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Review

Role of lipid mediators in the regulation of oxidative stress and inflammatory responses in dairy cattle

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ABSTRACT

Periparturient dairy cows experience an increased incidence and severity of several inflammatory-based diseases such as mastitis and metritis. Factors associated with the physiological adaptation to the onset of lactation can impact the efficiency of the inflammatory response at a time when it is most needed to eliminate infectious pathogens that cause these economically important diseases. Oxidative stress, for example, occurs when there is an imbalance between the production of oxygen radicals during periods of high metabolic demand and the reduced capabilities of the host's antioxidant defenses. The progressive development of oxidative stress in early lactation cows is thought to be a significant underlying factor leading to dysfunctional inflammatory responses. Reactive oxygen species (ROS) are also produced by leukocytes during inflammation resulting in positive feedback loops that can further escalate oxidative stress during the periparturient period. During oxidative stress, ROS can modify polyunsaturated fatty acids (PUFA) associated with cellular membranes, resulting in the biosynthesis of oxidized products called oxylipids. Depending on the PUFA substrate and oxidation pathway, oxylipids have the capacity of either enhancing or resolving inflammation. In mediating their effects, oxylipids can directly or indirectly target sites of ROS production and thus control the degree of oxidative stress. This review discusses the evidence supporting the roles of oxylipids in the regulation of oxidative stress and the subsequent development of uncontrolled inflammatory responses. Further, the utility of some of the oxylipids as oxidative stress markers that can be exploited in developing and monitoring therapies for inflammatory-based diseases in dairy cattle is discussed. Understanding of the link between some oxylipids and the development or resolution of oxidative stress could provide novel therapeutic targets to limit immunopathology, reduce antibiotic usage, and optimize the resolution of inflammatory-based diseases in periparturient dairy cows.

1. Introduction

Dairy cattle are susceptible to increased incidence and severity of disease during the periparturient period. Indeed, approximately 75% of disease incidence occurs during the first month of lactation (LeBlanc, 2006). Health problems that occur during early lactation can persist for extended periods and result in significant production losses (Ingvartsen, 2006; Pinedo et al., 2010). As such, a considerable amount of research was conducted over the last several decades with the goal of defining factors that contribute to compromised immunity and health disorders in periparturient dairy cows (Sordillo and Aitken, 2009; Raphael and Sordillo, 2013; Esposito et al., 2014). A major finding of these earlier studies was that uncontrolled or impaired inflammatory responses were linked directly to increased health disorders during this critical period in the cow's production cycle (Sordillo and Mavangira, 2014). Dairy cows undergo several physiological changes during the onset of lactation that can impact the magnitude and duration of the inflammatory responses. Coordinated shifts in nutrient partitioning must occur in order to meet the increased metabolic demands necessary for parturition and the onset of lactation. The conversion of nutrients into an energy source that can be used to fuel these normal physiological functions occurs through cellular respiration reactions. Oxygen is required for aerobic cellular respiration and reactive oxygen species (ROS) are metabolites formed in the mitochondria as a by-product of energy generation. Peroxisomes also play a role in the production of ROS, especially hydrogen peroxide, as they are involved in the shortening of long chain fatty acids subsequently channeled to metabolism in the mitochondria (Drackley, 1999). Oxidative stress occurs when there is an imbalance between the production of ROS during periods of high metabolic demand and the reduced capabilities of the host's antioxidant defenses. Ample evidence suggests that the progressive development of oxidative stress in periparturient dairy cows is a significant underlying factor leading to dysfunctional inflammatory responses (Sordillo and Aitken, 2009; Osorio et al., 2014). Polyunsaturated fatty acids (PUFA)

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associated with membrane phospholipids are primary targets of ROS modification during oxidative stress. One way that oxidative stress can impact inflammation is through the actions of oxidized PUFA products called oxylipids. Depending on the PUFA substrate and biosynthetic pathway, oxylipids function to either enhance inflammation or assist in its resolution. This paper will provide an overview of how the biosynthesis of oxylipids can regulate oxidative stress and inflammatory responses that are relevant to disease susceptibility in periparturient dairy cattle.

2. Defining oxidative stress

Oxidative stress refers to the damage occurring to cellular macromolecules as a consequence of an imbalance between oxidants and antioxidants (Halliwell, 2007). Macromolecules targeted for oxidative damage include lipids, proteins, and DNA. Oxidants comprise radical and non-radical molecules that mediate oxidation of the susceptible macromolecules. The bulk of the oxidants are ROS; however, reactive nitrogen species (RNS) also contribute to the overall pool of oxidants. Free radical oxidants, for example, have the capacity to induce proton removal by the presence of unpaired electrons (Villamena, 2013). Alternatively, the presence of highly electronegative atoms, including oxygen in H_2O_2 and nitrogen in peroxynitrite, result in asymmetric electron arrangements that confer the ability to induce oxidation reactions (Villamena, 2013). Collectively, ROS and RNS are referred to as reactive metabolites whose production occurs both in physiological and pathological states.

Reactive metabolites are normal products of metabolism and are essential for signaling functions, which are necessary for cellular processes including proliferation, differentiation, and metabolic adaptations. For example, the generation of ATP in the mitochondria through the Krebs' cycle and the electron transport chain generates O_2^- and H_2O_2 as byproducts. Approximately 1–3% of electrons during the mitochondrial oxidative phosphorylation reactions are transferred to oxygen to form superoxide (O_2^-) (Holmstrom and Finkel, 2014). Superoxide dismutase (SOD) enzymes catalyze the direct conversion of O_2^- to H_2O_2. Both O_2^- and H_2O_2 participate in phosphorylation of various proteins that are part of signaling networks such as mitogen-activated protein kinase (MAPK) phosphatases, by oxidizing thiol-containing cysteine residues (Sordillo and Mavangira, 2014).

The production of reactive metabolites increases during periods of increased metabolic demands such as during pregnancy in dairy cows (Bernabucci et al., 2005). Reactive metabolites also increase during regulated inflammatory processes to levels necessary for effective innate and adaptive immune functions (Sordillo and Aitken, 2009). Endogenous cellular protective responses function to limit reactive metabolite accumulation within physiological limits to prevent cellular damage. In contrast to the physiological production of reactive metabolite, uncontrolled inflammation is characterized by excessive levels of reactive metabolites that contribute to the pathology of diseases. For example, the oxidation of lipids occurs during acute coliform mastitis, contributing to the severity of disease especially in early lactation cows (Sordillo and Mavangira, 2014; Mavangira et al., 2016). Whereas mitochondria are a major source of excessive reactive metabolite production during inflammatory conditions, significant contributions also come from upregulated enzyme pathways. Inducible nitric oxide synthase (iNOS), xanthine oxidase (XO), and the nicotinamide adenine dinucleotide phosphate oxidase (NOX) enzymes are all upregulated by inflammatory stimuli. Inducible NOS (iNOS) is upregulated and generates excess nitric oxide which induces widespread vasodilation and generation of peroxynitrite in acute inflammation (Sorokin, 2016). Specifically, iNOS expression was documented in bovine endometrial cells induced by LPS and was identified as part of the inflammatory cascade associated with endometritis in cattle (Marini et al., 2016). The XO enzymes are stimulated by LPS, hypoxia, and cytokines including interleukin-1β, all of which are expressed by bovine mammary endothelial cells and are relevant to acute inflammatory diseases such as coliform mastitis (Silanikove et al., 2012, Wu et al., 2016a, 2016b).

Cells have an elaborate system of antioxidants that neutralize, metabolize and delay the production of oxidants. Antioxidants include endogenous enzymes such as superoxide dismutases (SOD), glutathione peroxidases (GPxs), thioredoxin reductases (Trx), peroxiredoxins, catalases, and heme oxygenase (HO). Dietary sources also contribute to the non-enzymatic pool of antioxidants which include trace minerals (selenium, copper, zinc), polyphenols, vitamins (A, C, D, and E), and the vitamin A precursor, beta-carotene (Sordillo, 2016). Enzymatic and non-enzymatic antioxidants work in concert to protect against ROS-induced cellular damage (Sordillo and Aitken, 2009). For example, SOD enzymes are dependent on trace minerals, copper (Cu) and manganese (Mn), in the dismutation of O_2^- to H_2O_2. Subsequently, the reduction of H_2O_2 to water and oxygen is mediated by catalases or the selenium (Se)-dependent GPx and Trx reductase enzymes. The reduction of H_2O_2 and other hydroperoxides is coupled to the oxidation of the tripeptide cofactor, reduced glutathione (GSH) to the oxidized state (GSSG). The GSSG is converted by the glutathione reductase system to GSH which becomes available for further GPx- or Trx-mediated metabolism (Halliwell, 2007; Sordillo and Aitken, 2009). Indeed, the balance between GSH and GSSG is crucial as its perturbations can alter cellular redox tone and affect signaling pathways and the development of oxidative stress. For example, exposure of bovine mammary and aortic endothelial cells to pro-oxidant challenge increased reactive metabolite production and cellular apoptosis that were ameliorated by Se supplementation (Sordillo et al., 2005, Ryman et al., 2015a, 2015b). Reduced GSH can scavenge pre-formed reactive metabolites and also participate in regenerating and maintaining the functional forms of other antioxidant enzymes such as vitamins. For example, vitamin E radicals formed during the neutralization of lipid free radicals in the cell membranes are recycled back to reduced vitamin E by peroxidase enzymes using GSH as a cofactor. Dietary micronutrients such as vitamin E and Se are recognized as an important tool to enhance antioxidant defense mechanisms and reduce health disorders of dairy cattle during periods of increased metabolic demands (Sordillo and Aitken, 2009; Sordillo, 2013).

The activation of antioxidant response genes is another important mechanism essential for limiting the excessive reactive metabolite accumulation. For example, the nuclear factor related erythroid factor 2 (NrF2) transcription factor is activated during oxidative stress and acts as a master regulator of several antioxidant response genes including those involved in the synthesis of HO-1, GSH, GPx and Trx enzymes (Ruiz et al., 2013). When unstimulated in the cytoplasm, NrF2 is bound to Kelch-Like-ECH Associated Protein 1 (KEAP-1) protein by interacting with cysteine residue which targets it for proteasomal degradation (Ruiz et al., 2013). During oxidative stress or in the presence of NrF2 agonist, oxidation of the cysteine residues dissociates NrF2 from KEAP-1 and translocates to the nucleus. After forming dimers with other transcription factors, NrF2 activates antioxidant response elements in the promoter regions of antioxidant genes (Ruiz et al., 2013). Several NrF2 target genes including the enzymes catalase, glutathione peroxidases, heme oxygenase, superoxide dismutases and acute phase proteins such as haptoglobin and serum amyloid A, showed increased expression in peripartal dairy cows (Gessner et al., 2013). Stabilizing Nrf2, targeted in human diseases to promote its antioxidant protective effects, could also be beneficial in dairy cattle during the oxidative stress prone periods such as the transition period (Bernabucci et al., 2005) and diseases including mastitis (Mavangira et al., 2016) and metritis (Kankofer, 2002). Enzymatic and non-enzymatic components collectively contribute to the overall cellular anti-oxidant potential, which is crucial for defense against oxidative cellular damage during inflammatory-based diseases.

The imbalance between oxidants and antioxidants develops as a consequence of one or a combination of several factors including overproduction of oxidants, depletion of antioxidant potential, and

deficiencies in antioxidant components (Valko et al., 2007). Increased production of ROS in peripartum dairy cattle, the decrease in the total antioxidant capacity, and the accumulation of lipid peroxidation products were demonstrated in several studies (Bernabucci et al., 2005; Osorio et al., 2014; Abuelo et al., 2015). The consequent direct structural damage or chemical modifications to lipids and proteins, negatively impact normal functions of plasma membranes. Lipids are the major macromolecules present in plasma membranes of cells and their internal organelles, and their oxidation can impact the function and viability of cells in several ways including increasing membrane fluidity and affecting the lipid structure and packing in lipid raft domains. Lipid peroxidation products and secondary by-products also may induce toxic modification of proteins and DNA resulting in cell death. Protein oxidation resulting from oxidative stress also can affect cellular function because of altered protein structure. Altered protein structure occurs when thiol groups in amino acid residues such as cysteine and lysine are covalently modified resulting in alteration or loss of function. The damage to DNA may be a direct oxidation of bases or adduct formation with either lipid or protein oxidation products affecting cellular structure, function, or viability (Celi, 2011). Understanding the formation of oxidant-induced damage to macromolecules is not only critical to identifying targets for anti-oxidant intervention during disease, but also as potential markers of oxidative stress to identify dairy cattle that may be of at greater risk of disease.

