biological fluids, it has been proposed that use of these methods could discover regulatory lipids in breath aerosols that could be predictive of pulmonary pathobiology [224,225]. The use of breath aerosols to test for bioactive lipids is being applied to study conditions such as *aspirin-exacerbated respiratory disease* (AERD), where high baseline levels of 15(S)-HETE are associated with aspirin sensitivity and activate the TRPV1 cough receptor [226– 228]. These methods are also being applied to study exercise induced asthma brought on by inflammatory lipid mediators [229]. The use of LC–MS on breath condensates could also be reapplied to earlier studies such as those on the effects of ozone injury to airway epithelial cells at an early phase [230] as well as to detection of lung cancer, whose feasibility was reported using gas chromatography coupled with mass spectroscopy [231].

Mass spectroscopy is the most commonly used tool to study lipids. However, as biophysics and bioengineering blend with lipidomics, terms such as Raman spectroscopy as well as Coherent anti-Stokes Raman Spectroscopy (CARS) are entering the lipidomics parlance. These techniques are powerful for their ability to enable label-free study of molecules in three dimensions [232,233].

4.2. Raman spectroscopy

One of the perceived drawbacks of LC–MS is that by nature it cannot give spatial information about lipids in defined cellular compartments and relies on bulk or fractionated analyses of extracted lipids [234]. While matrix-assisted laser desorption/ ionization (MALDI) can give spatial information and identify precise molecular compositions of large biomolecules, the equipment is more expensive than for Raman and it requires some initial processing such as pre-coating of the samples with crystal matrix material. The analysis also tends to destroy the tissue. The following references offer an excellent accounting of the process either alone or in combination with imaging modalities [235–237].

Raman spectroscopy (RS) is an optical technique that exploits inherent differences between the vibration frequencies of molecules in response to laser excitation and the consequent effect on inelastic light scattering to generate unique spectra or “fingerprints” for individual molecules. One of the most exciting adaptations of RS has been the use of *intrinsic* RS spectra to profile biological samples in vitro and in vivo. This type of *label-free*, pattern profiling from spontaneous Raman scattering can reflect cell-specific protein, lipid and phosphate content, and can even reveal intracellular distribution of metabolites. There are numerous permutations of RS, including Tip-enhanced RS for optical spectroscopy on a nano-scale (TERS), Coherent anti-Stokes RS for overcoming fluorescence interference of basic RS and increasing resolution (CARS), and Resonance RS for polypeptide analysis. Raman scattering can be amplified (e.g., Stimulated Raman Scattering-SRS), which can facilitate in vivo imaging at speeds approaching real time [238]. Utility of the method has been demonstrated in a variety of applications, but particularly in cancer studies [239]. Raman spectroscopy overcomes the need for label that could interfere with lipid packing, and can provide real time information on lipid accumulation and metabolism throughout a living cell over brief or extended time courses [240]. To examine the compartmentalization of EPA after uptake into living cells, spontaneous Raman spectra were generated for DHA, EPA, AA and OA (oleic acid), which have 6, 5, 4 and 1 C=C bond(s) respectively. The Raman shift for the unsaturated fatty acids was mapped to a band at 3015 cm^{-1}, where the peak intensities are roughly proportional to the amount of unsaturation in the lipids, so that the tallest peak at 3015 cm^{-1} is DHA and the lowest is OA. After incubating A549 human lung carcinoma cells in EPA, cells were profiled and subcellular localization of EPA was found in lipid drops based on the peak height at 3015 cm^{-1} [241]. Another advantage to the method is the absence of photo damage on repeated imaging. Additional studies have used the technique to examine cholesterol and DHA in the outer segment of retinal rods, and to look at lipid distribution in *Caenorhabditis elegans* [242–244]. Direct label-free observation of these molecules in relation to the relative microenvironment without the need for biochemical or histochemical analyses is proving to be an exciting new tool in lipidomics [245]. Single-cell laser-trapping Raman spectroscopy has been used for lipid profiling in real

time of microalgae under varied growth conditions. Therefore, the technique will likely find additional applications in cell culture overall [238,246]. To that end, the Raman-generated spectra on autophagic cells was recently used to identify a reporter peak of phospholipids at 718 cm(−1) that appeared to reflect cellular autophagy on starvation [247].

