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Regulation of Inflammation by Lipid Mediators in Oral Diseases

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Abstract

Lipid mediators (LM) of inflammation are a class of compounds derived from ω-3 and ω-6 fatty acids that play a wide role in modulating inflammatory responses. Some LM possess pro-inflammatory properties, while others possess pro-resolving characteristics, and the class switch from pro-inflammatory to pro-resolving is crucial for tissue homeostasis. In this article, we review the major classes of LM, focusing on their biosynthesis and signaling pathways, and their role in systemic and, especially, oral health and disease. We discuss the detection of these LM in various body fluids, focusing on diagnostic and therapeutic applications. We also present data showing gender-related differences in salivary LM levels in healthy controls, leading to a hypothesis on the etiology of inflammatory diseases, particularly, Sjögren's Syndrome. We conclude by enumerating open areas of research where further investigation of LM is likely to result in therapeutic and diagnostic advances.

Keywords

Resolvins; Lipoxins; Salivary Gland; Periodontal Disease; Oral Cancer

Introduction

Inflammation occurs following a challenge of host tissue by microorganisms, trauma, or other injuries (Gilroy and Lawrence, 2008). Following this challenge, pro-inflammatory signals are released to trigger key events such as recruitment of neutrophils from the blood to the site of the injury to clear microorganisms and cell debris through rapid phagocytosis and to release antimicrobial factors (Kolaczkowska and Kubes, 2013). Throughout this process, neutrophils undergo apoptosis and monocytes are recruited to clear the site of infection via lymphatic uptake (Ginhoux and Jung, 2014). This inflammatory stage bridges innate and adaptive immune responses, and leads to the recruitment of B- and T-cells (Lanier, 2013). All of these events result in the resolution of inflammation and restoration of tissue homeostasis (Serhan et al., 2008). Disruption of this process can lead to chronic inflammation, which is observed in autoimmune diseases (Tabas and Glass, 2013), and is thought to play a role in the development and tumor progression in cancer (Landskron et al., 2014). The onset and peak of inflammation is an active process controlled by several factors

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Conflict of Interest Statement

The authors declare no conflict of interest.

including cytokines and chemokines and recently, the resolution of inflammation has also been shown to be an active, rather than a passive, process (Buckley et al., 2013). For an in depth review of resolution, readers are encouraged to refer to the excellent reviews by Dr. Charles Serhan and colleagues (Serhan, 2014, Serhan et al., 2015a). Briefly, resolution of inflammation involves the cessation of polymorphonuclear leukocytes (PMNL) influx through the upregulation of PMNL apoptosis, restoration of normal cytokine gradients, and the clearance of cell debris by macrophages (Serhan, 2014, Serhan et al., 2015b, Basil and Levy, 2016).

One class of molecules that has been gaining prominence in relation to inflammation is the lipid mediators (LM) derived from polyunsaturated fatty acids (PUFA). PUFA are appreciated for their beneficial actions in the immune (Hubler and Kennedy, 2016), neural (Crupi et al., 2013, Bazinet and Layé, 2014, Hashimoto et al., 2014, Song et al., 2016) and cardiovascular systems (Dessì et al., 2013, Lorente-Cebrián et al., 2013, Nicholson et al., 2013, Colussi et al., 2014). Most notably, PUFA such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are precursors for the biosynthesis of a variety of LM (Tessaro et al., 2015). AA is an ω-6 PUFA that is generated from dietary linoleic acid through the successive actions of Δ6-desaturase, elongase and Δ5-desaturase (Astudillo et al., 2012) or from cellular phospholipids via cytosolic phospholipase 2 ($cLPA_2$) (Serini et al., 2009). EPA and DHA are ω-3 PUFA that can be generated in the body from α-linoleic acid via elongase and Δ5-desaturase (Neff et al., 2011), but the conversion rate is minute (Goyens et al., 2005), necessitating dietary intake of EPA and DHA. The major dietary source of EPA and DHA are marine animal oils (Tur et al., 2012), though recently algae oil has been identified as a vegetarian source of DHA (Lane et al., 2014). EPA and DHA have been shown to have direct anti-inflammatory properties through the inhibition of NLRP3 pathway (Zhou et al., 2011, Calder, 2013, Yan et al., 2013), and are transported to the site of inflammation via lipoproteins coinciding with edema generation (Kasuga et al., 2008). Omega-3 dietary supplementation has been investigated for the treatment of cardiovascular disease (Rizos et al., 2012), metabolic syndrome (Lorente-Cebrián et al., 2013), and depression (Lorente-Cebrián et al., 2013), among others. Interestingly, Omega-3 dietary supplementation has been investigated for the treatment of periodontitis in a variety of preclinical and clinical models (El-Sharkawy et al., 2010, Deore et al., 2014, Chee et al., 2016). More importantly, EPA and DHA are important substrates to produce pro-resolving LM, such as resolvins and protectins (Hong and Lu, 2013, Buckley et al., 2014, Spite et al., 2014), whose functions will be discussed in detail in the following sections. LM are generated via two major biosynthetic pathways, specifically, cyclooxygenase and lipoxygenase pathways. These pathways have been widely described in systemic diseases for over 30 years (Gwebu, 1979, Samuelson and Paoletti, 1982, Pace-Asciak and Granström, 1983), and have been investigated in conjunction with oral diseases (El Attar and Lin, 1983, Porteder et al., 1984, Mendieta et al., 1985, Williams et al., 1988, Offenbacher et al., 1989). Interestingly, many inflammatory systemic diseases are associated with increased incidence of oral diseases. For example, there is strong evidence of a link between periodontitis and atherosclerosis and other cardiovascular diseases (Dietrich et al., 2013, Loos et al., 2016), and between periodontitis and diabetes (Taylor et al., 1996, Hasturk and Kantarci, 2016). It has been suggested that some LM complicit in oral diseases are

potential risk factor markers of other systemic diseases (Bäck et al., 2007). This review seeks to provide an overview of the current state of the art regarding biosynthesis and functions of various LM. We also hope to provide clinical providers and researchers in the oral health field with a detailed account regarding the roles of pro-inflammatory and pro-resolving LM in both systemic and oral diseases. Additionally, we conclude by addressing some major questions, including the potential effects of gender differences on the progression of chronic inflammatory diseases, and future research directions regarding diagnostic and therapeutic potential of LM in oral health.

Lipid Mediators Involved In Inflammation

Several LM have been identified during a variety of physiological and pathological systemic conditions as well as in several oral diseases. This section will present the different LM, their synthetic pathways, receptors, and roles in both systemic and oral health and disease.

Leukotrienes

Leukotrienes are pro-inflammatory LM derived from AA, with a widespread role in the development of inflammation (Figure 1).

Biosynthesis—During inflammatory responses, intracellular Ca^{2+} concentration is increased, leading to translocation of 5-LOX into the nuclear membrane (Wong et al., 1991, Capra et al., 2015). In the presence of 5-lipoxygenase activating protein (FLAP) (Dixon et al., 1990), 5-LOX catalyzes the transformation of AA into 5-HPETE which is then transformed into Leukotriene A_4 (LTA_4). LTA_4 is an unstable intermediary, which is either hydrolyzed via leukotriene A_4-hydrolase into Leukotriene B_4 (LTB_4) (Andberg et al., 2013) or transformed via glutathione S-transferase into leukotriene C_4 (LTC_4) which undergoes sequential cleavage of glutamyl and glycine residue to progressively produce the more stable leukotriene D_4 (LTD_4) and leukotriene E_4 (LTE_4) (Saino et al., 2011). LTC_4, LTD_4, and LTE_4 will be collectively referred to as Cys-LT.

Signaling pathway—LTB_4 binds and activates one of two leukotriene receptors (BLT1 and BLT2), leading to increased cytosolic calcium concentrations driving calcium-activated signaling molecules (Yokomizo, 2014). While the exact BLT signaling mechanism is not well understood, it is thought to involve regulation of COX-2 mRNA production (Zhai et al., 2010). Other studies suggests that BLT activation results in increases in metalloproteinase expression (Bäck et al., 2007).