Lipid metabolism is involved in the development of oxidative stress because of its link to inflammation. Lipid metabolizing enzymes, including increased cyclooxygenase (COX) 2, lipoxygenase (LOX), and some cytochrome P450 (CYP) isoforms, are also regulated during inflammatory-based diseases. For example, the enhanced production of oxygenated lipid mediators from these pathways is enhanced during mastitis caused by both gram-positive and gram-negative bacteria (Mavangira et al., 2015; Ryman et al., 2015a, 2015b). Interestingly, some of these oxylipid metabolites can target several of the sources of excessive ROS formation during acute inflammation. For example, 20-hydroxyecosatetraenoic acid (20-HETE) is a CYP-derived oxylipid metabolite that enhances reactive metabolite production by increasing mitochondrial production and activating NOX enzymes (Han et al., 2013). Conversely, the expression of NOX enzymes was decreased by lipoxin A4 derived from the LOX pathway (Wu et al., 2015). Therefore, understanding the contribution of lipid metabolism is critical for enhancing the resolution of oxidative stress by decreasing pro-oxidant lipids and increasing those with antioxidant effects.

In many diseases, oxylipids were shown to regulate several parts of the initiation, progression, and resolution of inflammation. One way of oxylipid-dependent regulation of inflammation is by influencing the development of oxidative stress (Fig. 1). First, some lipid metabolizing enzyme pathways produce reactive metabolite, particularly O_2^-, as a by-product (Sordillo and Aitken, 2009). Second, some primary oxylipid metabolites such as hydroperoxides from the LOX pathway are potent reactive metabolite that directly induce cellular oxidative stress and apoptosis (Sordillo et al., 2005). Third, other oxylipid metabolites such as 20-HETE, exert their pro-oxidant effects indirectly by stimulating reactive metabolite production from sources such as the mitochondria and the NOX enzyme pathway (Han et al., 2013). Fourth, some oxylipids such as 15-deoxy-delta 12, 14-Prostaglandin J_2 (15-dPGJ_2) exert antioxidant effects by directly or indirectly targeting and decreasing production reactive metabolite from sources such as mitochondria (Garg and Chang, 2004). The link between oxylipids and oxidative stress, therefore, offers opportunities for modulating inflammatory processes by directly targeting the metabolic pathways of these metabolites. The following sections focus on the demonstrated links between some oxylipids and oxidative stress during diseases and the opportunities that exist for controlling oxidative stress by targeting oxylipid biosynthesis.

3. Role of oxylipids in oxidative stress

Omega 6 (n-6) Polyunsaturated fatty acids (PUFA) such as arachidonic acid (AA) and linoleic acid (LA) and omega 3 (n-3) PUFA including α-linolenic (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the common substrates for oxylipid synthesis (Raphael and Sordillo, 2013). Metabolism of the PUFA substrates occurs after their hydrolysis from cell membrane phospholipids catalyzed by members of the phospholipase (PL) enzyme family, predominantly by PLA2. Alternatively, PUFA are metabolized while still esterified in cell membranes, which may explain their ability to modify cell function by altering the properties of the cell membrane lipid bilayer (Milne et al., 2015). The enzymatic pathways of COX, LOX, and CYP are involved in metabolizing PUFA with evidence of substrate preferences. For example, CYP enzymes will readily oxygenate EPA and DHA over linoleic acid and arachidonic acid when incubated with equimolar concentrations of these PUFA (Arnold et al., 2010). Non-enzymatic pathways are also involved in the oxygenation of PUFA mediated by free radicals such as O_2^-. Together, the biosynthetic pathways generate several oxylipids with at least 158 metabolites identified to date from human plasma (Wang et al., 2014a,b). In comparison to humans and animal models of diseases, the oxylipid and other lipidomic profiles in dairy cattle continue to be defined, laying the foundation for investigating the roles of these metabolites in inflammation and oxidative stress.

The general mechanism of oxylipid biosynthesis follows the removal of susceptible hydrogen atoms from PUFA structure and the concurrent or subsequent insertion of one or more oxygen molecules. In the enzyme-mediated oxygenation of PUFA, the initial formation of radicals at the active site is required for hydrogen abstraction. The free radical for COX enzymes is formed on active site tyrosyl residues, whereas, heme and non-heme iron radicals are present in CYP and LOX enzymes, respectively. Non-enzymatic metabolism also follows the same general mechanism but the free radical-mediated proton removal lacks the stereospecificity demonstrated by enzymatic pathways leading to the formation of an assortment of oxylipids (Milne et al., 2015).

The oxygenation of PUFA generates lipid hydroperoxides that add to the pool of ROS during oxidative stress (Sordillo and Mavangira, 2014). The LOX enzymes exist as several isoforms including 5-, 8-, 12-, and 15-LOX based on the site of oxygen insertion in the PUFA substrate. The active site Fe^{2+} is oxidized to the ferric hydroxide in the process of dioxygen insertion into the PUFA substrate and subsequently reduced to the Fe^{2+} form after reduction of the hydroperoxide ion. The hydroperoxides are potent ROS metabolites that were shown to participate in the development of pathological conditions. For example, the LA derived-13-hydroxyoctadecadienoic acid (13-HODE), was predominantly formed from the enzymatic pathway during *S. uberis* mastitis and exposure of bovine mammary endothelial cells to the upstream hydroperoxide, 13-hydroperoxyoctadecadienoic acid (13-HpODE) contributed to vascular dysfunction (Ryman et al., 2015a,b, 2016). The specific cellular effects of 13-HpODE and the arachidonic acid-derived 15-hydroxyperoxyeicosatetraenoic acid (15-HpETE) relevant to the pathogenesis of mastitis and other systemic inflammatory-based disease in dairy cattle may include oxidative stress-dependent endothelial cell apoptosis (Sordillo et al., 2005; Ryman et al., 2016). Specifically, 15-HpETE enhanced apoptosis by inhibiting protein kinase B (also known as Akt) signaling, downregulating the anti-apoptotic factor Bcl2 and upregulating pro-apoptotic Bax and the executioner caspase 3 (Weaver et al., 2001; Ryman et al., 2015a,b). Since the effects of 15-HpETE and 13-HPODE are similar to the direct effects of H_2O_2, the findings from these previous studies suggest that the primary oxygenation metabolites serve as inherent reactive electrophiles that can exacerbate oxidative stress during acute inflammation.

The catalytic mechanism during PUFA oxygenation can produce O_2^- as a byproduct particularly when the reduction of oxygen is uncoupled from its insertion in a PUFA substrate. Studies have suggested that both

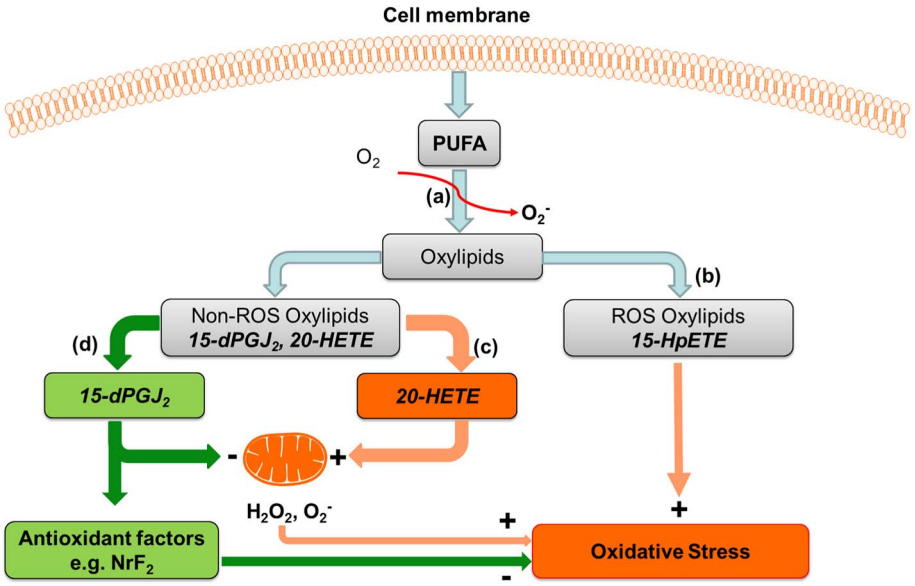

Fig. 1. (a) Polyunsaturated fatty acids (PUFA) released from the cell membrane phospholipids are metabolized enzymatically to produce oxylipids with the production reactive oxygen species (ROS) such as superoxide (O_2^-) in the process. (b) Some of the primary oxylipids are potent ROS such as the arachidonic acid-derived 15-hydroperoxyeicosatetraenoic acid (15-HpETE) that can directly damage cellular macromolecules. Other oxylipid metabolites target sites of reactive metabolite production like the mitochondria to induce production (c) such as is the case of the cytochrome P450-derived 20-hydroxyeicosatetraenoic acid (20-HETE). (d) Other oxylipids such as the dehydration product of prostaglandin D2 (15-dPGJ$_2$) decrease reactive metabolite production by directly decreasing production or by stimulating antioxidant factors such as nuclear factor E2-related factor 2 (Nrf_2). + induce production; − decrease production; green arrows, antioxidant pathways; orange arrows, pro-oxidant pathways. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

COX and LOX enzymes are inefficient sources of O_2^- due to their utilization of dioxygen in PUFA oxygenation (Noguchi et al., 2002). However, significant production of reactive metabolites was shown for hepatic CYP enzymes incubated with inhibitors of both SOD and catalase enzymes involved in the metabolism of O_2^- and H_2O_2, respectively (Bondy and Naderi, 1994). Co-incubation of hepatic microsomes with ethanol, toluene, and phenobarbital did not enhance the production of ROS, (Bondy and Naderi, 1994) suggesting that CYP could produce reactive metabolite with no substrate requirement. The substrate-independent reactive metabolite production by CYPs supports the apparent uncoupling of NADPH reduction from the subsequent activation and insertion of an oxygen atom into PUFA substrates. The apparent uncoupling is greatest in the CYP2E1 isoform which was described as a leaky enzyme demonstrating a coupling of NADPH reduction to substrate oxygenation of only 0.5–3% (Lu and Cederbaum, 2008). The catalytic production of reactive metabolite by CYP2E1 contributed significantly to the carbon tetrachloride-induced hepatotoxicity in a murine model of oxidative stress (Park et al., 2010). Several other CYP isoforms in hepatocytes (CYP4A, CYP3A4, 1A1, 1A2, and 2B6) and CYP2C9 in endothelial cells are important lipid metabolizing enzymes and generators of reactive metabolite (Westphal et al., 2015). These data suggest that the multiplicity of the CYP enzymes generating reactive metabolite may preclude effective modulation of oxidative stress during disease by targeting specific isoforms. Further, inhibiting CYP isoforms to reduce reactive metabolite production in acute illness is complicated by generalized suppression of several CYP isoforms (Westphal et al., 2015). Therefore, targeting the CYP-derived oxylipids may be more beneficial to limit reactive metabolite production while preserving essential functions of the CYP enzymes. Additional studies are needed in dairy cattle to determine the extent to which this pathway can be manipulated to control health disorders during the periparturient period.

4. Non-ROS oxylipids enhance or diminish production of ROS

4.1. Cyclooxygenase-derived oxylipids

Cyclooxygenases exist as constitutively expressed COX-1 and inducible COX-2 isoforms. With arachidonic acid as the PUFA substrate, hydrogen removal and insertion of dioxygen to form the unstable PGG_2 occurs at the oxygenase site followed by translocation to the peroxidase site where reduction to PGH_2 occurs. Subsequently, PGH_2 is converted to downstream prostanoids including PGD_2, PGE_2, PGF_2, PGI_2, and PGJ_2 by various PG synthases as well as conversion into thromboxanes (TX) A_2 and B_2 by thromboxane synthase. Many studies showed that the increased production of reactive metabolite following COX2-induction was due to the effects of the COX-derived oxylipids (Cho et al., 2011; Munoz et al., 2015). With the knowledge that COX inhibitors may suppress the constitutive physiological prostanoid production, targeting the specific oxylipid metabolites may offer better responses and reduce complications related to clinical use of COX 2 blockers.