Early neoplastic changes can be detected with RS, and malignancies can be discriminated from normal tissue based on the multiplexed RS spectral profiles [248–250]. The desired Raman scattering can be filtered from spectral background noise and fluorescence to generate cellular “fingerprints” that are unique and precise [234]. Algorithms that organize the comprehensive Raman spectrum, and that sort malignant and normal profiles through assignment by discriminant function analyses, already exist and have been applied, for example, to the analysis of human ductal carcinoma cells in a mouse model of human pancreatic cancer [251]. In addition to tissue analyses, biofluids such as serum appear to have potential spectral reporters of carcinoma as well with this methodology [252–254]. The technique was appreciated for its potential in medical applications more than a decade ago and has been steadily proving its value since then [255–257]. Raman spectra of neoplastic tissue are now actively being explored for novel cancer biomarkers [258]. Using Raman for optical biopsy, inflamed buccal mucosa has been profiled for oral cancers [259]. The applications have even found their way into dermatological research where Raman can report on the reaction of skin to cosmetics or therapeutic creams at a molecular level, including the packing of ceramides [260–262]. The source of tissue being imaged can be fresh or frozen and non-invasive measurements of tissue up to 50 mm have become possible with surface-enhanced RS (SERS) probes [263,264]. Theranostic SERS probes have also been developed that allow them to be used for both imaging and heat ablation [265]. With the arrival of near infrared receptor-targeted nanoprobes, the multimodal platform of Raman spectroscopy and microscopy is proving to be a powerful imaging combination whose application yields precise information in both time and space [266].

A multi-platform or “multi-modal” approach, where several technologies are bundled with Raman spectroscopy, can be used to examine tumor heterogeneity. For example, hypoxic regions can be visualized in breast solid tumor models using signatures of elevated lipid metabolism and other molecules that occur in response to hypoxia by using magnetic resonance (MR) imaging, MR spectroscopic imaging (MRSI), and optical imaging in combination [267]. Likewise, confocal Raman microscopy revealed that there are more lipid bodies (13.8%) in human colorectal adenocarcinoma Caco-2 cells than in the “normal” rat intestinal epithelial cell line IEC6 (1.8%). Furthermore, from the spectra of the two cell lines in comparison to reference standards, it was determined that lipid bodies in Caco-2 cells have a larger peak corresponding to arachidonic acid [268]. RS has been used in several breast cancer studies [248,269,270]. In the study by Brozek-Pluska et al., cancerous and non cancerous cells from the same patient were profiled for lipid content. The Raman spectra from the cancer cells were similar to the spectral profiles of gamma linolenic acid and arachidonic acid, a known precursor of procarcinogenic lipid metabolites, whereas the spectra from the normal tissue were comparable to those seen for oleic acid and omega 3 fatty acids. It should be noted though, that in the cancer cells the spectrum was dominated more by protein rather than lipid peaks as might be expected for cells that are actively growing.

The determination of lipid localization in addition to cellular lipid composition by Raman spectroscopy is proving to be valuable for studying such issues as cell polarity, which is an important factor in metastasis. The basal and apical sides of 3D-cultured breast acini were probed by Raman spectroscopy where it was found that lipids on the apical side were more ordered in comparison to the basal side. When polarity was disrupted by calcium chelation or by addition of arachidonic acid, which caused two tight junction proteins (ZO1 and ZO2) to move from the poles, the inverse order was observed [271]. Interestingly, in endothelial cells ZO1 is also mobilized by the activity of sphingosine-1-phosphate [272].

Defects in phosphatidylinositol processing are associated with dissolution of the primary cilium in response to serum, and inhibition of ceramide synthesis severely impairs cilium formation in Madin-Darby Canine Kidney (MDCK) cells but can be rescued by exogenous application of ceramide or ceramide analogs [273,274]. Centrosomes and primary cilia have been shown to be effective reporters of cell polarity, and the loss of the primary cilium appears to be associated with breast cancer [275–277]. Therefore, given the examples of Raman spectroscopy to study lipids in breast cancer, this would appear to be another novel application of the technology, i.e., linkage of lipids, cell organelles, polarity and cancer.

5. Conclusion

The *paths less traveled* along the lipid continuum are actively being paved by researchers in their quest for additional therapeutics targeted at diseases whose underlying culprit is lipid-mediated inflammation. New therapeutic targets have emerged as novel receptors are de-orphaned and paired with their lipid ligands or as the synergistic effects of lipids with existing chemotherapies are revealed through systems biology and proteo/ lipidomic approaches. Lipids are also being applied as therapeutic agents, as novel pathways that mitigate inflammation are mapped out and marine-enhanced sources are explored for new activities. The evolving convergence of basic and clinical science with biophysics and bioengineering has opened exploration into what lipids have to tell us regarding their place and function in such complex diseases such as cancer. On September 19, 2012 the United States House of Representatives passed the Recalcitrant Cancer Research Act (H.R. 733) in a unanimous vote. The goal of the National Cancer Institute under this bill is to identify major advances for prevention and treatment as well as detection and diagnosis of cancer. Lipidomics together with emerging spectroscopy methods will be leading the way.