The Cys-LTs (*i.e.*, LTC_4, LTD_4 LTE_4), act on one of two cysteinyl leukotriene receptors (CYSLTR1 and CYSLTR2) (Kanaoka and Boyce, 2014). The exact downstream pathways of Cys-LTs are also unclear, but it is known that LTD_4 activates *c-kit* (Al Azzam et al., 2015), while LTE_4 activates PPARγ (Paruchuri et al., 2008). Cys-LT activity can be regulated with Protein Kinase C (Kondeti et al., 2013).

Role in systemic health and disease—Recent studies on the involvement of leukotrienes in prominent systemic diseases suggest some potential therapeutic approaches. As an example, BLT1 activation with LTB_4 inhibits TGF-β1 cell cycle arrest causing

dysregulation of cell proliferation, suggesting a possible role for LTB_4 in cancer (Jeon et al., 2015). Similarly, LTB_4 inhibits L-type Ca^{2+} channels via p38 signaling in vascular smooth muscle cells, which may indicate a pathological role for LTB_4 in atherosclerosis (Liu et al., 2015). In fact, a variety of promising BLT inhibitors are being tested in animal models of different diseases. For instance, treatment with the BLT1 antagonists BIIL284, CP105696, and U-75302 reduces atherosclerosis (Ketelhuth et al., 2015), insulin resistance (Li et al., 2015), and Chronic obstructive pulmonary disease (COPD) (Dong et al., 2016), respectively. Finally, a 5-LOX inhibitor, zileuton, which inhibits the synthesis of both LTB_4 and Cys-LT, has been approved for the treatment of chronic asthma (Kubavat et al., 2013), and is being investigated as a treatment for colon polyps (Gounaris et al., 2015), sickle cell disease (Quarmyne et al., 2013), and stroke (Costa Silva et al., 2015).

Role in oral health and disease—Leukotrienes are well established as inflammatory mediators in periodontal disease (Yucel-Lindberg and Båge, 2013). Elevated LTB_4 levels in gingival crevicular fluid are correlated with gingival inflammation (Tsai et al., 1998), and are strongly correlated with periodontal disease indices, clinical attachment loss, and alveolar bone loss (Pradeep et al., 2007). LTB_4 levels are also elevated following periodontal surgery (O'Brien et al., 1996). Furthermore, elevated levels of CysLT have been detected in the submandibular glands from rats with experimental periodontitis (Busch et al., 2009). Higher LT levels are also associated with endodontic inflammation (pulpitis), having been observed in periapical and pulpal lesions (Okiji et al., 1991, Lim et al., 1996, Shon et al., 2000). However, treatments for oral diseases based on these promising findings have been limited to preclinical models with no translation into clinical therapies. For example, LT synthesis inhibitors, specifically phenidone and ketoconazole, were shown to reduce both the infiltration of PMNL within periodontal pockets and osteoclastic bone resorption in a hamster periodontitis model (Baroukh and Saffar, 1990, Baroukh and Saffar, 1991, Baroukh and Saffar, 1992). Zileuton was shown to reduce the incidence of oral squamous cell carcinoma in a hamster model (Li et al., 2005). In both models, reduction in disease severity was accompanied by lower LTB_4 levels.

Prostaglandins

Prostaglandins are LM derived from AA that play an important regulatory role in physiological processes, but also have crucial pro-inflammatory effects (Figure 2).

Biosynthesis—All stable prostaglandins, including Prostaglandin D_2 (PGD_2), Prostaglandin E_2 (PGE_2), Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and Thromboxane B_2 (TXB_2) are produced through the activity of cyclooxygenase-1 (COX-1) and -2 (COX-2) (Nugteren and Hazelhof, 1973, Kudalkar et al., 2015). COX-1 is constitutively expressed in most tissues and regulates a host of homeostatic functions, while COX-2 expression is typically induced in response to inflammatory assault (Islam et al., 2016). The two cyclooxygenases (COX) function similarly by catalyzing the conversion of AA into PGG_2 via a first peroxidation step, then into PGH_2 via a reduction step (Aronoff et al., 2006). PGH_2 is converted into: 1) PGD_2 via two forms of PGD synthase, 2) PGE_2 via three forms of PGE synthase, 3) $PGF_{2\alpha}$ via two forms of PGF synthase, and 4) TXA_2 from TXA synthase (Chen et al., 2013a). The synthesis of PGG_2 via COX activity is the rate limiting step, and therefore, any dysfunction

will have profound downstream effects. Prostaglandin breakdown is mediated via 15-hydroxyl prostaglandin dehydrogenase, with a specialized prostaglandin transporter moving extracellular prostaglandins into the cytoplasm for enzymatic inactivation (Schuster et al., 2015).

Signaling pathway—PGD_2 signaling involves a primary prostaglandin receptor, DP1 (Boie et al., 1995), and a secondary receptor, DP2, also termed CRTH2 (Nagata and Hirai, 2003). PGD_2 binding to PD receptors leads to the activation of adenylyl cyclase resulting in cAMP formation (Hammad et al., 2007, Ayabe et al., 2013). Increased cAMP expression leads to activation of protein kinases, which regulate normal developmental processes such as sex determination via SOX9 phosphorylation (Malki et al., 2005). However, cAMP-dependent protein kinase activity induced by DP1 can also play pathological roles in inflammation. Particularly, cAMP inhibits IL-1β induced production of matrix metalloproteinases, leading to osteoarthritis (Zayed et al., 2008). Additionally, cAMP reduces IL-12 release by dendritic cells, leading to T-helper cell polarized responses (Theiner et al., 2006). Interestingly, PGD_2 exhibits neuroprotective effects through DP1 signaling (Wu et al., 2007), but neurotoxic effects through its conversion to its cyclopentenone metabolites (Liu et al., 2013). DP1 cell signaling also mediates ERK1/2 signaling, which provides a cooperative mechanism to promote additional cell surface expression of DP1 (Binda et al., 2014). The DP2 receptor (also known as CRTH2) is less specific to PGD_2, being capable of binding other prostaglandin synthesis metabolites that decrease cAMP expression while increasing intracellular Ca^{2+} (Hirai et al., 2001).

PGE_2 exerts its effects through four receptors (EP1-EP4TP), EP1 and EP2 being low affinity, while EP3 and EP4 are high affinity PGE_2 receptors (Kalinski, 2012). EP2 and EP4 are G_s-coupled receptors that function largely by activating the cAMP/PKA/CREB pathway (Fujino et al., 2005), but also activate the GSK3/β-catenin pathway (Fujino et al., 2002). EP4 also activates the PI3K-dependent ERK1/2 pathway (Fujino et al., 2003), and additionally controls integrin-mediated signaling pathways (Lee et al., 2013). EP1 and EP3 on the other hand, are G_i-coupled receptors that function primarily by inhibiting cAMP and increasing Ca^{2+} (Morimoto et al., 2014).

$PGF_{2\alpha}$ has a single G_q-coupled receptor, FP, which activates the PI3/DAG/PKC signaling pathway, leading to elevated intracellular Ca^{2+} and MAP kinase activation (Woodward et al., 2011). Additionally, $PGF_{2\alpha}$/FP interaction regulates CXCR2 activation via a PKC/Ca^{2+}/calcineurin pathway (Sales et al., 2009).

Finally, Thromboxane A_2 exerts its effects through the Thromboxane Prostanoid receptor (TP), which has two isoforms, TPα, which is present in platelets (Habib et al., 1999), and TPβ, which is present in endothelial and smooth muscle cells (Kinsella, 2001) TP is a G_q- and G_{12}-coupled receptor activating the PI3/DAG/PKC pathway (Ting et al., 2012, Capra et al., 2014). G_{12} activation via TP signaling also activates Rho kinase signaling, leading to myosin light chain phosphorylation (Klages et al., 1999) and mediating plate shape change during blood coagulation (Aburima et al., 2013). TXA_2 is a transient molecule that is converted into the more stable, but biologically inactive, Thromboxane B_2 (TXB_2) (Hamberg et al., 1975, Halushka, 2016).