A major downstream product of PGH_2 during inflammation is PGE_2 that mediates its effects through the PGE_2 prostanoid (EP) receptor subtypes 1, 2, 3 and 4. Production of PGE_2 induces oxidative stress in a receptor-dependent manner in models of neuronal degenerative diseases such as Alzheimer's disease. For example, cerebral PGE_2 production increased ROS formation and development of neuronal oxidative stress detected by increased concentrations of markers including arachidonic acid-derived F_2-isoprostanes (F_2-IsoP) and DHA-derived neuroprostanes (Montine et al., 2002). Deletion of the EP_2 and EP_3 receptors in the neuronal tissue in mice and neural cell cultures diminished oxidative-stress related changes (Montine et al., 2002). In contrast, the deletion of EP_2 receptors in a model of intracerebral hemorrhage exacerbated O_2^- production and oxidative carbonylation of proteins suggesting that EP_2 receptor activation was protective (Wu et al., 2016a, 2016b). The specific sources of reactive metabolite after PGE_2 stimulation appears to be the NOX enzymes based on EP_4 receptor activation detected in human hepatocytes in response to LPS and phorbol myristate acetate (PMA) (Sancho et al., 2011). Dairy cows with mastitis show increased PGE_2 production in the face of decreasing activities of antioxidant enzymes (Atroshi et al., 1996) and low dietary Se (Maddox et al., 1990). Similarly, cows with endometritis showed increased PGE_2 concentrations. Studies using endometrial explants and isolated stromal or epithelial cells showed that LPS was responsible for PGE_2 production, but was also associated increased expression of EP2 and EP4 (Herath et al., 2009). The possibility exists that the detrimental effects of PGE_2 may be limited by EP receptor antagonists or enhancing the degradative PG dehydrogenase enzymes, however, further studies are needed to refine this hypothesis.

Prostaglandin I_2 is not just a vasodilator but also a modulator of inflammatory processes, particularly in conditions characterized by oxidative stress. Overexpression of PGI synthase in murine models of acute lung injury prevented bleomycin-induced oxidative stress by enhancing the expression of antioxidant enzymes (Zhou et al., 2011). In another model, supplementation of the PGI_2 agonist, beraprost sodium, prevented aluminum-induced hippocampal oxidative stress suggesting

that relative deficiencies of certain oxylipids promote oxidative stress (Pan et al., 2015). Deficiency of PGI_2 may be as a result of the direct nitration and inhibition of PGI synthase by peroxynitrite produced by the reaction of O_2^- and nitric oxide as demonstrated in endothelial cells (Weaver et al., 2001). Oxidative stress, therefore, may have a dual effect on PGI_2 synthesis, first increasing production by indirectly stimulating the COX2 pathway and, secondly, by the direct inhibition of the activity of PGI synthase. The effects nitric oxide on PGI_2 synthesis and potentially oxidative stress in bovine inflammatory conditions are unknown, however, experimental bovine *Escherichia coli* mastitis was characterized by acute increases in nitric oxide in milk (Blum et al., 2000). Exposure of bovine mammary epithelial cells to a nitric oxide donor alone or in combination with cytokines including TNF-α altered production of various prostaglandins (Piotrowska-Tomala et al., 2012). Nitric oxide production is also increased in dairy cattle with puerperal endometritis (Li et al., 2010). Thus, the elevations of nitric oxide in inflammatory conditions including mastitis and metritis may benefit from supplementation of PGI_2 mimetics to limit the oxidative stress responses and therefore, the inflammatory process.

Some COX-derived oxylipids have demonstrated roles as antioxidant inducers through a variety of mechanisms. For example, 15-dPGJ_2, formed from the dehydration of PGD_2 was shown to be protective by activating PPARγ receptors (Haskew-Layton et al., 2013). Through the activation of antioxidant response elements, 15-dPGJ_2 resulted in the induction of several antioxidant enzymes including heme oxygenase-1, SOD, and glutathione synthesizing enzymes (Shibata, 2015). In a murine macrophage cell line, RAW264.7, 15-dPGJ_2 inhibited inflammasome activation, which was associated with increased production of reactive metabolites during innate immune defenses (Maier et al., 2015). In vitro studies using bovine mammary epithelial cells showed that 15-dPGJ_2 partially stimulated a pro-inflammatory response while activating anti-oxidant genes including SOD and ferritin heavy chain (Lutzow et al., 2008). The multiple targets by which 15-dPGJ_2 may afford anti-oxidant protection and the inhibition of both NFκB and inflammasome activation, make 15-dPGJ_2 an attractive therapeutic target as responses may be cell and tissue specific. The oxylipid, 15-dPGJ_2, could therefore represent a novel therapy modality with unique properties that not only stimulate an inflammatory response but also activate protective mechanisms such as the antioxidant genes to limit damaging inflammation.

4.2. Lipoxygenase-derived oxylipids

Apart from being ROS species themselves, hydroperoxides increased production of other reactive metabolite from sources including the mitochondria and the NOX enzyme system. For example, the 13-HpODE induced mitochondrial reactive metabolite production and cellular apoptosis via cytochrome *c* release, loss of mitochondrial membrane potential, and increased mitochondrial Fe^{2+} uptake in bovine aortic endothelial cells targeted antioxidants (Dhanasekaran et al., 2005). The activation of NOX was linked to subsequent mitochondrial reactive metabolite production based on the depletion of mitochondrial GSH following NOX activation in endothelial cells (Doughan et al., 2008). Reduction of 15-HpETE to the hydroxy derivative (15-HETE) also induced mitochondrial ROS production in pulmonary endothelial and smooth muscle cells (Li et al., 2016). The possibility of multiple targets by the same hydroperoxides suggests that specifically targeting the pathway of their production may be more efficient in controlling oxidative stress by limiting their overall abundance of hydroperoxides in inflammatory conditions.

Changes in cellular redox status are also involved in the activation of LOX enzymes and may represent a possibility for positive feedback relationships that perpetuate detrimental oxidative damage. The ratio of reduced to oxidized coupled molecules such as reduced GSH to oxidized GSH as well as reduced Trx to oxidized Trx determine the cellular redox status (Sordillo and Aitken, 2009). Both GSH and Trx are essential co-factors in the reduction of hydroperoxides and other reactive metabolites in reactions mediated by GPx and Trx reductase enzymes, respectively. In the process, GSH and Trx are converted to oxidized forms which must be reduced by the glutathione reductase and Trx reductase enzymes, respectively (Mattmiller et al., 2013). Maintenance of a normal GSH/GSSG ratio is critical as the depletion of GSH in bovine aortic and mammary endothelial cells was associated with increased production of reactive metabolites and lipid hydroperoxides (Cao et al., 2000; Weaver et al., 2001). In vivo, the expression of a specific isoform of the LOX enzymes, 15-LOX1, was markedly increased in bovine mammary tissue in the peri-parturient period (Aitken et al., 2009). The dependence of GSH/GSSG system on the availability of Se means that altered levels of this trace mineral can result in a reduction in the decrease of the GSH/GSSG ratio and the development of oxidative stress.

The activation of another LOX isoform, 5-LOX, in B-lymphocytes was dependent on the production of O_2^- and hydroperoxides produced from granulocytes (Werz et al., 2000). The metabolism of arachidonic acid by 5-LOX initially generates 5-hydroperoxyeicosatetraenoic acid (5-HpETE). Sequential reduction of 5-HpETE to the hydroxyl (5-HETE) and dehydrogenation to the ketone derivative (5-oxoETE) both require reactive metabolite production. The NOX-associated oxidative burst in eosinophils and monocytes, increased the formation of the 5-oxoETE because the NOX enzymes generate NADP in releasing O_2^-. Similar oxidative stress-dependent formation of 5-oxoETE formation was also shown in structural cells including human endothelial cells and intestinal and airway epithelial cells (Erlemann et al., 2006, 2007). Because 5-oxoETE is a potent chemoattractant of leukocytes to inflammatory sites, the overproduction of 5-oxoETE could result in uncontrolled infiltration with inflammatory cells. Indirectly, excessive formation of 5-oxoETE may perpetuate the oxidative stress-inflammatory cycle by attracting immune cells with the reactive metabolite production capacity such as neutrophils and monocytes. Targeting formation of 5-LOX-derived oxylipids may be desirable to break the oxidative stress-oxylipid synthesis cycle during inflammation.

Some LOX-derived oxylipids may indirectly exert anti-inflammatory effects by modulating oxidative stress. For example, the DHA-derived LOX metabolite, resolvin D1, decreased oxidative stress in a murine LPS-model of acute lung injury, in part, by the reduction in lipid peroxidation, increased SOD activity, and the induction of the antioxidant HO-1 enzyme (Wang et al., 2014a,b). Another LOX-derived DHA metabolite, protectin, inhibited ROS production in human neutrophils stimulated by PMA by inhibiting the phosphorylation of the NOX enzyme complex (Liu et al., 2014). Induction of ROS in RAW264.7 murine cells by 3-morpholinosydnonimine hydrochloride was diminished by the downstream LOX metabolites, 9-oxo-ODE and lipoxin A_4 (LXA_4) (Mattmiller et al., 2014). A possible mechanism for LXA_4 may be the demonstrated activation of NrF2 activity in an oxygen-glucose deprivation oxidative stress model in astrocytes (Wu et al., 2015). Several metabolites derived from the LOX metabolism of several PUFA, referred to as special pro-resolving metabolites ameliorate inflammatory conditions in part by diminishing oxidative stress responses (Serhan et al., 2008). Therefore, relative deficiencies of pro-resolving oxylipids may exacerbate the oxidative stress responses in various diseases.

A possible formation of reactive metabolite related to LOX catalysis is the release of Fe^{2+} from the active site following suicidal inactivation. The inactivation follows the oxidation of the labile histidine residues in the active site that are responsible for chelating Fe^{2+} in place (Cheng and Li, 2007). The released Fe^{2+} becomes available for the generation of ROS including soluble hydroxyl or lipid hydroxyl radicals through the Fenton reaction. The use of inhibitors of ROS generation such as deferoxamine, which chelate transition metals including Fe^{2+} demonstrated the involvement of free Fe^{2+} in mediating oxidative stress (Cheng and Li, 2007). In endotoxin induced bovine mastitis and in mammary epithelial cell culture, deferoxamine decreased tissue damage of disease by decreasing damaging ROS production via Fe^{2+}

chelation (Lauzon et al., 2005, 2006). The degree to which the LOX enzymes may contribute to the labile pools of Fe^{2+} with consequent increased ROS formation thus perpetuating the oxylipid-ROS generation cycle remains to be elucidated.