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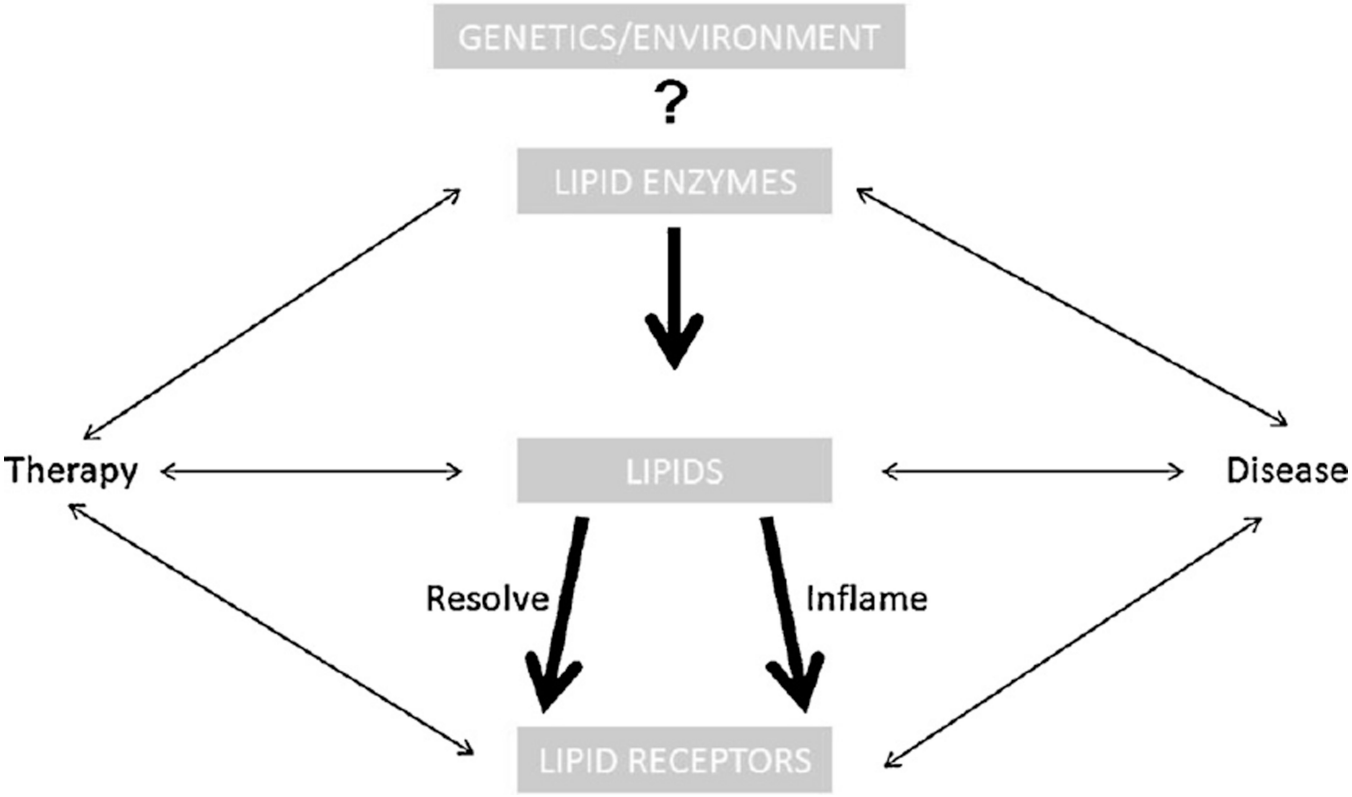

Fig. 1. The continuum of bioactive lipid pathways

Whether prostaglandins or resolvins bind lipid receptors in a therapeutic context, or HETE molecules interact with receptors to push cancer toward metastasis, there is evidence to support nearly every direction and sub circuit depicted on the schematic. Every major class of lipid enzymes has been determined to contribute in some form or other to disease progression and/or healing. Lipidomics, systems biology, and biophysics technologies are paving the paths between the mile markers established over decades of ground breaking work.

Recommended reading: Chemical Reviews, Special Issue: 2011 Lipid Biochemistry, Metabolism, and Signaling (October 2011) 111(10). ISSN 0009-2665 Useful sites:
http://www.lipidmaps.org/
http://www.lipidomicnet.org/index.php/Main_Page
http://en.wikipedia.org/wiki/Raman_spectroscopy)
http://en.wikipedia.org/wiki/Coherent_anti-Stokes_Raman_spectroscopy.