Role in Systemic Health and Disease—PGD_2 has well known roles in female reproduction, specifically in the regulation of placental communication (Rossitto et al., 2015), and in male testis development (Moniot et al., 2014). It additionally regulates multiple neurological functions, such as sleep induction (Urade and Lazarus, 2013) and homeostasis (Porkka-Heiskanen, 2013), seizure suppression (Kaushik et al., 2014), and PNS myelination (Trimarco et al., 2014). PGD_2 also has a potential role in bone anabolism following fracture (Gallant et al., 2010). Additionally, PGD_2 has been shown to mitigate several inflammatory-mediated diseases, such as metabolic syndrome (Evans et al., 2013), cancer (Fukuoka et al., 2013, Tsai et al., 2013a), and acute lung injury (van den Brule et al., 2014). However, PGD_2 is most known for its pro-inflammatory properties in a variety of pathologies. Notably, it exacerbates adjuvant induced joint inflammation (Tsubosaka et al., 2014), allergic rhinitis (Nakano et al., 2016), Crohn's disease (Le Loupp et al., 2015, Radnai et al., 2016), and mast cell-induced vitreoretinopathy (Kuo et al., 2015). It also plays a role in depression-related behavior (Onaka et al., 2015) and in pain, being implicated in esophageal nociception (Zhang et al., 2013a), migraine (Antonova et al., 2013), and neuropathic spinal pain (Kanda et al., 2013). Additionally, PGD_2 inhibits hair growth, being elevated in the bald scalp, and is an attractive therapeutic target for male-pattern baldness (Garza et al., 2012, Schmidt, 2016). PGD_2-modulating therapeutics, such as DP antagonists have been shown to have anti-inflammatory effects. For example, the orally delivered DP2 antagonist QAW039 results in significant increase in bronchial epithelial integrity in asthmatics (Berair et al., 2015). DP1 antagonist ONO-4053 was more effective than LTR antagonists for the treatment of seasonal allergic rhinitis and congestion by potentially modulating histamine in addition to PGD_2 (Okada et al., 2015, Hajime and Okubo, 2016). Specific inhibition of PGD synthase is another promising therapeutic approach, with multiple PGD synthase inhibitors being identified for the treatment of various inflammatory disorders (Edfeldt et al., 2015).

PGE_2 has multiple normal physiological functions, most importantly labor induction (Goetzl, 2014). Additionally, the lung is a privileged site for beneficial actions of PGE_2 (Vancheri et al., 2004). As an example, inhaled PGE_2 improves pulmonary fibrosis (Ivanova et al., 2013). However, like PGD_2, PGE_2 is more known for its pathological effects. For instance, PGE_2 signaling creates a carcinoma stem cell niche (Li et al., 2012), promotes intestinal cancer growth via DNA methylation (Xia et al., 2012). Tumor-derived PGE_2 induces myeloid-derived suppressor cells and suppresses natural killer cell activity (Mao et al., 2014). EP1 is involved in cancer metastasis, its deletion suppressing metastasis in breast cancer cells (Reader et al., 2015) and colon cancer cells (O'Callaghan et al., 2013). Similarly, EP4 antagonist treatment suppresses angiogenesis, metastasis, and stem-like functions in murine breast cancer cells (Majumder et al., 2014, Majumder et al., 2015). A PGE_2 neutralizing antibody suppresses cancer stem cell chemoresistance (Kurtova et al., 2015).

$PGF_{2\alpha}$ plays an important reproductive role in pregnancy by regulating luteolysis (De Rensis et al., 2012), partially through upregulation of *Slit/Robo* expression (Zhang et al., 2013b). It has strong pro-contraction effects on the uterus (Ravanos et al., 2015). Elevated $PGF_{2\alpha}$ levels are associated with endometriosis (Ahmad et al., 2015, Rakhila et al., 2015).

Additionally, inhibiting $PGF_{2\alpha}$ via a selective FP antagonist AS604872 exacerbates intracranial aneurysm and aortic dissection in a hypertensive rat model (Fukuda et al., 2014). The $PGF_{2\alpha}$ isoform 8-iso-$PGF_{2\alpha}$ is a reliable indicator of oxidative stress and can be used to assess the efficacy of treatments for cardiovascular disease (Rizos et al., 2013).

Thromboxane A_2 plays an important role in thrombus formation through platelet activation and vascular reactivity (Ally and Horrobin, 1980, FitzGerald, 1991, Daniel et al., 1999), and some compounds have anti-thrombotic effects by binding to TP receptors (Guerrero et al., 2005). As an immune modulator, TXA_2 regulates JAK3/STAT5 signaling to promote early B-cell development (Yang et al., 2014), and mediates neutrophil control of the magnitude and spread of the immune response (Yang and Unanue, 2013). TXA_2 has been shown to promote cell proliferation in lung adenocarcinoma (Huang et al., 2014), implicating a potential role in cancer. Certain polymorphisms in the TXA2R gene were found to be correlated with an increase in the risk for acute cerebral infarction (Wang et al., 2014). Decreases in TXA_2 formation via COX-2 inhibition improves glomerular filtration rate in endotoxemic mice (Mederle et al., 2015).

Role in Oral Health and Disease—While PGD_2 has been implicated in a variety of general diseases; it has not been shown to play a major role in the progression of oral diseases. One report found that oral squamous cell carcinomas secrete PGD_2 to attract eosinophils and that PGD synthase inhibitor HQL-79 reduced this migration (Davoine et al., 2013). Single nucleotide polymorphisms (SNP) in the PGD synthase gene appear with higher frequency in aggressive periodontitis patients (Suzuki et al., 2004). Additionally, SNP in the PGD synthase gene are linked to smoking and associated with head and neck cancer (Lee et al., 2015).

PGE_2 has a better established role in oral disease. For example, human gingival fibroblasts exposed to LPS from periodontopathogenic bacteria produce PGE_2 through COX-2 (Noguchi et al., 1996). Additionally, orthodontic tooth movement is known to increase the incidence of periodontitis. Research suggests that mechanical forces induce COX-2 overexpression in periodontal ligament cells, leading to a dramatic increase in PGE_2 release (Shimizu et al., 1998, Yamaguchi and Garlet, 2015). PGE_2 is associated with periodontal disease and bone loss, and COX inhibitors have been proposed as a treatment (Lohinai et al., 2001, Yamaguchi and Kasai, 2005, Noguchi et al., 2007). Gingival biopsies from periodontal patients reveal that COX-2 expression leading to PGE_2 production correlates with connective tissue loss (Mesa et al., 2012, Mesa et al., 2014), and it is hypothesized that PGE_2 inhibits *in vitro* mineral deposition by periodontal ligament cells via the modulation of TWIST1 & RUNX2 expression (Manokawinchoke et al., 2014). PGE_2 production can be inhibited by IL-4 and IFNγ in periodontal ligament fibroblasts (Noguchi et al., 1999b), and by lidocaine irrigation in periodontal treatment (Camargo et al., 2015b).

$PGF_{2\alpha}$ has a potential role in periodontal pathogenesis by upregulating multiple pro-inflammatory factors in gingival fibroblasts, such as ICAM-1 expression (Noguchi et al., 1999a), IL-6 (Noguchi et al., 2001a), and (Noguchi et al., 2001b). Non-surgical periodontal therapy which reduces a variety of canonical pro-inflammatory markers also reduces $PGF_{2\alpha}$ levels (Koromantzos et al., 2011).

For dental applications, TXA_2 activity is relevant for the care of dental extraction patients. Since TXA_2 is a potent activator of platelet aggregation, special care needs to be taken with regards to prescribing aspirin (Nizarali and Rafique, 2013) or interrupting antiplatelet therapy (Lu et al.). Additionally, gingival TXB_2 levels have long been known to be elevated in animal models of periodontal disease (Rifkin and Tai, 1981).

Lipoxins

Lipoxins are LM derived either directly from AA, or from the conversion of LTA_4. They possess a variety of immunomodulatory and anti-inflammatory actions (Figure 3).