4.3. Cytochrome P450-derived oxylipids

Apart from the catalytic formation of reactive metabolites by CYP enzymes, the concurrent metabolism of PUFA into oxylipids may be more significant in altering cellular redox balance. In dairy cattle, intramammary infusion of LPS or *E. coli* was associated with decreased expression and transcription of CYP450 genes in the liver (Jørgensen et al., 2012). This was concurrent with the increased transcription of genes involved in the responses to oxidative stress including GPxs (Jørgensen et al., 2012). Suppression of CYP450 was also shown in murine models particularly following exposure to LPS (Theken et al., 2011). The CYP2C subfamily has the main PUFA metabolizing isoforms which generate oxylipids whose effects on oxidative stress depend on parent substrate. The 2C9 isoforms enhance ROS production and pro-inflammatory effects of linoleic acid in endothelial cells by activating NFκB (Viswanathan et al., 2003). Increased permeability of endothelial cell monolayers to albumin after exposure to linoleic acid were predominantly the result of the formation of oxylipids known as epoxyoctadecenoic acids (EpOME). The endothelial cell permeability was further enhanced by the subsequent conversion of the EpOMEs to dihydroxy metabolites (DiHOMEs) by the soluble epoxide hydrolase enzyme (sEH) (Slim et al., 2001). In contrast, arachidonic acid epoxygenation by CYP2C9 and CYP2C8 into various epoxyeicosatrienoic acids (EET) isomers resulted in anti-oxidative and anti-apoptotic effects in endothelial cells and other cell lines (Dhanasekaran et al., 2006). The differential effects of metabolites from similar pathways illustrate the complexity of substrate-CYP interaction in modulating oxidative stress. Thus, by altering the proportions of available substrates, oxidative stress responses may be attenuated in conditions where CYP expression and activity are enhanced. Our studies in naturally occurring bovine coliform mastitis showed increased epoxygenation products (Mavangira et al., 2015), contrary to the demonstrated suppression of CYP genes in other studies. The knowledge of the deferential effects of CYP-derived epoxides that are dependent on PUFA substrate can be useful in identifying oxylipids whose protective effects can be promoted either through substrate or functional mimetic compounds. Inhibition of the sEH enzyme could also limit the formation of more toxic oxylipids such as linoleic acid-derived DiHOMEs while simultaneously enhancing the beneficial types such as the arachidonic acid-derived EETs.

The beneficial effects of EETs are mediated, in part, by their modulation of redox-sensitive transcription factors including NrF2. Oxidative stress and apoptosis of HUVECs induced by TNFα were prevented by direct exposure to 11,12-EET and transfection with CYP2C8. The effects were attributed to EET-mediated stimulation of the antioxidant regulator, NrF2 which in turn decreased TNFα-induced ROS production (Liu et al., 2015). Another EET isomer, 14,15-EET, also decreased oxidative stress by suppressing the expression of a transcriptional repressor of the HO-1 antioxidant protein known as Bach (Yu et al., 2015). A reciprocal relationship also may exist in which activation of transcription factors that promote antioxidant activity also induce the expression of CYPs involved in EETs biosynthesis. For example, the activation of Nrf2 in HepG2 cells induced the expression of CYP2J2 (Lee and Murray, 2010).

The effect of oxidative stress on CYP expression is not clear and may vary among animal species, tissue and cell type, the inciting stimulus, and specific CYP isoforms. Carbon tetrachloride-induced oxidative stress in mice was associated with increased CYP2E1 expression and lipid peroxidation, suggesting a direct activation of this CYP isoform (Park et al., 2010). In contrast, the expression of several CYP isoforms was downregulated in-vivo during murine LPS-sepsis models with recovery occurring 24 to 48 h later (Theken et al., 2011). The differential activation of CYPs in various health conditions related to periparturient dairy cows merits future investigations based on what is known in other species. A better understanding of CYP activation within the context of dairy cattle health disorders may identify optimal periods for either blocking or enhancing expression of CYP enzymes to promote the production of antioxidant oxylipids.

Another major CYP-derived oxylipid formed from the hydroxylation of arachidonic acid to 20-HETE is associated with oxidative stress-related vascular dysfunction in cardiovascular and cerebral circulations (Waldman et al., 2016). Several mechanism for induction of ROS formation were shown for 20-HETE and include increased NFκB (Ishizuka et al., 2008) activation of NOX enzyme complex and mitochondrial ROS production (Lakhkar et al., 2016; Waldman et al., 2016). Chemical inhibition of 20-HETE biosynthesis in cerebral ischemia and in-vivo models of spontaneous hypertension abolished the oxidative stress mediated pathology (Han et al., 2013; Toth et al., 2013). The detrimental effects of 20-HETE in chronic inflammatory conditions mediated through oxidative stress are in contrast to some reported effects of 20-HETE in acute inflammatory conditions. For example, the production of 20-HETE was diminished in an in-vivo murine LPS-induced sepsis model which is characterized by oxidative stress (Tunctan et al. 2013). Follow-up studies utilizing 20-HETE mimetics in the sepsis models was shown to improve clinical effects of LPS administration such as the development of hypotension (Tunctan et al., 2013a,b; Senol et al., 2016). In contrast, other studies demonstrated that murine acute inflammation models induced by LPS administration or the cecal ligation and puncture technique were associated with several orders of magnitude in the increase of 20-HETE (Willenberg et al., 2015). In dairy cattle, 20-HETE concentrations were previously observed to be stable from 14 days before calving through 84 days after calving (Raphael et al., 2014). In naturally occurring bovine coliform mastitis, significant 20-HETE production was detected simultaneously with increased oxidative stress as determined by reactive metabolite production and elevated 15-F_{2t}-Isop lipid peroxidation products (Mavangira et al., 2015, 2016). The differential effects of 20-HETE on oxidative stress in chronic and acute inflammatory require further studies to determine the usefulness of 20-HETE as a therapeutic target in different inflammatory conditions.

5. Other lipid mediators and oxidative stress

Much of the focus of this paper has been devoted towards the oxylipid products of lipid metabolism, however, other lipid mediators can induce oxidative stress and may be relevant in inflammatory conditions of the dairy cow. Other lipid mediators can be derived from the major phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine, phosphatidylinositol, cardiolipin, sphingomyelin and glycosphingolipids (Pamplona, 2008). Platelet activating factor (PAF) is one such lipid mediator with signaling properties, whose production is increased during oxidative stress as was shown in bovine aortic endothelial cells (BAEC) cultured in se-deficient medium (Cao et al., 2001). Exposure of monocytes to PAF and lipid hydroperoxides from dairy cattle increased superoxide production (Löhrke et al., 2005). It is also conceivable that changes in sphingolipids could influence oxidant status of dairy cattle. This is supported by the evidence that higher body condition dairy cows suffered greater oxidative stress compared to those with lower body condition (Bernabucci et al., 2005). In similarly over conditioned dairy cows (obese), greater plasma concentrations of sphingolipids and in particular, ceramide, were reported (Rico et al., 2015). Ceramide is an intracellular mediator that links NOX stimulation and the resulting increased mitochondrial ROS production. Because of the various changes described thus far in the bovine lipidome, understanding the contribution of various lipid mediators to oxidative stress and inflammation is important to understanding an overall interaction of several metabolites including those defined by proteomics, transcriptomes, and

lipidomics.

6. Oxylipids are useful biomarkers of oxidative stress

Many studies in dairy cattle evaluating the presence of oxidative stress or its amelioration by supplementation of PUFA substrates or their precursors are hampered by the challenges currently recognized in the accurate diagnosis of oxidative stress. These challenges, outlined by Celi (2011), may be addressed by further evaluating effectiveness of macromolecular (DNA, protein, and lipids) damage products. Because, PUFAs are highly susceptible to peroxidation during oxidative stress, specific peroxidation metabolites offer a better opportunity for accurate oxidative stress diagnosis in dairy cattle. The metabolism of PUFA occurring non-enzymatically with free radical-mediated hydrogen abstraction, followed by addition of oxygen, and intramolecular rearrangement generates stable oxylipid products. The metabolism of arachidonic acid, for example, generates isomers of prostaglandins known as isoprostanes (IsoPs) (Milne et al., 2015). Isoprostanes exist for each COX-derived prostanoid class of which several diastereomeric metabolites can be produced. Conversely, intramolecular rearrangements in some isoprostane classes such as IsoPs D_2 and E_2 are possible, adding to the pool of COX-derived oxylipid prostanoids such as PGD_2 and PGE_2. The metabolism of other long chain fatty acids such as the n-3 PUFA also involves the formation of isoprostane-like metabolites at much greater rates of reactivity than arachidonic acid because of increasing double bonds (Milne et al., 2015).

Isoprostanes are currently considered the gold standard markers of oxidative stress and were utilized in human conditions with oxidative stress including sepsis, atherosclerosis, coronary heart disease (Milne et al., 2015). The F_2-isoprostanes, specifically, were shown to reliably detect oxidative stress induced by the free radical generators, carbon tetrachloride induced and 2,2′-azobis-2-methyl-propanimidamide, dihydrochloride (AAPH), and in LPS-induced sepsis in mice. Across animal species with various disease conditions, urinary concentrations of a specific F_2-IsoP (15-F_{2t}-IsoP) were explored in an attempt to determine the contribution of oxidative stress (Soffler et al., 2010). In dairy cattle specifically, 15-F_{2t}-IsoP concentrations were elevated during coliform mastitis (Mavangira et al., 2016) and in cattle with retained fetal membranes (Kankofer, 2002). Retained fetal membranes frequently predispose dairy cattle to the development of metritis. Both mastitis and metritis are examples of dairy cow diseases whose incidence increases with declining antioxidant capacity (Miller et al., 1993), and the demonstration of 15-F_{2t}-IsoP in these diseases suggests a utility of this oxylipid in assessing the role of oxidative stress in inflammatory conditions of dairy cattle.

In addition to their utility as biomarkers of oxidative stress, IsoPs have potent effects on inflammatory processes, through differential effects on oxidative stress responses depending on the PUFA substrate. For example, F_2-IsoPs from arachidonic acid exacerbate oxidative stress by mediating TXA_2-like effects through TP receptor activation (Comporti et al., 2008; Bauer et al., 2014). In contrast, arachidonic acid-derived J_2 and A_2 IsoPs and the EPA-derived F_3-isoprostanes limited proinflammatory responses through the inhibition of NFκB activation by stimuli including LPS, TNFα and IL-1β in macrophages (Brooks et al., 2011). Thus, the greater reactivity of n-3 PUFAs relative to n-6 may be utilized to modulate oxidative stress responses during disease. Another significant contribution of the free-radical-mediated peroxidation is the potential contribution to the enzymatically-derived oxylipids. For example, PGE_2 and PGD_2 may be biosynthesized independent of the COX pathway from the molecular re-arrangement of the free radical-generated IsoPs of the E and D series, respectively (Gao et al., 2003). Prostaglandin $F_{2\alpha}$ is another prostanoid also produced through free radical peroxidation adding to the enzymatically derived $PGF_{2\alpha}$ (van't Erve et al., 2016). The combined source of $PGF_{2\alpha}$ may increase its pool which may also be associated with increased oxidative stress. Thus, in addition to being valuable oxidative stress biomarkers, the formation of some oxylipids may represent alternate pathways of biosynthesis, representing a contribution of previously unrecognized perturbations in the redox and oxidant status in some inflammatory conditions.

Other than the IsoPs, arachidonic acid- derived and linoleic acid-derived hydroxyl metabolites have been utilized as oxidative stress markers. For example, 9-HETE was substantially increased in atherosclerotic plaques from clinically symptomatic coronary heart disease patients (Mallat et al., 1999). Similarly, 9-HODE from linoleic acid metabolism was increased at levels even greater than the F_2-IsoPs in unstable atherosclerotic plaques (Jira et al., 1998). Although the oxidant status was not investigated, oxidized linoleic acid oxylipids were abundant in mammary tissues during *Streptococcus uberis* bovine mastitis (Ryman et al., 2015a,b). These data suggest that other oxylipids may detect oxidative in some conditions especially in situations of imminent catastrophic pathology. More significantly, the multiplicity of oxylipids identified thus far may broaden the available oxidative stress biomarkers which may further improve detection.