Table 1

Disease etiologies regulated by 12(S)-HETE and potentially 12-HETER1.

Cancer	**12(S)-HETE:pleiotropic effects: angiogenesis, cell proliferation,migration, invasion, endothelial cell retraction [95,278,279]
	13(S)-HODE: circadian regulation and cancer [280–282]
Zellweger spectrum of peroxisome biogenesis disorders (PBD-ZSD)	
	**impaired peroxisome fcn,cells unable to metabolize 12-HETE; blood, organ system metabolism affected, leads to damage of brain white matter [283,284]
Hypertension	**mediation of angiotensin II–induced intracellular calcium transients [223,285,286]
Atherosclerosis	**plaque formation [287,288]
Diabetes	**ischemic/proliferative retinopathy, human islet cell death [223,289–292]
Parkinson's	** Glutathione (GSH) depletion–related cell death [293,294]
Alzheimer's	** c-jun-dependent apoptosis pathway, regulates BACE proteolytic pathway [172,295–297]
Neurological functions	**modulates neural peptide secretion, LHRH, the target of chemical castration in PCa treatment, intermediates activate TRPV1 in sensory neurons [298–300]

Table 2

Studies on drug development and efficacy of co-modulation of lipid mediator pathways.

LOX(s)/COX-

- Effects of flavocoxid, a dual inhibitor of COX and 5-lipoxygenase enzymes, on benign prostatic hyperplasia PMID: 22471974
- Dual inhibition of 5-LOX and COX-2 suppresses esophageal squamous cell carcinoma PMID: 21652147
- Synthesis of celecoxib analogs that possess a N-hydroxypyrid-2(1H)one 5-lipoxygenase pharmacophore: biological evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity PMID:18945614
- Comparative protection against liver inflammation and fibrosis by a selective cyclooxygenase-2 inhibitor and a nonredox-type 5-lipoxygenase inhibitor PMID:17766677
- New approaches to the modulation of the cyclooxygenase-2 and 5-lipoxygenase pathways PMID:17305572
- Design, synthesis, and biological evaluation of (E)-3-(4-methanesulfonylphenyl)-2-(aryl)acrylic acids as dual inhibitors of cyclooxygenases and lipoxygenases PMID:16931030
- Dual inhibition of 5-LOX and COX-2 suppresses colon cancer formation promoted by cigarette smoke PMID:15637091
- Dual inhibition of cyclooxygenases-2 and 5-lipoxygenase by deoxypodophyllotoxin in mouse bone marrow-derived mast cells PMID:15187418
- Licofelone, a dual lipoxygenase-cyclooxygenase inhibitor, downregulates polymorphonuclear leukocyte and platelet function PMID:12393068
- Anti-inflammatory activity of a dual inhibitor of cyclooxygenase and lipoxygenase pathways, CBS-1108 (2-acetylthiophene-2-thiazolylhydrazone) PMID:3935121

LOX/TXA2S-

- In vitro effects of E3040, a dual inhibitor of 5-lipoxygenase and thromboxane A(2) synthetase, on eicosanoid production PMID: 11430933

COX/TPR-

- Cyclooxygenases, thromboxane, and atherosclerosis: plaque destabilization by cyclooxygenase-2 inhibition combined with thromboxane receptor antagonism PMID:15655126

Other combinations-

- C6-ceramide and targeted inhibition of acid ceramidase induce synergistic decreases in breast cancer cell growth PMID:21935601
- GDC-0941, a novel class I selective PI3K inhibitor, enhances the efficacy of docetaxel in human breast cancer models by increasing cell death in vitro and in vivo PMID:22586300
- Atorvastatin sensitizes human non-small cell lung carcinomas to carboplatin via suppression of AKT activation and upregulation of TIMP-1 PMID:22305890
- Inhibition of acid ceramidase by a 2-substituted aminoethanol amide synergistically sensitizes prostate cancer cells to N-(4-hydroxyphenyl) retinamide PMID:21557271
- Methyl jasmonate down-regulates survivin expression and sensitizes colon carcinoma cells towards TRAIL-induced cytotoxicity PMID:21486277
- S-adenosylhomocysteine hydrolase inhibition by 3-deazaneplanocin A analogues induces anti-cancer effects in breast cancer cell lines and synergy with both histone deacetylase and HER2 inhibition PMID:20556507
- Phase 2 trial of weekly intravenous 1,25 dihydroxy cholecalciferol (calcitriol) in combination with dexamethasone for castration-resistant prostate cancer PMID:20166215
- Drugs that target lipoxygenases and leukotrienes as emerging therapies for asthma and cancer PMID:15032639