Biosynthesis—Lipoxins are notable for possessing dual anti-inflammatory and pro-resolving roles in the body (Serhan, 1994, Serhan et al., 2008) and are synthesized through two major pathways. In mucosal membranes, leukocyte-epithelial interaction triggers the synthesis of lipoxin A_4 (LXA_4) and its isoform, lipoxin B_4 (LXB_4) through the conversion via lipoxin hydrolases of 15-HETE, an intermediary product of 15-LOX activity on AA (Serhan, 1997). In the blood, leukocyte-platelet interactions trigger the synthesis of lipoxins via lipoxins-synthase activity of 12-LOX on LTA_4 (Serhan, 2005).

Signaling pathway—The primary action of LXA_4 and its aspirin-triggered epimers (ATL) occurs via the specific binding to the LXA_4 receptor (ALX/FPR2) to regulate gene expression, transmigration and chemotaxis *in vitro* and *in vivo* (Chiang et al., 2005, Chiang et al., 2006). ALX/FPR2 is a G_i-protein coupled receptor that is a member of the N-formyl peptide receptor family that, in humans, also includes FPR1 and FPR3. (Rabiet et al., 2011, Dorward et al., 2015). ALX/FPR2 expressed on leukocytes, neutrophils, monocytes, and lymphocytes (Fiore et al., 1994, Takano et al., 1997). FPR1 is the primary receptor for the pro-inflammatory formyl peptides (Boulay et al., 1990, Gao et al., 1994), while the function of FPR3 remains largely unknown, but is hypothesized to modulate the activity of FPR1 and ALX/FPR2 (Rabiet et al., 2011, Dorward et al., 2015).

Intracellular signaling pathways can either be activated or inhibited by LXA_4 binding to ALX/FPR2 (Jozsef et al., 2002). While LXA_4 increases intracellular Ca^{2+} levels, the chelation of calcium does not change the LXA_4-mediated adherence response of monocytes, indicating that Ca^{2+} is not the second messenger for LXA_4 signaling (Romano et al., 1996). The events triggered by the LXA_4 or ATL binding can be very rapid, occurring within seconds or minutes, or can be late responses that occur many hours after exposure (Serhan, 2014). LXA_4 and ATL trigger a variety of downstream pathways to achieve their anti-inflammatory and pro-resolving pathways. For example, LXA_4 inhibits TNF-α secretion by blocking ERK activation (Ariel et al., 2003), and can exert protective effects against ischemia/reperfusion injury via p38 MAPK activation (Chen et al., 2013b). LXA_4 has also been shown to down regulate pro-inflammatory genes by reducing NF-κB-mediated transcription activation (Bucci, 2014).

Role in systemic health and disease—As a LM, LXA_4 is notable for possessing both anti-inflammatory and pro-resolving properties. Anti-inflammatory actions of LXA_4 include the following: a) inhibition of tumor growth by targeting IL-10 production (Wang et al.,

2015), b) attenuation of acute rejection following liver transplant through the modulation of cytokine balance (Liao et al., 2013), c) inhibition of neuroinflammation and neuropathic pain after spinal cord injury (Martini et al., 2016), d) reduction of Alzheimer-like pathology in mice (Dunn et al., 2015), e) inhibition of endometriosis development in mice (Xu et al., 2012), f) mitigation of cardiac ischemia-reperfusion injury (Chen et al., 2013c) and g) attenuation of adipose inflammation (Börgeson et al., 2012). Disruption of LXA_4 signaling leads to an exacerbation of inflammation (Bozinovski et al., 2012). LXA_4 has been suggested as a potential therapeutic target for neurodegenerative disease due to its allosteric enhancement of the CB1 cannabinoid receptor (Pamplona et al., 2012). Furthermore, LXA_4 and ATL have been shown to enhance the action of dexamethasone towards the complete inhibition of neutrophil adhesion to endothelial cells both *in vitro* (Filep et al., 1999) and *in vivo* (Perretti et al., 2002). Synthetic LXA_4 analogs, were shown to have antifibrotic effects in cystic fibrosis (Guilherme et al., 2013) and to modulate the interaction of epithelial and tumor cells (Vieira et al., 2014). Finally, a LXA_4 receptor agonist, BML-111, promoted neurovascular protection in an ischemic stroke rat model (Hawkins et al., 2014).

As inflammation progresses, leukotriene generation by neutrophils decreases and 15-LOX-mediated synthesis of lipoxins commences prompting a lipid mediator class switch (Levy et al., 2001). Lipoxins act as a stop signal for neutrophil migration and a go signal for clearance of apoptotic neutrophils (Uddin and Levy, 2011). LXA_4 exerts direct modulatory effects on multiple immune cells, including upregulating natural killer and type 2 innate lymphoid cell activation (Barnig et al., 2013) and decreasing memory B-cell responses (Ramon et al., 2014). It directly acts to stimulate macrophage clearance of apoptotic neutrophils and bacteria (Prescott and McKay, 2011).

Role in oral health and disease—LXA_4 has been suggested as an immunomodulatory molecule in periodontal disease, inhibiting leukocyte recruitment to *Porphyromonas gingivalis* (Pouliot et al., 2000). More recently, LXA_4 was shown to activate bone regeneration in a pig model of periodontitis (Van Dyke et al., 2015), and to induce proliferation and migration of human periodontal stem cells (Cianci et al., 2016). Additionally, LXA_4 might play a role in modulating salivary gland inflammation by inhibiting immune cell binding to salivary epithelial cells (Chinthamani et al., 2012).

Resolvins

Resolvins are highly potent anti-inflammatory and pro-resolution agents derived from DHA and EPA that control the duration and magnitude of inflammation in animal models of complex diseases (Arita et al., 2007, Arita and Serhan, 2007, Bannenberg et al., 2007, Campbell et al., 2007) (Figure 4).

Biosynthesis—D-series resolvins are derived by the hydroxylation of DHA, via two distinct biosynthesis pathways. The first involves multiple 15-LOX-catalyzed hydroxylation steps of DHA to produce 17S-H(p)DHA, which is then transformed into 17S-resolvins D1 through D6 (Serhan et al., 2004), whereas the second involves aspirin-dependent COX-2 mediated hydroxylation of DHA into 17R-H(p)DHA, which is then transformed into 17R-RvD1-4 (Sun et al., 2007). The 17S- and 17R- resolvins are diastereomers with extremely

similar bioactivity (Weylandt et al., 2012). A 17R-epimer of RvD1, termed AT-RvD1, can also be generated in aspirin-treated monocytes and macrophages (Ariel and Serhan, 2007). E-series resolvins, on the other hand, are derived from EPA. Resolvin E1 (RvE1) is generated by an initial oxygenation step via aspirin-dependent COX-2 or cytochrome P450 monoxygenase activity to form 18R-H(p)EPE, which is then converted to RvE1 via 5-LOX activity (Arita et al., 2005b). RvE_2 is produced through the hydroxylation of 18R-H(p)EPE generated from EPA (Tjonahen et al., 2006, Ogawa et al., 2009).

Signaling Pathway—RvD1 and AT-RvD1 exert their activity in a dose-dependent manner through binding to two distinct receptors, ALX/FPR2 and GPR32 (Krishnamoorthy et al., 2012). Notable effects of RvD1 signaling include blocking the upregulation of TNFα-induced IL-1β transcripts (Hong et al., 2003) and upregulating IL-10 and miR-208a, a key regulator of immune responses (Krishnamoorthy et al., 2012). Both RvD1 receptors are PTX-sensitive and do not employ the classical Ca^{2+} or cAMP second messengers in PMN cells (Krishnamoorthy et al., 2010). More recently however, RvD1 was found to elicit a Ca^{2+} response and increase Akt phosphorylation in salivary epithelial cells, suggesting that ALX/FPR2 could activate PI3K pathways in some salivary cells (Leigh et al., 2014, Nelson et al., 2014). RvD2 binds to GPR18, also known as DRV2, to activate cAMP signaling (Chiang et al., 2015).

RvE1 interacts with two distinct G protein-coupled receptors binds to control inflammation and promote resolution. The first is ChemR23, a G protein coupled receptor, and causes $G_{i/o}$ activation and phosphorylation of ERK, while the second is the leukotriene B4 receptor 1 (BLT1) on human PMNL (Arita et al., 2007).