7. Regulation of oxylipid metabolizing systems – opportunities for intervention

The importance of regulating oxidative stress in pathological inflammatory conditions in dairy cattle was recognized for a long time. For example, diseases including mastitis, metritis and retained placenta have increased incidence because of underlying oxidative stress. Conversely, the supplementation of antioxidants including Se and vitamin E in the periparturient period was associated with decreased post-partum disorders (Miller et al., 1993). However, not all antioxidant supplementation result in beneficial outcomes. Bouwstra et al. (2010a,b) showed an increased occurrence of mastitis following supplementation of vitamin E at low or high doses in animals starting with plasma vitamin E concentration of > 14.5 μg/mL. Such a discrepancy may be explained by the possibility of vitamin E participating in the sequential free radical formation as a consequence of a deficient vitamin E regeneration system (VERS) (Bouwstra et al., 2010a,b). It is also possible that excess vitamin E might have decreased the physiological amounts of RM required for normal signaling processes, a situation referred to as reductive stress. Considering the work by Bouwstra et al., it is important to recognize the following points. First, Vit E supplementation appears to work better when the VERS is concurrently enhanced. For example, combined Vit E and Se supplementation offered better protection than either alone, probably because of free radical chain termination and efficient regeneration of the VERS through the Se-dependent GPx system. Secondly, there was no direct determination of more sensitive oxidative stress markers including DNA, protein and better lipid peroxidation markers. MDA, despite being a commonly utilized lipid peroxidation marker in the past, has major draw backs due to poor specificity and sensitivity (Celi, 2011). The lack of beneficial effects of Vit E supplementation in dairy cows developing mastitis is similar to the lack of clinical improvement in antioxidant supplementation in humans which have been explained by reasons including study design limitations where pathology had already occurred, inability to deliver antioxidants at sites where they are needed, and challenges of accurately assessing oxidative stress (Biswas, 2016). Targeting oxylipid biosynthesis not only offers alternative markers for oxidative stress diagnosis, but also the potential for limiting oxidative stress-related disease pathology by diminishing pro-oxidant or enhancing antioxidant oxylipids formation. The feasibility of targeting oxylipids and other lipid mediators will rely on first defining oxylipid profiles during health and their patterns of change during various inflammatory disorders of dairy cattle. The regulation of oxylipid biosynthesis occurs at several levels including modification of type and abundance of available substrate, modulation of the lipid biosynthetic pathways through pharmacologic, and the degree of metabolism of specific oxylipids.

7.1. Modification of oxylipids through supplementation of PUFA substrate

Modification of dietary PUFA substrate may be the obvious approach to modifying oxylipid biosynthesis. In humans (Calder, 2008) and in pigs (Bruins et al., 2013), the supplementation of PUFA altered oxylipid profiles in peripheral blood leukocytes and plasma, respectively. The ruminant however, presents specific challenges of ruminal degradtion and/or modification of dietary PUFA effectively limiting what becomes available for intestinal aborption (Lock and Bauman, 2004). Recent studies in dairy cattle found that supplementation with n-3 PUFA through direct infusion into the abomasum could effectively modify both plasma and peripheral blood leukocyte PUFA content (Ryman et al., 2017). Further, ex-vivo agonist challenges of these leukocytes showed differential oxylipid production with *S. uberis* inducing 15-oxoODE while LPS induced 5,6-LXA_4, both oxylipids with predominantly antiinflammatory properties (Ryman et al., 2016). Evidence suggestive of the potential for n-3 PUFA supplementation in reducing inflammatory gene expression including IL-6, and IL-8 was accompanied by decreased ROS production in BAEC (Contreras et al., 2012). These changes were also associated with decreases in 9-HODE, an oxylipid linked to the non-enzymatic lipid peroxidation. Although supplementation of some fatty acids such as conjugated linoleic acids afforded protection from oxidative damage in mammary epithelial cells (Basiricò et al., 2015, 2017), benefits have not always translated to in-vivo use in cattle (Hanschke et al., 2016). Similarly, use of forages including flaxseed and linseed that have high concentrations of ALA, the precursor for the anti-inflammatory and anti-oxidative n-3 PUFA (EPA and DHA), showed conflicting results. Increased oxidative capacity by PUFA supplementation was explained by increased substrate available for peroxidation because co-supplementation with a combination of vitamin E and polyphenols as antioxidants (Gobert et al., 2009) and an antioxidant supplement (Wang et al., 2010) ameliorated lipid peroxidation. The challenge in balancing the resulting pro- and anti-oxidative oxylipids following n-3 supplementation may explain the variable results from human studies including clinical trials as well as in dairy cattle. Much remains to be determined on how substrate supplementation can be fine-tuned to balance the anti-oxidative oxylipids and those with pro-oxidative effects during disease in dairy cattle.

7.2. Pharmacological partial inhibition and preservation of specific oxylipids

Oxylipids can be modified by pharmacological inhibition of biosynthetic pathways involved; however, use of inhibitors may be associated with the development of complications. For example, prolonged non-steroidal anti-inflammatory drug (NSAID) use was associated with cardiovascular complications, renal tissue damage, and gastrointestinal ulceration (Ghosh et al., 2015). In addition, use of a COX2 inhibitor, rofecoxib, in mice was associated with the accumulation 20-HETE in plasma, which may provide an alternate explanation for the cardiovascular complications other than the altered PGI_2/TXA_2 ratio due to prolonged NSAID use (Liu et al., 2010). The complications associated with drugs currently used in humans and veterinary medicine may be minimized by using the concept of polypharmacology where drugs are combined at lower doses that only exert intended effects due to combined pharmacodynamic interactions (Meirer et al., 2014). This approach is expected to ensure partial production of oxylipid species necessary for mediating effective proinflammatory effects as well as those that promote inflammation resolution. Examples of polypharmacological approaches that affect oxylipid biosynthesis include the dual COX2/sEH inhibitor (Hye Khan et al., 2016) that decreased oxidative stress in diabetic rats and a dual COX/5-LOX inhibitor (Kumar et al., 2015) that decreased oxidative stress, inflammatory cytokine production, and improved cognitive function in a mouse model of neurodegeneration. Treatment of bovine *Klebsiella pneumoniae* mastitis with a combination of flunixin meglumine (COX-blocker) and nordihydroguaiaretic acid (LOX-blocker) decreased PGE_2 and TXA_2 concentrations in milk and improved signs of mammary gland inflammation (Rose et al., 1991). Further studies are required to determine whether improved inflammatory and oxidative responses are the result of oxylipid profile changes and determine optimal drug combinations for different inflammatory states.

7.3. Modification of oxylipid production via modulation of other biosynthetic pathways

Evidence exists suggesting that enhancing production of oxylipids in one pathway will influence the production of oxylipids via other pathways. For example using sEH inhibitors prolongs the presence of EETs that are beneficial in both being anti-oxidative and anti-inflammatory during murine LPS-induced sepsis. In turn, the elevated EETs were associated with decreased proinflammatory oxylipids including PGE_2 and TXB_2 (Schmelzer et al., 2005). In other diseases, humans with severe asthma characterized by oxidative stress had decreased concentrations of the anti-inflammatory and anti-oxidative lipoxin A_4. Whole blood leukocytes and bronchoalveolar lavage fluid cells collected from asthmatic patients incubated with sEH inhibitors demonstrated increased production of lipoxin A_4 (Ono et al., 2014). Another useful approach is a modification of COX2 enzymes by acetylation of the active site using aspirin to switch from PGH_2 to 15*R*-HETE which is further converted to a more potent anti-inflammatory isomer of LXA_4, 15-epi-LXA_4, by peripheral blood leukocytes (Serhan, 1997). It is unclear if the use of salicylate in dairy cattle will be beneficial given that 3rd or greater lactation cows treated with salicylate had an increased risk of metritis (Farney et al., 2013). In a related study, the removal of salicylate treatment in drinking water for early lactation dairy cows resulted in increased production of the proinflammatory oxylipids including 9- and 13-HODE and TXB_2 (Farney et al., 2013). Thus, pharmacological inhibitors can be used to preferentially promote the production of oxylipids with anti-oxidant properties while simultaneously inhibiting those with pro-oxidant properties.

7.4. Influencing the profiles of oxylipid metabolism through regulatory mechanisms

Another level for influencing oxylipid biosynthesis is targeting pathways through modifying cellular redox status. Redox regulation of oxylipid biosynthesis was recently reviewed with particular emphasis on the role played by the trace mineral Se (Mattmiller et al., 2013). Se is essential for maintaining the glutathione-peroxidase system vital for cellular redox balance. Dairy cows consuming insufficient dietary Se had increased proinflammatory oxylipid production (Maddox et al., 1990). In vitro, Se deficiency of various cells altered redox tone and oxylipid biosynthesis (Cao et al., 2000; Weaver et al., 2001; Sordillo et al., 2005; Mattmiller et al., 2014). Supplementation of other antioxidants such as vitamins C and E in mice fed low and high fat diets decreased F_2-IsoP and 9-HETE concentrations while increasing CYP-derived and LOX-derived oxylipids (Picklo and Newman, 2015). The use of Se and its benefits in modulating inflammation in dairy cattle has been reviewed elsewhere (Sordillo, 2013). Research continues to explore ways of enhancing the Se availability in dairy cow diets such as utilizing more bioavailable Se sources like Se-yeast and Se-fertilized forages (Hall et al., 2014; Seboussi et al., 2016). Improving oxidant status in postpartum dairy cattle can also be achieved by other methods using rumen protected ingredients such as methionine (Osorio et al., 2014). Further research is needed to determine if use of antioxidants improves outcomes of inflammatory diseases by modifying lipid mediator profiles.

The positive feedback link between oxylipid production and oxidative stress is illustrated classically by the dependency of the LOX pathway on cellular redox status. Depletion of Se in RAW264.7 cells

modulated the production of several oxylipids (Mattmiller et al., 2014) suggesting that Se represents a viable target for controlling oxidative stress in diseases. In turn, the LOX-derived oxylipids induce oxidative stress by activating several ROS producing pathways and activation of redox-sensitive transcription factors such as activator protein 1. Thus, understanding the changes in the LOX-derived oxylipid metabolite profiles in inflammatory diseases is crucial to determine whether interventions should target the production of and limiting the degradation of the anti-oxidative oxylipids.

8. Conclusions and future directions

The accumulated evidence on the roles of PUFA oxidizing pathways and the metabolic products produced in enhancing ROS production provides insights on opportunities for modulating oxidative status in several pathologies of the periparturient dairy cow. Approaches for enhancing oxylipids with antioxidant benefits include substrate modification, pharmacological inhibition of metabolic pathways, and targeting regulatory aspects of oxylipid biosynthesis such as Se-dependent regulation. The success of any of these approaches in diminishing oxidative stress depends on understanding many aspects of oxylipid biosynthesis during disease. First, defining the roles of individual oxylipids during disease is critical to determine the utility of targeting the given metabolite. Second, changes of oxylipid profiles in different diseases should be evaluated based on the knowledge that oxylipid profiles will differ among the various pathophysiological states. Knowledge of disease-specific oxylipid profiles will not only allow customized interventions but also provide other diagnostic metabolites that can be used for the detection of oxidative stress. Evidence has shown that the commonly used isoprostane oxylipids as gold standard oxidative stress biomarkers in humans may not always detect oxidative stress responses suggesting that other oxylipids must be explored. Combination strategies such as utilizing PUFA supplementation and combined pharmacological modification of pathways may be the more efficacious at altering oxylipid profiles to impact oxidative stress responses. Finally, the continual improvements in diagnostic methods such as the mass spectrometry and nuclear magnetic resonance techniques will be useful in defining interactions of relevant oxylipid biosynthetic pathways during oxidative stress. Several metabolomics approaches in disease frequently evaluate nucleic acid, protein, and carbohydrate metabolism but omit the metabolites produced through the oxylipid biosynthesis and consequently their contribution to pathological processes during disease. The comprehensive metabolomics approaches may be utilized to determine the contributions of various metabolites in oxidative stress and particularly explore the roles played by oxylipids to identify opportunities for limiting inflammatory pathology in humans and animals.

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References

Abuelo, A., Hernández, J., Benedito, J.L., Castillo, C., 2015. The importance of the oxidative status of dairy cattle in the periparturient period: revisiting antioxidant supplementation. J. Anim. Physiol. Anim. Nutr. 99 (6), 1003–1016.

Aitken, S.L., Karcher, E.L., Rezamand, P., Gandy, J.C., Vande Haar, M.J., Capuco, A.V., Sordillo, L.M., 2009. Evaluation of antioxidant and proinflammatory gene expression in bovine mammary tissue during the periparturient period. J. Dairy Sci. 92 (2), 589–598.

Arnold, C., Konkel, A., Fischer, R., Schunck, W.H., 2010. Cytochrome p450-dependent metabolism of omega-6 and omega-3 long-chain polyunsaturated fatty acids. Pharmacol. Rep. 62 (3), 536–547.

Atroshi, F., Parantainen, J., Sankari, S., Jarvinen, M., Lindberg, L.A., Saloniemi, H., 1996. Changes in inflammation-related blood constituents of mastitic cows. Vet. Res. 27 (2), 125–132.

Basiricò, L., Morera, P., Dipasquale, D., Tröscher, A., Serra, A., Mele, M., Bernabucci, U., 2015. Conjugated linoleic acid isomers strongly improve the redox status of bovine mammary epithelial cells (BME-UV1). J. Dairy Sci. 98 (10), 7071–7082.

Basiricò, L., Morera, P., Dipasquale, D., Tröscher, A., Bernabucci, U., 2017. Comparison between conjugated linoleic acid and essential fatty acids in preventing oxidative stress in bovine mammary epithelial cells. J. Dairy Sci. 100 (3), 2299–2309.

Bauer, J., Ripperger, A., Frantz, S., Ergün, S., Schwedhelm, E., Benndorf, R.A., 2014. Pathophysiology of isoprostanes in the cardiovascular system: implications of isoprostane-mediated thromboxane A2 receptor activation. Br. J. Pharmacol. 171 (13), 3115–3131.

Bernabucci, U., Ronchi, B., Lacetera, N., Nardone, A., 2005. Influence of body condition score on relationships between metabolic status and oxidative stress in periparturient dairy cows. J. Dairy Sci. 88 (6), 2017–2026.

Biswas, S.K., 2016. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxidative Med. Cell. Longev. 2016, 5698931.

Blum, J.W., Dosogne, H., Hoeben, D., Vangroenweghe, F., Hammon, H.M., Bruckmaier, R.M., Burvenich, C., 2000. Tumor necrosis factor-α and nitrite/nitrate responses during acute mastitis induced by *Escherichia coli* infection and endotoxin in dairy cows. Domest. Anim. Endocrinol. 19 (4), 223–235.

Bondy, S.C., Naderi, S., 1994. Contribution of hepatic cytochrome p450 systems to the generation of reactive oxygen species. Biochem. Pharmacol. 48 (1), 155–159.

Bouwstra, R.J., Nielen, M., Stegeman, J.A., Dobbelaar, P., Newbold, J.R., Jansen, E.H.J.M., van Werven, T., 2010a. Vitamin E supplementation during the dry period in dairy cattle. Part I: adverse effect on incidence of mastitis postpartum in a double-blind randomized field trial. J. Dairy Sci. 93 (12), 5684–5695.

Bouwstra, R.J., Nielen, M., Newbold, J.R., Jansen, E.H.J.M., Jelinek, H.F., van Werven, T., 2010b. Vitamin E supplementation during the dry period in dairy cattle. Part II: oxidative stress following vitamin E supplementation may increase clinical mastitis incidence postpartum. J. Dairy Sci. 93 (12), 5696–5706.

Brooks, J.D., Musiek, E.S., Koestner, T.R., Stankowski, J.N., Howard, J.R., Brunoldi, E.M., Porta, A., Zanoni, G., Vidari, G., Morrow, J.D., Milne, G.L., McLaughlin, B., 2011. The fatty acid oxidation product 15-A3t-isoprostane is a potent inhibitor of NFκB transcription and macrophage transformation. J. Neurochem. 119 (3), 604–616.

Bruins, M.J., Dane, A.D., Strassburg, K., Vreeken, R.J., Newman, J.W., Salem Jr., N., Tyburczy, C., Brenna, J.T., 2013. Plasma oxylipin profiling identifies polyunsaturated vicinal diols as responsive to arachidonic acid and docosahexaenoic acid intake in growing piglets. J. Lipid Res. 54 (6), 1598–1607.

Calder, P.C., 2008. The relationship between the fatty acid composition of immune cells and their function. Prostaglandins Leukot. Essent. Fat. Acids 79 (3), 101–108.

Cao, Y.Z., Reddy, C.C., Sordillo, L.M., 2000. Altered eicosanoid biosynthesis in selenium-deficient endothelial cells. Free Radic. Biol. Med. 28 (3), 381–389.

Cao, Y.Z., Cohen, Z.S., Weaver, J.A., Sordillo, L.M., 2001. Selenium modulates 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine (PAF) biosynthesis in bovine aortic endothelial cells. Antioxid. Redox Signal. 3 (6), 1147–1152.

Celi, P., 2011. Biomarkers of oxidative stress in ruminant medicine. Immunopharmacol. Immunotoxicol. 33 (2), 233–240.

Cheng, Z., Li, Y., 2007. What is responsible for the initiating chemistry of iron-mediated lipid peroxidation: an update? Chem. Rev. 107 (3), 748–766.

Cho, K.J., Seo, J.M., Kim, J.H., 2011. Bioactive lipoxygenase metabolites stimulation of NADPH oxidases and reactive oxygen species. Mol. Cell 32 (1), 1–5.

Comporti, M., Signorini, C., Arezzini, B., Vecchio, D., Monaco, B., Gardi, C., 2008. F 2-isoprostanes are not just markers of oxidative stress. Free Radic. Biol. Med. 44 (3), 247–256.

Contreras, G.A., Raphael, W., Mattmiller, S.A., Gandy, J., Sordillo, L.M., 2012. Nonesterified fatty acids modify inflammatory response and eicosanoid biosynthesis in bovine endothelial cells. J. Dairy Sci. 95 (9), 5011–5023.

Dhanasekaran, A., Kotamraju, S., Karunakaran, C., Kalivendi, S.V., Thomas, S., Joseph, J., Kalyanaraman, B., 2005. Mitochondria superoxide dismutase mimetic inhibits peroxide-induced oxidative damage and apoptosis: role of mitochondrial superoxide. Free Radic. Biol. Med. 39 (5), 567–583.

Dhanasekaran, A., Al-Saghir, R., Lopez, B., Zhu, D., Gutterman, D.D., Jacobs, E.R., Medhora, M., 2006. Protective effects of epoxyeicosatrienoic acids on human endothelial cells from the pulmonary and coronary vasculature. Am. J. Physiol. Heart Circ. Physiol. 291 (2), H517–531.

Doughan, A.K., Harrison, D.G., Dikalov, S.I., 2008. Molecular mechanisms of angiotensin II–mediated mitochondrial dysfunction: linking mitochondrial oxidative damage and vascular endothelial dysfunction. Circ. Res. 102 (4), 488–496.

Drackley, J.K., 1999. Biology of dairy cows during the transition period: the final frontier? J. Dairy Sci. 82 (11), 2259–2273.

Erlemann, K.R., Cossette, C., Gravel, S., Stamatiou, P.B., Lee, G.J., Rokach, J., Powell, W.S., 2006. Metabolism of 5-hydroxy-6,8,11,14-eicosatetraenoic acid by human endothelial cells. Biochem. Biophys. Res. Commun. 350 (1), 151–156.

Erlemann, K.R., Cossette, C., Gravel, S., Lesimple, A., Lee, G.J., Saha, G., Rokach, J., Powell, W.S., 2007. Airway epithelial cells synthesize the lipid mediator 5-oxo-ete in response to oxidative stress. Free Radic. Biol. Med. 42 (5), 654–664.

van't Erve, T.J., Lih, F.B., Jelsema, C., Deterding, L.J., Eling, T.E., Mason, R.P., Kadiiska, M.B., 2016. Reinterpreting the best biomarker of oxidative stress: the 8-iso-prostaglandin f2α/prostaglandin f2α ratio shows complex origins of lipid peroxidation biomarkers in animal models. Free Radic. Biol. Med. 95, 65–73.

Esposito, G., Irons, P.C., Webb, E.C., Chapwanya, A., 2014. Interactions between negative energy balance, metabolic diseases, uterine health and immune response in transition dairy cows. Anim. Reprod. Sci. 144 (3), 60–71.

Farney, J.K., Mamedova, L.K., Coetzee, J.F., Minton, J.E., Hollis, L.C., Bradford, B.J., 2013. Sodium salicylate treatment in early lactation increases whole-lactation milk