Role in systemic health and disease—Both RvD1 and its 17(R) epimer modulate innate immune responses such as reducing PMNL transendothelial migration (Serhan et al., 2002), and exhibiting a dose-dependent reduction in leukocyte infiltration (Serhan et al., 2002). They also exert effects of multiple lymphocyte type; for example, increasing IgM and IgG production from activated B cells (Ramon et al., 2012). RvD1 produced beneficial effects in multiple inflammatory murine models. Examples include: 1) reducing functional and morphological kidney injury following bilateral ischemia/reperfusion injury (Marcheselli et al., 2003, Duffield et al., 2006), 2) decreasing adipose tissue macrophage accumulation to improve insulin sensitivity in obese-diabetic mice (Hellmann et al., 2011), 3) attenuating arthritis severity and enhancing collagen repair in arthritic mice (Norling et al., 2016), 4) alleviating inflammation associated with endometriosis (Dmitrieva et al., 2014), 5) reducing mucosal inflammation following acute lung injury (Eickmeier et al., 2013), and alleviating allergic airway responses (Rogerio et al., 2012) and chronic emphysema (Hsiao et al., 2015). RvD2 appears to be a potent regulator of leukocytes, controlling microbial sepsis (Spite et al., 2009) and responding to E. coli peritonitis (Gao et al., 2013). RvD2 also appears to modulate variety of vascular injuries, including venous thrombosis (Diaz et al., 2015), aortic aneurysm (Pope et al., 2014), and peripheral vascular ischemia and subsequent revascularization (Zhang et al., 2014). The effects of RvD3 and RvD4 have not yet been established in great detail. Thus far, RvD3 is known to exert potent antineutrophil activity and strongly upregulate apoptotic PMN phagocytosis (Dalli et al.,

2013, Norris et al., 2016), while RvD4 plays a similar role in sterile peritonitis and *Staphylococcus aureus* skin infection (Winkler et al., 2016).

RvE1 displays potent, stereoselective actions *in vitro* and *in vivo* (Hasturk et al., 2007, Haworth et al., 2008). RvE1 is anti-inflammatory, pro-resolving, and tissue-protective. RvE1 stops neutrophil infiltration *in vivo* and retards their transendothelial migration (Arita et al., 2007), attenuates IL-12 production by dendritic cells and reduces their mobility toward pathogens, and has protective actions in a mouse model of colitis (Arita et al., 2005b). RvE1 may attenuate TNFα-mediated signals; for example, RvE1 reduces TNFα-mediated activation of NFκB in the human embryonic kidney 293 cell line (HEK293) (Arita et al., 2005a) and in a TNFα-induced mouse model of dermal inflammation (Arita et al., 2007). RvE1 also acts on epithelial cells, having been shown to reduce proinflammatory mediator release from corneal epithelial cells (Yuan et al., 2012) and promote intestinal mucosal wound repair (Quiros et al., 2016). Preliminary studies show that RvE1 is effective at attenuating atherosclerosis and augmenting the actions of anti-atherogenic drugs (Salic et al., 2014, Hasturk et al., 2015, Salic et al., 2016).

Since resolvins are rapidly hydrolyzable, more stable analogs have been developed that exhibit similar bioactivity, for example, sulfido-conjugates (e.g. 8-glutathionyl, 7,17-dihydroxy-4Z,9,11,13Z,15E,19Z-docosahexaenoic acid and 8-cysteinylglycinyl, 7,17-dihydroxy-4Z,9,11,13Z,15E,19Z-docosahexaenoic acid) (Dalli et al., 2015) and the benzo-diacetylenic-conjugate benzo-diacetylenic-17R-RvD1-methyl ester (BDA-RvD1) (Orr et al., 2015). Another approach to improve the stability of resolvins is the use of controlled release technology. For example, RvD1-containing nanoparticles were shown to limit PMN infiltration and improve wound healing in mouse models of peritonitis (Norling et al., 2011).

Role in oral health and disease—RvD1 plays a protective role in periodontitis, enhancing periodontal ligament fibroblast proliferation and wound closure (Mustafa et al., 2013), and is secreted by human periodontal stem cells (Cianci et al., 2016). It has been shown to promote wound healing in a mouse model of TMD (Norling et al., 2011). RvD1 has recently been of interest for the mitigation of salivary gland inflammation. For example, RvD1 biosynthetic pathways have been discovered in the salivary gland epithelium (Leigh et al., 2014), and RvD1 blocks cytokine signaling in salivary epithelium to promote cell survival and tissue integrity in rat parotid Par-C10 cells (Odusanwo et al., 2012). This was also shown to be true in mouse submandibular gland (SMG) cells coupled with the confirmation of the presence and functionality of the ALX/FPR2 (Nelson et al., 2014). Loss of ALX/FPR2 results in unresolved acute inflammation and SMG dysfunction (xerostomia) *in vivo* (Wang et al., 2016). AT-RvD1 can also reduce the expression of inflammatory genes and reduce apoptosis in a mouse model of Sjögren's Syndrome (SS) (Easley et al., 2015).

RvE1 reduces oral inflammation and alveolar bone loss (Hasturk et al., 2007) and generation of reactive oxygen species (Damgaard et al., 2016) in *Porphyromonas gingivalis*–induced periodontitis. In localized aggressive periodontitis, RvE1 rescues impaired phagocytosis activity (Fredman et al., 2011), reduces the expression of CXCL1 and osteoclast activity in ligature-induced periodontitis (Lee, 2015), and has been shown to directly act on bone cells

to promote bone preservation (Van Dyke, 2011, Gyurko and Van Dyke, 2014). Additionally, RvE1 has a protective effect against pulp inflammation in a rat model (Dondoni et al., 2014).

Lipid mediators in body fluids

The ubiquity of LM in physiological and pathological processes has led to an increased interest in identifying LM in various body fluids. Particularly, as they represent a simple and noninvasive approach for research and diagnostic purposes.

Serum & plasma—Serum levels of various LM have been investigated to study whether they correlated with certain diseases. High serum LTB_4 levels have been shown to be correlated with an elevated risk of acute coronary syndrome in adults (He et al., 2014). Additionally, high LTB_4 levels may predispose children to tonsillar hypertrophy (Alexopoulos et al., 2015). Further, serum levels of Cys-LTs are elevated during anaphylaxis and have been suggested to be a reliable marker of this condition (Nassiri et al., 2016). Finally, elevated serum levels of LTB_4 and Cys-LTs are correlated with higher levels of circulating neutrophils in children with sleep-disordered breathing (Shen et al., 2014).

Increased PGE_2 serum levels indicate overexpression of aromatase (Subbaramaiah et al., 2012), which is linked to hormone-related breast cancer (Subbaramaiah et al., 2008). Additionally, PGE_2 serum levels, along with 8-Isoprostane, C-reactive protein, and amyloid A, have been suggested as inflammatory markers for antiphospholipid syndrome (Sciascia et al., 2012). Similarly, serum thromboxane levels are an indicator of platelet inhibition by aspirin, and can thus be used for epidemiological studies on the effects of aspirin (Reny et al., 2012, Zantek et al., 2014). However, measurement methods for serum thromboxane need to be standardized to produce consistent results across studies (Brun et al., 2016).

In contrast to the pro-inflammatory leukotrienes and prostaglandins, decreased lipoxin serum levels are typically observed in several pathological conditions. For example, lowered LXA_4 serum levels were found in patients with sepsis (Tsai et al., 2013b) and in wheezy infants (Eke Gungor et al., 2014). Serum LXA_4 levels were also found to have an inverse relationship to the risk of metabolic syndrome (Yu et al., 2015). Of note to dental professionals, periodontitis patients might have elevated LXA_4 serum levels compared with healthy controls (Doğan et al., 2015).

RvD1 and RvE1 serum levels have been investigated as markers for the efficacy of diclofenac in acute pancreatitis treatment, with increased resolvin and lipoxin serum levels observed in the drug receiving group (Zhao et al., 2014). Additionally, higher RvD1 serum levels have been described as a potential biomarker for Familial Mediterranean Fever (Taylan et al., 2015).

Urine—Similar to serum, urine levels of various LM have been used to investigate multiple diseases. High levels of urinary leukotriene have been observed in pediatric patients with wheezing and recurrent asthma (Morales et al., 2016). High levels of urinary leukotrienes have also been detected in adult individuals with systemic mastocytosis (Lueke et al., 2016), as well as in aspirin-intolerant asthmatic individuals (Yamaguchi et al., 2015, Hagan et al.,

2016). Urinary leukotriene levels are directly correlated to the severity of arterial occlusive disease following transluminal angioplasty (Maga et al., 2016). Additionally, they are inversely correlated with renal function in Type 2 diabetes (Rafnsson and Bäck, 2013). Therefore, they have been suggested as prognostic markers for these diseases.

While levels of total unmodified prostaglandin in urine have been correlated with only a few diseases (e.g., cardiovascular disease (Raatz et al., 2012) and anaphylaxis (Lieberman, 2013)), levels of prostaglandin metabolites in urine have attracted more scrutiny. High levels of the PGD_2 metabolite tetranor PGDM in urine, have been correlated with Duchenne muscular dystrophy, systemic mastocytosis, rheumatoid arthritis, colitis, and colon cancer (Nakagawa et al., 2013b, Nakagawa et al., 2013a, Iwanaga et al., 2014, Cho et al., 2015). High levels of urinary PGE_2 metabolite levels appear to be associated with colorectal adenoma (Shrubsole et al., 2012, Davenport et al., 2015), pancreatic cancer (Zhao et al., 2015), and breast cancer in postmenopausal women (Cui et al., 2014). Additionally, elevated levels of urinary thromboxane have been suggested as a predictor of atherthrombotic risk (Neath et al., 2013).

In contrast to the pro-inflammatory LM, there is a dearth of studies examining urinary levels of pro-resolving LM. Decreased urine levels of lipoxins and resolvins have been hypothesized to be related to inflammatory bowel disease (Das, 2016), while elevated urinary LXA_4/creatinine ratio has been observed in systematic lupus erythematosus (Abdou et al., 2015).

Sputum and Exhaled breath condensate—Lung fluids are an obvious target for analysis of LM involved in inflammatory lung diseases. Asthmatic patients had elevated sputum levels of Cys-LTs and PGE_2 compared to healthy subjects (Papadaki et al., 2013), with smoking asthmatics exhibiting even higher sputum levels of these LM (Kontogianni et al., 2013). COPD patients, on the other hand, only exhibited elevated PGE_2 sputum levels, but no differences in Cys-LT levels, compared to healthy controls (Drozdovszky et al., 2013). An analysis of sputum from adult cystic fibrosis patients found elevated levels of LTB_4 and PGE_2 (Yang et al., 2012). Pediatric cystic fibrosis patients, however, did not have elevated LTB_4 sputum levels, but the ratio of LXA_4 to LTB_4 was depressed (Ringholz et al., 2014). Accurate measurements of LTB_4 using UPLC-MS/MS require a refinement of sputum processing due to the instability of LTB_4 in the presence of standard preparation reagents (Jian et al., 2013). In exhaled breath condensate (EBC), similar findings with regards to higher leukotriene levels were observed as well. For example, smoking asthmatic patients displayed elevated EBC Cys-LT levels (Celik et al., 2013). Cys-LT EBC levels are correlated with the severity of asthma (Kazani et al., 2013). Cys-LT levels in exhaled breath condensate were found to be elevated in children with asthma and allergic rhinitis (Wan et al., 2013). 8-iso-PGE_2 levels in exhaled breath condensate were found to be elevated in aspirin-hypersensitive asthmatics (Mastalerz et al., 2015). Lipoxin/Leukotriene imbalance was also detected in exhaled breath condensate of severe refractory asthma patients (Sedlák et al., 2014). Exhaled breath condensate has recently emerged as a simple and accurate medium to aid the diagnosis and evaluation of inflammatory severity in asthmatic patients (Thomas et al., 2013).

LXA_4 sputum levels in pediatric severe asthmatics were found to be depressed, along with reduced ALX/FPR2 expression in induced sputum cells (Gagliardo et al., 2016). Conversely, LXA_4 levels in exhaled breath condensate were found to be elevated in asthmatic children with exercise-induced bronchoconstriction (Tahan et al., 2016). Such investigations are eminently useful for understanding the pathologies of different respiratory disorders. As for resolvins, there is currently a lack of rigorous analysis of the levels of resolvins in sputum and exhaled breath condensate. More research into this area would contribute greatly to the understanding of the development and resolution of various respiratory conditions.

Breast milk—Breast milk is extremely important for developing innate immunity and healthy intestinal homeostasis in babies (Cederlund et al., 2013, Jakaitis and Denning, 2014). Elevated PUFA levels in breast milk decrease during the first month after birth, but lipoxin and resolvin levels remain stable, indicating an important role in neonatal immunity (Weiss et al., 2013). LM profile in breast milk could be associated with conditions that affect neonatal health. For example, maternal smoking can negatively affect the LM profile in breast milk (Szlagatys-Sidorkiewicz et al., 2013). Furthermore, mastitis results in elevated LTB_4 and decreased lipoxin and resolvin levels (Arnardottir et al., 2015)

Synovial fluid—LM profiling of synovial fluid from rheumatoid arthritis reveals the presence of both pro-inflammatory and pro-resolving LM (Giera et al., 2012). Elevated levels of PGD_2 and PGE_2 in synovial fluid from arthritic patients have been linked to dendritic cells in the synovial fluid (Moghaddami et al., 2013). Of note for dental clinicians, synovial fluid from painful, dysfunctional temporomandibular joints (TMJ) was found to contain elevated levels of LTB_4 and PGE_2 (Quinn and Bazan, 1990). LTB4 synovial fluids were found to be prognostic markers for the success of arthrocentesis of the TMJ, with higher LTB4 levels indicating unsuccessful treatment (Kaneyama et al., 2007). Similarly, glucosamine-chondroitin sulfate treatment for TMJ derangement results in lower PGE2 synovial fluid levels (Damlar et al., 2015).

Gingival crevicular fluid—Gingival crevicular fluid (GCF) is an important periodontal diagnostic marker (Gupta, 2013). LTB_4 levels in GCF are higher in chronic periodontitis patients (Emingil et al., 2001, Pradeep et al., 2007). Similarly, PGE_2 levels in GCF are a strong marker of gingivitis and periodontitis (Heasman et al., 1998, Camargo et al., 2015a), and are correlated with the severity of periodontal disease (Kumar et al., 2013). GCF from orthodontic patients displaying gingival inflammation who received a chlorhexidine/thymol-containing dental varnish administered exhibited a reduction in LTB_4 and PGE_2 levels (Sköld et al., 1998, Yucel-Lindberg et al., 1999).

GCF levels of pro-resolving LM are generally decreased in periodontal patients. For example, LXA_4 levels were found to be significantly lower in periodontal patients compared to healthy controls, combined with a negative correlation between LXA_4 levels and clinical attachment loss (Tarannum and Faizuddin, 2016). GCF LXA_4 levels were similarly found to be lowest in smokers with aggressive periodontitis (Heasman et al., 1998). The ration of pro-resolving and pro-inflammatory LM has been suggested as a better marker for aggressive periodontitis (Elabdeen et al., 2013).

Saliva—Saliva diagnostics are an intuitive and comprehensive approach for oral diseases (Zhang et al., 2015), and they have recently emerged as a method for determining general health status without the invasiveness of traditional methods (Punyadeera and Slowey, 2013, Schafer et al., 2014). Metabolomic and bioinformatic approaches are bringing these applications even closer (Ai et al., 2012, Zhang et al., 2012). The development of higher sensitivity assays should accelerate the adoption of salivary diagnostics over serum (Khaitan et al., 2015). In addition to the traditional inflammatory biomarkers, salivary levels of LM can also be used for diagnostic and prognostic purposes, though they lag behind other body fluids. For example, elevated salivary LTB_4 and PGE_2 are correlated with arterial stiffness (Labat et al., 2013). Aspirin-intolerant asthma patients exhibit elevated Cys-LT levels in saliva (Gaber et al., 2008, Ono et al., 2011). Salivary prostaglandin levels have long been suggested to be indicators of major depression (Ohishi et al., 1988, Nishino et al., 1989).