and milk fat yield in mature dairy cows. J. Dairy Sci. 96 (12), 7709–7718.
Gao, L., Zackert, W.E., Hasford, J.J., Danekis, M.E., Milne, G.L., Remmert, C., Reese, J., Yin, H., Tai, H.H., Dey, S.K., Porter, N.A., Morrow, J.D., 2003. Formation of prostaglandins E2 and D2 via the isoprostane pathway: a mechanism for the generation of bioactive prostaglandins independent of cyclooxygenase. J. Biol. Chem. 278 (31), 28479–28489.
Garg, T.K., Chang, J.Y., 2004. 15-deoxy-delta 12, 14-prostaglandin J2 prevents reactive oxygen species generation and mitochondrial membrane depolarization induced by oxidative stress. BMC Pharmacol. 4 (1), 6–21.
Gessner, D.K., Schlegel, G., Keller, J., Schwarz, F.J., Ringseis, R., Eder, K., 2013. Expression of target genes of nuclear factor E2-related factor 2 in the liver of dairy cows in the transition period and at different stages of lactation. J. Dairy Sci. 96 (3), 1038–1043.
Ghosh, R., Alajbegovic, A., Gomes, A.V., 2015. NSAIDS and cardiovascular diseases: role of reactive oxygen species. Oxidative Med. Cell. Longev. 2015, 536962.
Gobert, M., Martin, B., Ferlay, A., Chilliard, Y., Graulet, B., Pradel, P., Bauchart, D., Durand, D., 2009. Plant polyphenols associated with vitamin E can reduce plasma lipoperoxidation in dairy cows given n-3 polyunsaturated fatty acids. J. Dairy Sci. 92 (12), 6095–6104.
Hall, J.A., Bobe, G., Vorachek, W.R., Estill, C.T., Mosher, W.D., Pirelli, G.J., Gamroth, M., 2014. Effect of supranutritional maternal and colostral selenium supplementation on passive absorption of immunoglobulin G in selenium-replete dairy calves. J. Dairy Sci. 97 (7), 4379–4391.
Halliwell, B., 2007. Biochemistry of oxidative stress. Biochem. Soc. Trans. 35 (5), 1147–1150.
Han, Y., Zhao, H., Tang, H., Li, X., Tan, J., Zeng, Q., Sun, C., 2013. 20-hydroxyeicosatetraenoic acid mediates isolated heart ischemia/reperfusion injury by increasing NADPH oxidase-derived reactive oxygen species production. Circ. J. 77 (7), 1807–1816.
Hanschke, N., Kankofer, M., Ruda, L., Höltershinken, M., Meyer, U., Frank, J., Dänicke, S., Rehage, J., 2016. The effect of conjugated linoleic acid supplements on oxidative and antioxidative status of dairy cows. J. Dairy Sci. 99 (10), 8090–8102.
Haskew-Layton, R.E., Payappilly, J.B., Xu, H., Bennett, S.A., Ratan, R.R., 2013. 15-deoxy-delta12,14-prostaglandin j2 (15d-PGJ2) protects neurons from oxidative death via an Nrf2 astrocyte-specific mechanism independent of PPARγ. J. Neurochem. 124 (4), 536–547.
Herath, S., Lilly, S.T., Fischer, D.P., Williams, E.J., Dobson, H., Bryant, C.E., Sheldon, I.M., 2009. Bacterial lipopolysaccharide induces an endocrine switch from prostaglandin F2alpha to prostaglandin E2 in bovine endometrium. Endocrinology 150 (4), 1912–1920.
Holmstrom, K.M., Finkel, T., 2014. Cellular mechanisms and physiological consequences of redox-dependent signalling. Nat. Rev. Mol. Cell Biol. 15 (6), 411–421.
Hye Khan, M.A., Hwang, S.H., Sharma, A., Corbett, J.A., Hammock, B.D., Imig, J.D., 2016. A dual cox-2/seh inhibitor improves the metabolic profile and reduces kidney injury in zucker diabetic fatty rat. Prostaglandins Other Lipid Mediat 125, 40–47.
Ingvartsen, K.L., 2006. Feeding- and management-related diseases in the transition cow: physiological adaptations around calving and strategies to reduce feeding-related diseases. Anim. Feed Sci. Technol. 126 (3), 175–213.
Ishizuka, T., Cheng, J., Singh, H., Vitto, M.D., Manthati, V.L., Falck, J.R., Laniado-Schwartzman, M., 2008. 20-hydroxyeicosatetraenoic acid stimulates nuclear factor-κB activation and the production of inflammatory cytokines in human endothelial cells. J. Pharmacol. Exp. Ther. 324 (1), 103–110.
Jira, W., Spiteller, G., Carson, W., Schramm, A., 1998. Strong increase in hydroxy fatty acids derived from linoleic acid in human low density lipoproteins of atherosclerotic patients. Chem. Phys. Lipids 91 (1), 1–11.
Jørgensen, H.B., Buitenhuis, B., Røntved, C.M., Jiang, L., Ingvartsen, K.L., Sørensen, P., 2012. Transcriptional profiling of the bovine hepatic response to experimentally induced *E. coli* mastitis. Physiol. Genomics 44 (11), 595–606.
Kankofer, M., 2002. 8-iso-prostaglandin F2α as a marker of tissue oxidative damage in bovine retained placenta. Prostaglandins Other Lipid Mediat 70 (1), 51–59.
Kumar, A., Sharma, S., Prashar, A., andDeshmukh, R., 2015. Effect of licofelone-a dual cox/5-lox inhibitor in intracerebroventricular streptozotocin-induced behavioral and biochemical abnormalities in rats. J. Mol. Neurosci. 55 (3), 749–759.
Lakhkar, A., Dhagia, V., Joshi, S.R., Gotlinger, K., Patel, D., Sun, D., Wolin, M.S., Schwartzman, M.L., Gupte, S.A., 2016. 20-HETE-induced mitochondrial superoxide production and inflammatory phenotype in vascular smooth muscle is prevented by glucose-6-phosphate dehydrogenase inhibition. Am. J. Physiol. Heart Circ. Physiol. 310 (9), H1107–H1117.
Lauzon, K., Zhao, X., Bouetard, A., Delbecchi, L., Paquette, B., Lacasse, P., 2005. Antioxidants to prevent bovine neutrophil-induced mammary epithelial cell damage. J. Dairy Sci. 88 (12), 4295–4303.
Lauzon, K., Zhao, X., Lacasse, P., 2006. Deferoxamine reduces tissue damage during endotoxin-induced mastitis in dairy cows. J. Dairy Sci. 89 (10), 3846–3857.
LeBlanc, S., 2006. Monitoring programs for transition dairy cows. In: Proceedings of the 26th World Buiatrics Congress, Nice.
Lee, A.C., Murray, M., 2010. Up-regulation of human CYP2J2 in HepG2 cells by butylated hydroxyanisole is mediated by c-jun and Nrf2. Mol. Pharmacol. 77 (6), 987–994.
Li, D., Liu, Y., Li, Y., Lv, Y., Pei, X., Guo, D., 2010. Significance of nitric oxide concentration in plasma and uterine secretes with puerperal endometritis in dairy cows. Vet. Res. Commun. 34 (4), 315–321.
Li, Q., Mao, M., Qiu, Y., Liu, G., Sheng, T., Yu, X., Wang, S., Zhu, D., 2016. Key role of ROS in the process of 15-lipoxygenase/15-hydroxyeicosatetraenoiccid-induced pulmonary vascular remodeling in hypoxia pulmonary hypertension. PLoS One 11 (2), e0149164.
Liu, J.Y., Li, N., Yang, J., Li, N., Qiu, H., Ai, D., Chiamvimonvat, N., Zhu, Y., andHammock, B. D., 2010. Metabolic profiling of murine plasma reveals an unexpected biomarker in rofecoxib-mediated cardiovascular events. Proc. Natl. Acad. Sci. U. S. A. 107 (39), 17017–17022.
Liu, M., Boussetta, T., Makni-Maalej, K., Fay, M., Driss, F., El-Benna, J., Lagarde, M., Guichardant, M., 2014. Protectin DX, a double lipoxygenase product of DHA, inhibits both ROS production in human neutrophils and cyclooxygenase activities. Lipids 49 (1), 49–57.
Liu, W.J., Wang, T., Wang, B., Liu, X.T., He, X.W., Liu, Y.J., Li, Z.X., Tan, R., Zeng, H. S., 2015. CYP2C8-derived epoxyeicosatrienoic acids decrease oxidative stress-induced endothelial apoptosis in development of atherosclerosis: role of Nrf2 activation. J. Huazhong Univ. Sci. Technol. Med. Sci. 35 (5), 640–645.
Lock, A.L., Bauman, D.E., 2004. Modifying milk fat composition of dairy cows to enhance fatty acids beneficial to human health. Lipids 39 (12), 1197–1206.
Löhrke, B., Viergutz, T., Kanitz, W., Losand, B., Weiss, D.G., Simko, M., 2005. Short communication: Hydroperoxides in circulating lipids from dairy cows: implications for bioactivity of endogenous-oxidized lipids. J. Dairy Sci. 88 (5), 1708–1710.
Lu, Y., Cederbaum, A.I., 2008. Cyp2e1 and oxidative liver injury by alcohol. Free Radic. Biol. Med. 44 (5), 723–738.
Lutzow, Y.S., Gray, C., Tellam, R., 2008. 15-Deoxy-Δ12,14-prostaglandin J2 induces chemokine expression, oxidative stress and microfilament reorganization in bovine mammary epithelial cells. J. Dairy Res. 75 (1), 55–63.
Maddox, J.F., Eberhart, R.J., Reddy, C.C., Scholz, R.W., 1990. The effect of dietary selenium on eicosanoid concentration in blood and milk during coliform mastitis. J. Dairy Sci. 73 (Supplement 1), 151.
Maier, N.K., Leppla, S.H., Moayeri, M., 2015. The cyclopentenone prostaglandin 15d-PGJ2 inhibits the NLRP1 and NLRP3 inflammasomes. J. Immunol. 194 (6), 2776–2785.
Mallat, Z., Nakamura, T., Ohan, J., Leseche, G., Tedgui, A., Maclouf, J., Murphy, R.C., 1999. The relationship of hydroxyeicosatetraenoic acids and f2-isoprostanes to plaque instability in human carotid atherosclerosis. J. Clin. Invest. 103 (3), 421–427.
Marini, M.G., Perrini, C., Esposti, P., Corradetti, B., Bizzaro, D., Riccaboni, P., Fantinato, E., Urbani, G., Gelati, G., Cremonesi, F., Lange-Consiglio, A., 2016. Effects of platelet-rich plasma in a model of bovine endometrial inflammation in vitro. Reprod. Biol. Endocrinol. 14 (1), 58.
Mattmiller, S.A., Carlson, B.A., Sordillo, L.M., 2013. Regulation of inflammation by selenium and selenoproteins: impact on eicosanoid biosynthesis. J. Nutr. Sci. 2, e28.
Mattmiller, S.A., Carlson, B.A., Gandy, J.C., Sordillo, L.M., 2014. Reduced macrophage selenoprotein expression alters oxidized lipid metabolite biosynthesis from arachidonic and linoleic acid. J. Nutr. Biochem. 25 (6), 647–654.
Mavangira, V., Gandy, J.C., Zhang, C., Ryman, V.E., Daniel Jones, A., Sordillo, L.M., 2015. Polyunsaturated fatty acids influence differential biosynthesis of oxylipids and other lipid mediators during bovine coliform mastitis. J. Dairy Sci. 98 (9), 6202–6215.
Mavangira, V., Mangual, M.J., Gandy, J.C., Sordillo, L.M., 2016. 15-f2t -isoprostane concentrations and oxidant status in lactating dairy cattle with acute coliform mastitis. J. Vet. Intern. Med. 30 (1), 339–347.
Meirer, K., Steinhilber, D., Proschak, E., 2014. Inhibitors of the arachidonic acid cascade: interfering with multiple pathways. Basic Clin. Pharmacol. Toxicol. 114 (1), 83–91.
Miller, J.K., Brzezinska-Slebodzinska, E., Madsen, F.C., 1993. Oxidative stress, antioxidants, and animal function. J. Dairy Sci. 76 (9), 2812–2823.
Milne, G.L., Dai, Q., Roberts II, L.J., 2015. The isoprostanes-25 years later. Biochim. Biophys. Acta 1851 (4), 433–445.
Montine, T.J., Milatovic, D., Gupta, R.C., Valyi-Nagy, T., Morrow, J.D., Breyer, R.M., 2002. Neuronal oxidative damage from activated innate immunity is EP2 receptor-dependent. J. Neurochem. 83 (2), 463–470.
Munoz, M., Sanchez, A., Pilar Martinez, M., Benedito, S., Lopez-Oliva, M.E., Garcia-Sacristan, A., Hernandez, M., Prieto, D., 2015. COX-2 is involved in vascular oxidative stress and endothelial dysfunction of renal interlobar arteries from obese Zucker rats. Free Radic. Biol. Med. 84, 77–90.
Noguchi, N., Yamashita, H., Hamahara, J., Nakamura, A., Kühn, H., Niki, E., 2002. The specificity of lipoxygenase-catalyzed lipid peroxidation and the effects of radical-scavenging antioxidants. Biol. Chem. 383 (3–4), 619–626.
Ono, E., Dutile, S., Kazani, S., Wechsler, M.E., Yang, J., Hammock, B.D., Douda, D.N., Tabet, Y., Khaddaj-Mallat, R., Sirois, M., Sirois, C., Rizcallah, E., Rousseau, E., Martin, R., Sutherland, E.R., Castro, M., Jarjour, N.N., Israel, E., Levy, B.D., 2014. Lipoxin generation is related to soluble epoxide hydrolase activity in severe asthma. Am. J. Respir. Crit. Care Med. 190 (8), 886–897.
Osorio, J.S., Trevisi, E., Ji, P., Drackley, J.K., Luchini, D., Bertoni, G., Loor, J.J., 2014. Biomarkers of inflammation, metabolism, and oxidative stress in blood, liver, and milk reveal a better immunometabolic status in peripartal cows supplemented with smartamine m or metasmart. J. Dairy Sci. 97 (12), 7437–7450.
Pamplona, R., 2008. Membrane phospholipids, lipoxidative damage and molecular integrity: a causal role in aging and longevity. Biochim. Biophys. Acta 1777 (10), 1249–1262.
Pan, Y., Yu, L., Lei, W., Guo, Y., Wang, J., Yu, H., Tang, Y., Yang, J., 2015. Beraprost sodium protects against chronic brain injury in aluminum-overload rats. Behav. Brain Funct. 11, 6.
Park, C.M., Cha, Y.S., Youn, H.J., Cho, C.W., Song, Y.S., 2010. Amelioration of oxidative stress by dandelion extract through CYP2E1 suppression against acute liver injury induced by carbon tetrachloride in sprague-dawley rats. Phytother. Res. 24 (9), 1347–1353.
Picklo Sr., M.J., Newman, J.W., 2015. Antioxidant supplementation and obesity have independent effects on hepatic oxylipin profiles in insulin-resistant, obesity-prone rats. Free Radic. Biol. Med. 89, 182–191.
Pinedo, P.J., De Vries, A., Webb, D.W., 2010. Dynamics of culling risk with disposal codes reported by dairy herd improvement dairy herds. J. Dairy Sci. 93 (5), 2250–2261.
Piotrowska-Tomala, K.K., Siemieniuch, M.J., Szóstek, A.Z., Korzekwa, A.J., Woclawek-