Saliva levels of various LM are more widely used for studying oral diseases than for systemic diseases. For example, patients with radiotherapy-caused oral mucositis displayed higher saliva levels of PGD_2, PGE_2, and PGF_2 (Grunberg et al., 2013). Similarly, a different study found elevated levels of LTA_4 hydrolase in oral mucositis patients (Jehmlich et al., 2015). Elevated salivary levels of PGE2 were found to be correlated with gingivitis (Syndergaard et al., 2014, Gümüş et al., 2016) and periodontitis (Sánchez et al., 2013b). In chronic periodontitis patients, salivary LTB_4 levels were to found to correlate with the severity of alveolar bone loss (Sánchez et al., 2013a). Ratios of pro-resolving LM to pro-inflammatory LM that were found to be correlated with aggressive periodontitis in GCF were not found to be similarly correlated in saliva (Elabdeen et al., 2013). No studies to date have examined salivary levels of pro-resolving LM, such as lipoxins and resolvins, for diagnostic studies of oral disease.

One interesting aspect of saliva diagnostics is the potential to explain the etiology of various diseases. Some diseases display marked gender differences, notably SS, which affects older females primarily. Differences in LM levels have been observed between males and females in multiple diseases, such as diabetes (Tessaro et al., 2015), COPD (Balgoma et al., 2016), Alzheimer's (Pomponi et al., 2011), and metabolic syndrome (Yu et al., 2015).

To test this hypothesis in saliva, we investigated differences in salivary LM levels between healthy male and female donors. For this previously unpublished study, we recruited patients and students at the University of Utah School of Dentistry student clinics, who were between 18 and 40 years old and had no history or visible signs of gingivitis or periodontitis (11 females and 19 males). All human specimen usage was conducted under the strict guidelines and approval of the University of Utah Health Sciences Institutional Review Board, and informed consent was obtained for each patient (IRB approval: IRB_00081821 on October 29th 2015). Donor demographic information is shown in Table 1. Unstimulated whole saliva was collected by having subjects spit into a sterile 50 mL conical tube for five minutes after a brief mouth rinse with water, then transported to the laboratory on ice. We opted for the spitting method over cotton-based methods due to the potential of interference with immunoassay results (Shirtcliff et al., 2001). Samples were centrifuged at 5000 × g for 10 minutes at 4°C to pellet out debris, and the supernatant was collected and broken up via trituration with a 19G hypodermic needle to reduce its viscosity. Saliva was consecutively

filtered through a 40 μm and a 0.2 μm filter to remove debris and bacteria, respectively. Enzyme-linked immunosorbent assays (ELISA) were performed immediately for the following LM: LTB_4, PGD_2, PGE_2, PGF2α, TXB_2, RvD1, and RvD2 (Cayman Chemical, Ann Arbor, MI). Measured LM concentrations (mean ± standard deviation) are shown in Table 2.

Using this method, we show that we can detect salivary levels of LTB_4, PGD_2, PGE_2, $PGF_{2\alpha}$, TXB_2, RvD_1, and RvD_2. We observed significantly lower $PGF_{2\alpha}$ in female saliva as compared to male saliva. As indicated above, $PGF_{2\alpha}$ plays a role in many female functions such as reproduction and menstrual cycle (Wilks et al., 1973, Downie et al., 1974); therefore, we could speculate that females demand and use this lipid mediator for more functions than males, thereby levels in saliva are decreased. Additionally, we observed that saliva levels of RvD2 from male subjects were significantly lower than female subjects. This finding raises interesting questions regarding the etiology of some inflammatory diseases that skew females, such as SS. One hypothesis that needs further investigation is that higher levels of pro-resolving LM, such as RvD2, might indicate the presence of inflammatory assaults that the body is attempting to resolve over time, leading to persistent chronic inflammation. More research needs to be conducted to confirm such a hypothesis, including comparing saliva LM levels of SS patients to healthy subjects, and investigating whether gender-related differences that are observed in healthy subjects disappear in SS patients.

Summary

The diverse role of LM in the development of various systemic and oral inflammatory diseases presents a challenge and an opportunity to oral health clinicians and researchers. In this review, we have presented an overview of the most important LM that control inflammation, a brief summary of biosynthesis and signaling pathways, and roles in systemic and oral health. Understanding the distinct signaling pathways and functions of LM will be crucial for designing treatment approaches and therapeutics (*i.e.,* a clear picture of how LM profile shifts from pro-inflammatory to pro-resolving). LM influence both systemic and oral diseases, which are often interrelated, making it important to understand the impact of systemic diseases in oral health and vice versa. Additionally, lipid mediators will be useful as diagnostic tools. Particularly, lipidomic profiling should be included in the current repertoire of diagnostic and prognostic indicators of both systemic and oral health. Finally, saliva LM mediator levels could be an additional tool to study the etiology, development, and treatment for a variety oral diseases, including periodontitis, SS, and oral cancer.

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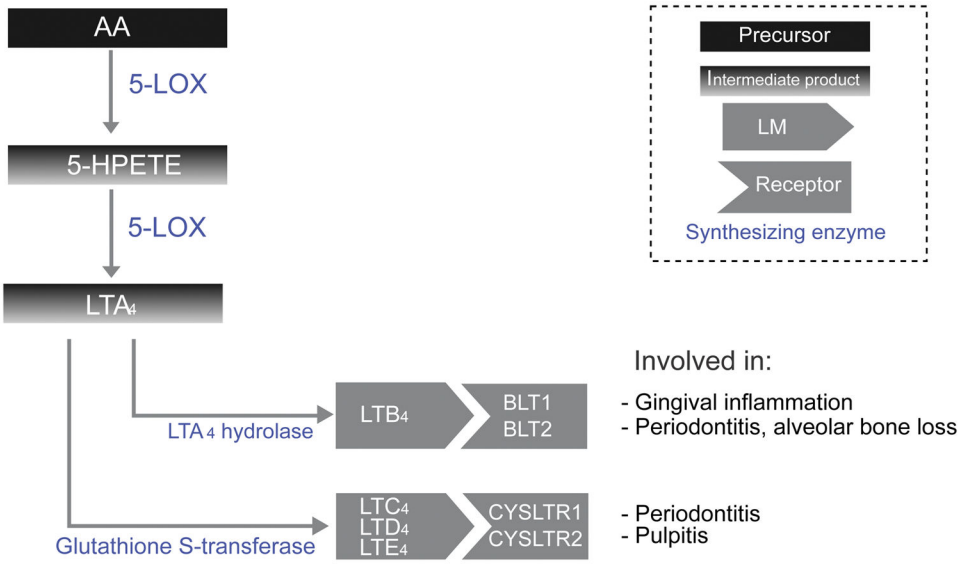

Figure 1. Leukotrienes biosynthetic pathways

This diagram depicts biosynthesis of leukotrienes from arachidonic acid, including intermediate products, as well as various leukotriene receptors, and their role in oral disease.