Potocka, I., Galváo, A.M., Okuda, K., Skarzynski, D.J., 2012. Lipopolysaccharides, cytokines, and nitric oxide affect secretion of prostaglandins and leukotrienes by bovine mammary gland epithelial cells. Domest. Anim. Endocrinol. 43 (4), 278–288.
Raphael, W., Sordillo, L.M., 2013. Dietary polyunsaturated fatty acids and inflammation: the role of phospholipid biosynthesis. Int. J. Mol. Sci. 14 (10), 21167–21188.
Raphael, W., Halbert, L., Contreras, G.A., Sordillo, L.M., 2014. Association between polyunsaturated fatty acid-derived oxylipid biosynthesis and leukocyte inflammatory marker expression in periparturient dairy cows. J. Dairy Sci. 97 (6), 3615–3625.
Rico, J.E., Bandaru, V.V., Dorskind, J.M., Haughey, N.J., McFadden, J.W., 2015. Plasma ceramides are elevated in overweight Holstein dairy cows experiencing greater lipolysis and insulin resistance during the transition from late pregnancy to early lactation. J. Dairy Sci. 98 (11), 7757–7770.
Rose, D.M., Giri, S.N., Cullor, J.S., Bushnell, R.B., 1991. The combined use of lipoxygenase and cyclooxygenase inhibitors in *Klebsiella pneumoniae*-induced bovine mastitis. J. Vet. Med. 38 (2), 99–106.
Ruiz, S., Pergola, P.E., Zager, R.A., Vaziri, N.D., 2013. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int. 83 (6), 1029–1041.
Ryman, V.E., Packiriswamy, N., Sordillo, L.M., 2015a. Role of endothelial cells in bovine mammary gland health and disease. Anim. Health Res. Rev. 16 (2), 135–149.
Ryman, V.E., Pighetti, G.M., Lippolis, J.D., Gandy, J.C., Applegate, C.M., Sordillo, L.M., 2015b. Quantification of bovine oxylipids during intramammary *Streptococcus uberis* infection. Prostaglandins Other Lipid Mediat. 121 (Pt B), 207–217.
Ryman, V.E., Packiriswamy, N., Sordillo, L.M., 2016. Apoptosis of endothelial cells by 13-hpode contributes to impairment of endothelial barrier integrity. Mediat. Inflamm. 2016, 13.
Ryman, V.E., Packiriswamy, N., Norby, B., Schmidt, S.E., Lock, A.L., Sordillo, L.M., 2017. Supplementation of linoleic acid (c18:2n-6) or alpha-linolenic acid (c18:3n-3) changes microbial agonist-induced oxylipid biosynthesis. J. Dairy Sci. 100 (3), 1870–1887.
Sancho, P., Martín-Sanz, P., Fabregat, I., 2011. Reciprocal regulation of NADPH oxidases and the cyclooxygenase-2 pathway. Free Radic. Biol. Med. 51 (9), 1789–1798.
Schmelzer, K.R., Kubala, L., Newman, J.W., Kim, I.H., Eiserich, J.P., J. P., and Hammock, B. D., 2005. Soluble epoxide hydrolase is a therapeutic target for acute inflammation. Proc. Natl. Acad. Sci. U. S. A. 102 (28), 9772–9777.
Seboussi, R., Tremblay, G.F., Ouellet, V., Chouinard, P.Y., Chorfi, Y., Belanger, G., Charbonneau, E., 2016. Selenium-fertilized forage as a way to supplement lactating dairy cows. J. Dairy Sci. 99 (7), 5358–5369.
Senol, S.P., Temiz, M., Guden, D.S., Cecen, P., Sari, A.N., Sahan-Firat, S., Falck, J.R., Dakarapu, R., Malik, K.U., Tunctan, B., 2016. Contribution of PPARα/β/γ, AP-1, importin-α3, and RXRα to the protective effect of 5,14-HEDGE, a 20-HETE mimetic, against hypotension, tachycardia, and inflammation in a rat model of septic shock. Inflamm. Res. 65 (5), 367–387.
Serhan, C.N., 1997. Lipoxins and novel aspirin-triggered 15-epi-lipoxins (ATL): a jungle of cell-cell interactions or a therapeutic opportunity? Prostaglandins 53 (2), 107–137.
Serhan, C.N., Chiang, N., Van Dyke, T.E., 2008. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat. Rev. Immunol. 8 (5), 349–361.
Shibata, T., 2015. 15-deoxy-δ12,14-prostaglandin J2 as an electrophilic mediator. Biosci. Biotechnol. Biochem. 79 (7), 1044–1049.
Silanikove, N., Rauch-Cohen, A., Shapiro, F., Arieli, A., Merin, U., Leitner, G., 2012. Lipopolysaccharide challenge of the mammary gland in cows induces nitrosative stress that impairs milk oxidative stability. Animal 6 (9), 1451–1459.
Slim, R., Hammock, B.D., Toborek, M., Robertson, L.W., Newman, J.W., Morisseau, C.H., Watkins, B.A., Saraswathi, V., Hennig, B., 2001. The role of methyl-linoleic acid epoxide and diol metabolites in the amplified toxicity of linoleic acid and polychlorinated biphenyls to vascular endothelial cells. Toxicol. Appl. Pharmacol. 171 (3), 184–193.
Soffler, C., Campbell, V.L., Hassel, D.M., 2010. Measurement of urinary f2-isoprostanes as markers of in vivo lipid peroxidation: a comparison of enzyme immunoassays with gas chromatography–mass spectrometry in domestic animal species. J. Vet. Diagn. Investig. 22 (2), 200–209.
Sordillo, L.M., 2013. Selenium-dependent regulation of oxidative stress and immunity in periparturient dairy cattle. Vet. Med. Int. 2013, 154045.
Sordillo, L.M., 2016. Nutritional strategies to optimize dairy cattle immunity. J. Dairy Sci. 99 (6), 4967–4982.
Sordillo, L.M., Aitken, S.L., 2009. Impact of oxidative stress on the health and immune function of dairy cattle. Vet. Immunol. Immunopathol. 128 (1–3), 104–109.
Sordillo, L.M., Mavangira, V., 2014. The nexus between nutrient metabolism, oxidative stress and inflammation in transition cows. Anim. Prod. Sci. 54 (9), 1204–1214.
Sordillo, L.M., Weaver, J.A., Cao, Y.Z., Corl, C., Sylte, M.J., Mullarky, I.K., 2005. Enhanced 15-HpETE production during oxidant stress induces apoptosis of endothelial cells. Prostaglandins Other Lipid Mediat 76 (1–4), 19–34.
Sorokin, A., 2016. Nitric oxide synthase and cyclooxygenase pathways: a complex interplay in cellular signaling. Curr. Med. Chem. 23 (24), 2559–2578.
Theken, K.N., Deng, Y., Kannon, M.A., Miller, T.M., Poloyac, S.M., Lee, C.R., 2011. Activation of the acute inflammatory response alters cytochrome p450 expression and eicosanoid metabolism. Drug Metab. Dispos. 39 (1), 22–29.
Toth, P., Csiszar, A., Sosnowska, D., Tucsek, Z., Cseplo, P., Springo, Z., Tarantini, S., Sonntag, W.E., Ungvari, Z., Koller, A., 2013. Treatment with the cytochrome p450 ω-hydroxylase inhibitor HET0016 attenuates cerebrovascular inflammation, oxidative stress and improves vasomotor function in spontaneously hypertensive rats. Br. J. Pharmacol. 168 (8), 1878–1888.
Tunctan, B., Korkmaz, B., Sari, A.N., Kacan, M., Unsal, D., Serin, M.S., Buharalioglu, C.K., Sahan-Firat, S., Cuez, T., Schunck, W.H., Falck, J.R., Malik, K.U., 2013a. 5,14-HEDGE, a 20-HETE mimetic, reverses hypotension and improves survival in a rodent model of septic shock: contribution of soluble epoxide hydrolase, CYP2C23, MEK1/ERK1/2/IKKbeta/IkappaB-alpha/NF-kappaB pathway, and proinflammatory cytokine formation. Prostaglandins Other Lipid Mediat 102–103, 31–41.
Tunctan, B., Sari, A.N., Kacan, M., Unsal, D., Buharalioglu, C.K., Sahan-Firat, S., Korkmaz, B., Falck, J.R., Malik, K.U., 2013b. NS-398 reverses hypotension in endotoxemic rats: contribution of eicosanoids, NO, and peroxynitrite. Prostaglandins Other Lipid Med. 104–105, 93–108.
Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39 (1), 44–84.
Villamena, F.A., 2013. Chemistry of reactive species. In: Molecular Basis of Oxidative Stress. John Wiley & Sons, Inc., pp. 1–48.
Viswanathan, S., Hammock, B.D., Newman, J.W., Meerarani, P., Toborek, M., Hennig, B., 2003. Involvement of CYP 2C9 in mediating the proinflammatory effects of linoleic acid in vascular endothelial cells. J. Am. Coll. Nutr. 22 (6), 502–510.
Waldman, M., Peterson, S.J., Arad, M., Hochhauser, E., 2016. The role of 20-HETE in cardiovascular diseases and its risk factors. Prostaglandins Other Lipid Med 125, 108–117.
Wang, Y.M., Wang, J.H., Wang, C., Chen, B., Liu, J.X., Cao, H., Guo, F.C., Vázquez-Añón, M., 2010. Effect of different rumen-inert fatty acids supplemented with a dietary antioxidant on performance and antioxidative status of early-lactation cows. J. Dairy Sci. 93 (8), 3738–3745.
Wang, L., Yuan, R., Yao, C., Wu, Q., Christelle, M., Xie, W., Zhang, X., Sun, W., Wang, H., Yao, S., 2014a. Effects of resolvin d1 on inflammatory responses and oxidative stress of lipopolysaccharide-induced acute lung injury in mice. Chin. Med. J. 127 (5), 803–809.
Wang, Y., Armando, A.M., Quehenberger, O., Yan, C., Dennis, E.A., 2014b. Comprehensive ultra-performance liquid chromatographic separation and mass spectrometric analysis of eicosanoid metabolites in human samples. J. Chromatogr. A 1359, 60–69.
Weaver, J.A., Maddox, J.F., Cao, Y.Z., Mullarky, I.K., Sordillo, L.M., 2001. Increased 15-HpETE production decreases prostacyclin synthase activity during oxidant stress in aortic endothelial cells. Free Radic. Biol. Med. 30 (3), 299–308.
Werz, O., Szellas, D., Steinhilber, D., 2000. Reactive oxygen species released from granulocytes stimulate 5-lipoxygenase activity in a B-lymphocytic cell line. Eur. J. Biochem. 267 (5), 1263–1269.
Westphal, C., Konkel, A., Schunck, W.H., 2015. Cytochrome p450 enzymes in the bioactivation of polyunsaturated fatty acids and their role in cardiovascular disease. Adv. Exp. Med. Biol. 851, 151–187.
Willenberg, I., Rund, K., Rong, S., Shushakova, N., Gueler, F., Schebb, N.H., 2015. Characterization of changes in plasma and tissue oxylipin levels in LPS and CLP-induced murine sepsis. Inflamm. Res. 65 (2), 133–142.
Wu, L., Li, H.H., Wu, Q., Miao, S., Liu, Z.J., Wu, P., Ye, D.Y., 2015. Lipoxin A4 activates Nrf2 pathway and ameliorates cell damage in cultured cortical astrocytes exposed to oxygen-glucose deprivation/reperfusion insults. J. Mol. Neurosci. 56 (4), 848–857.
Wu, H., Wu, T., Han, X., Wan, J., Jiang, C., Chen, W., Lu, H., Yang, Q., andWang, J., 2016a. Cerebroprotection by the neuronal pge2 receptor ep2 after intracerebral hemorrhage in middle-aged mice. J. Cereb. Blood Flow Metab. 37 (1), 39–51.
Wu, T., Wang, C., Ding, L., Shen, Y., Cui, H., Wang, M., Wang, H., 2016b. Arginine relieves the inflammatory response and enhances the casein expression in bovine mammary epithelial cells induced by lipopolysaccharide. Mediat. Inflamm. 2016, 9618795.
Yu, G., Zeng, X., Wang, H., Hou, Q., Tan, C., Xu, Q., Wang, H., 2015. 14,15-epoxyeicosatrienoic acid suppresses cigarette smoke extract-induced apoptosis in lung epithelial cells by inhibiting endoplasmic reticulum stress. Cell. Physiol. Biochem. 36 (2), 474–486.
Zhou, W., Dowell, D.R., Geraci, M.W., Blackwell, T.S., Collins, R.D., Polosukhin, V.V., Lawson, W.E., Wu, P., Sussan, T., Biswal, S., Goleniewska, K., O'Neal, J., Newcomb, D.C., Toki, S., Morrow, J.D., Peebles, R.S., 2011. PGI synthase overexpression protects against bleomycin-induced mortality and is associated with increased NQO 1 expression. Am. J. Phys. Lung Cell. Mol. Phys. 301 (4), L615–L622.