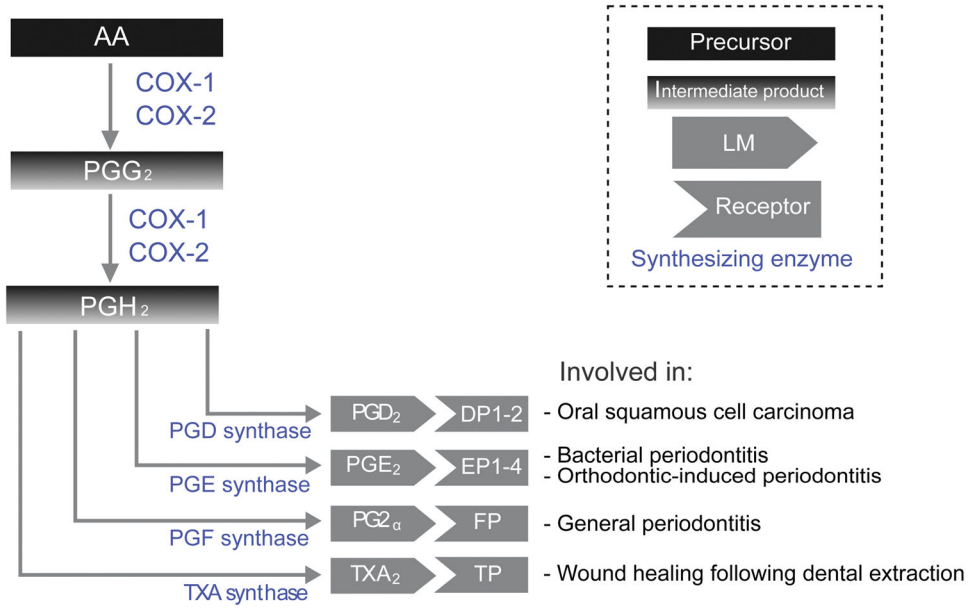

Figure 2. Prostaglandins biosynthetic pathways

This diagram depicts biosynthesis of prostaglandins from arachidonic acid, including intermediate products, as well as various prostaglandin receptors, and their role in oral disease.

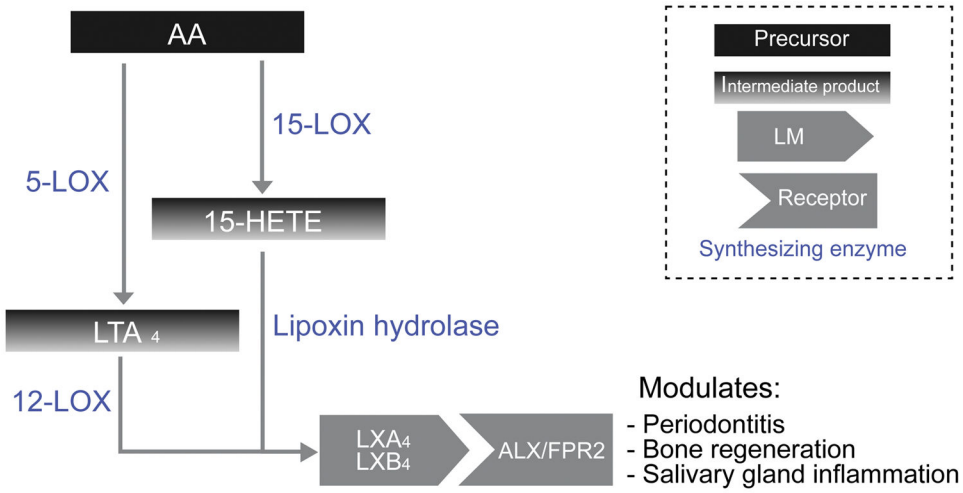

Figure 3. Lipoxins biosynthetic pathways

This diagram depicts biosynthesis of leukotrienes from arachidonic acid, including intermediate products, as well as various lipoxin receptors, and their role in oral disease.

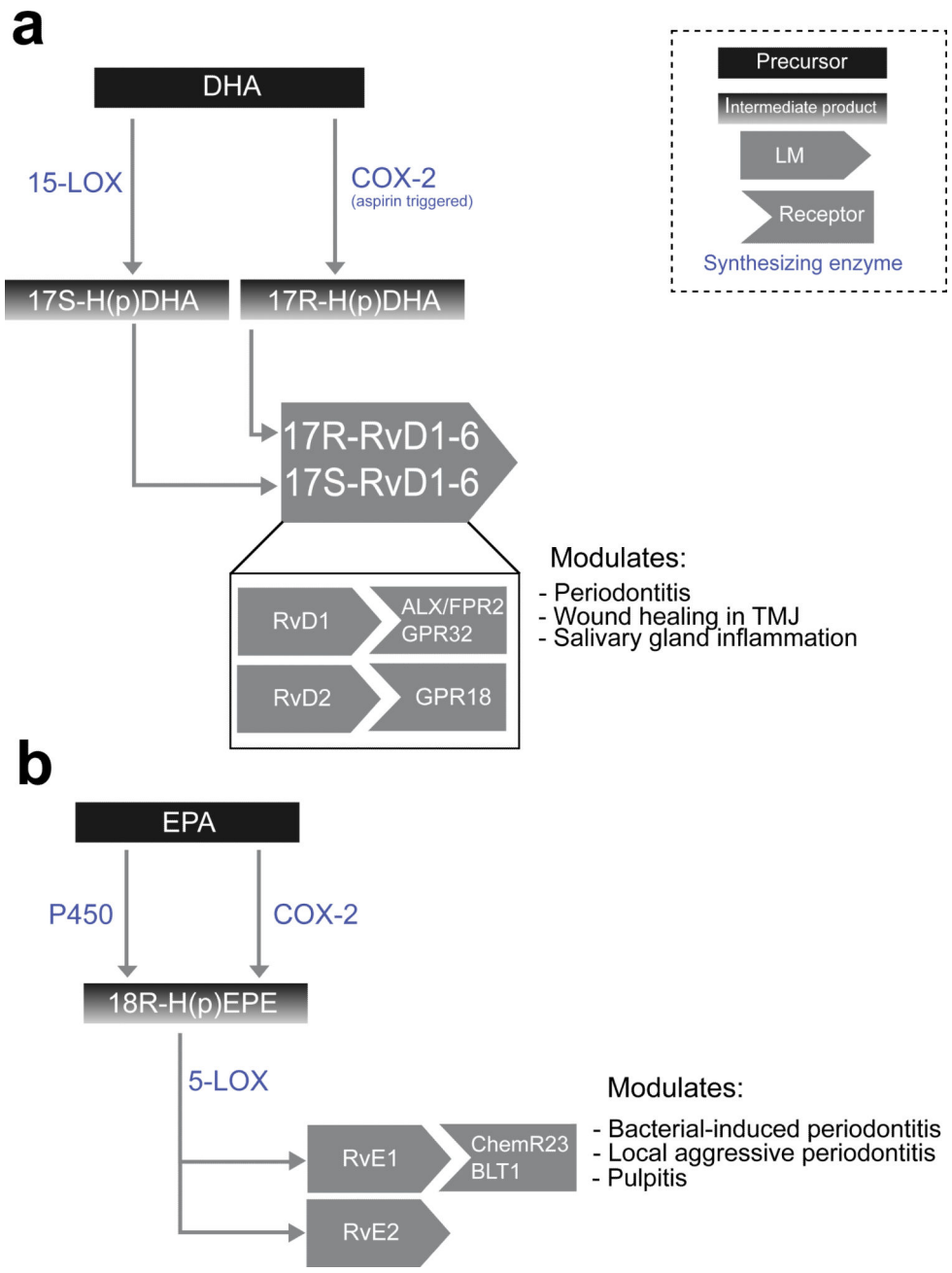

Figure 4. Resolvins biosynthetic pathways

This diagram depicts biosynthesis of (a) D-series resolvins from DHA and (b) E-series resolvins from EPA, including intermediate products, as well as various resolvin receptors, and their role in oral disease.

Table 1

Saliva donor demographics

	Male	Female
N	19	11
Age (years, mean ± standard deviation)	27.6 ± 3.3	27.8 ± 3.1

Table 2

LM concentrations pg/mL (mean ± standard deviation)

	Male	**Female**	**Results**
LTB_4	786 ± 654.7	666 ± 745.2	n.s.
PGD_2	1393 ± 696.1	1505 ± 866.9	n.s.
PGE_2	843.2 ± 901.7	433.9 ± 448.3	n.s.
$PGF_{2\alpha}$	306.2 ± 235.6	174.1 ± 116	$P = 0.026$
TXB_2	557 ± 502.9	471.6 ± 296.2	n.s.
RvD1	297.9 ± 189.3	409 ± 286.3	n.s.
RvD2	93.98 ± 45.37	179.8 ± 92.15	$P = 0.041$

n.s.= non-significant