



Medicine in focus

Oxidation specific epitopes in asthma: New possibilities for treatment

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ABSTRACT

Oxidative stress is an important feature of asthma pathophysiology that is not currently targeted by any of our frontline treatments. Reactive oxygen species, generated during times of heightened oxidative stress, can damage cellular lipids causing the production of oxidation specific epitopes (OSE). OSEs are elevated in chronic inflammatory diseases and promoting their clearance by the body, through pattern recognition receptors and IgM antibodies, prevents and resolves inflammation and tissue damage in animal models. Current research on OSEs in asthma is limited. Although they are present in the lungs of people with asthma during periods of exacerbation or allergen exposure, we do not know if they are linked with disease pathobiology. This article reviews our current understanding of OSEs in asthma and explores whether targeting OSE clearance mechanisms may be a novel therapeutic intervention for asthma.

1. Introduction

Asthma is a chronic inflammatory disorder of the airways that is associated with paroxysmal episodes of wheezing, coughing and airway narrowing that compromises airflow, causes significant distress, and diminishes quality of life. Inflammation in asthma is complex, involving orchestration of mucosal and systemic immune systems and a variety of biomolecules. A variety of environmental triggers, including viral infections, air pollution, aeroallergens, are implicated in both the pathogenesis of asthma and perpetuation of airway inflammation (Hogg, 1999; Wang et al., 2018b; Wooding et al., 2019). Oxidative stress is a constant component of airway inflammation and its presence is associated with disease severity and diminished response to therapy (Fatani, 2014; Kwon et al., 2012; Marwick et al., 2008). Furthermore, current asthma treatments do not correct the redox imbalance in the lungs, allowing the peroxidation and nitrosylation of lipids, proteins and nucleic acids to go unhindered. The degree to which uncontrolled oxidative stress and the effects of bio-activated oxidized molecules contribute to asthma pathogenesis is unclear. This review will focus on oxidation specific epitopes (OSEs) and their potential as important mediators of asthma pathobiology and pathophysiology. We describe a variety of OSE moieties, including those that contain oxidized phospholipids (OxPLs), and naturally occurring antibodies and pattern recognition receptors (PRRs) that recognize them. We also summarize

evidence for OSEs and PRRs in the lung, how they associate with asthma, and discuss the potential of OSEs and their receptors as future targets for asthma therapies.

2. Oxidation specific epitopes

Although necessary for many life sustaining reactions within a cell, oxidation reactions produce reactive oxygen species (ROS) that can damage cellular components, including lipids, proteins, and DNA. This can produce potentially bioactive and harmful molecules. The cell has a number of antioxidant systems in place to counteract the excessive action of ROS. When these systems fail, an abundance of bioactive oxidized molecules can be formed, resulting in tissue damage and inflammation, which can contribute to chronic disease. Emerging evidence suggest that some of these oxidized molecules can act as damage-associated molecular patterns (DAMPs) that are recognized by and activate cellular and soluble PRRs (Fig. 1). In this way, non-enzymatic oxidation of molecules, specifically lipids, can form complex OSEs (Binder et al., 2016; Miller et al., 2011). Non-enzymatic oxidation involves ROS/RNS (reactive nitrogen species) free radical attack on double-bonds in the fatty acid tails of phospholipids. Lipid derived OSEs include several well-known markers of oxidative stress: malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and OxPLs. OSEs can be recognized by the innate immune system by mimicking the microbial DAMPs that PRRs

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recognize. The innate immune system mediates clearance of OSEs. If this process is impaired, OSEs can contribute to chronic inflammation (Fig. 2) (Chen and Nuñez, 2010).

3. The immune system and OSEs

OSEs are recognized by cell surface PRRs, soluble PRRs, and endogenously occurring IgM antibodies (Fig. 1) (Miller et al., 2011; Weismann and Binder, 2012). The innate immune system is fine tuned to detect and orchestrate responses to OSEs as their presence typically indicates cellular damage or apoptosis. OSEs trigger homeostatic immune system mechanisms that remove damaged or apoptotic cells and contribute to restoring tissue function. PRRs and IgM antibodies facilitate the uptake of OSEs and the phagocytosis of damaged cells by macrophage to initiate inflammation and restore of tissue function (Miller et al., 2011).

A number of endogenously produced IgM antibodies can neutralize OSEs and facilitate their clearance (Chou et al., 2009; Tsimikas et al., 2007). Among the best studied is E06, which recognizes oxidized phosphatidylcholine moieties, present in oxidized LDL and on apoptotic or damaged cells, to facilitate efferocytosis and prevent foam cell formation (Chang et al., 1999; Hörkö et al., 1999). Antibodies specific to MDA, 4-HNE, and oxidized cardiolipin have also been identified and are likely important in the neutralization and clearance of these molecules (Chou et al., 2009; Hörkö et al., 1999; Tsiantoulas et al., 2015).

There are also soluble, circulating PRRs that can bind to and neutralize OSEs (Fig. 1). The best known is C-reactive protein (CRP), a recognized marker of chronic systemic inflammation. CRP binds OxPLs and, in conjunction with MDA-binding members of the complement cascade, enhances efferocytosis by macrophages (Chang et al., 2002). Complement components include anaphylatoxin C3a and complement factor H (Venekoski et al., 2001; Weismann et al., 2011). All of these receptors facilitate the uptake of OSEs by macrophages and the initiation of inflammation to restore tissue function (Fig. 1).

Cell surface PRRs for OSEs are expressed by immune and structural cells, and modulate inflammation to facilitate OSE clearance. Scavenger receptors, including CD36, scavenger receptor A1/2 and B1 (SRB1), and lectin-like oxidized LDL receptor 1 bind OSEs and mediate their eventual uptake by macrophages, thus orchestrating the inflammatory response (Fig. 1) (Gillotte-Taylor et al., 2001; Greenberg et al., 2006; Kumano-Kuramochi et al., 2012; Shechter et al., 1981). Toll-like receptors (TLR) regulate airway immune responses, and can recognize and be activated by OSEs. TLR4 and TLR6 heterodimerize to bind OxPLs, a response that triggers inflammation linked to atherosclerosis and acute lung injury

(Imai et al., 2008; Stewart et al., 2010). Furthermore, TLR2, in conjunction with CD36, is involved in macrophage clearance of 2-(ω -carboxyethyl) pyrrole, an OSE involved with wound healing and chronic inflammation responses (Kim et al., 2015). Table 1 provides relative RNA abundance information for each PRR in four broad lung cell types: endothelium, epithelium, mesenchyme, and immune.

4. OSEs in disease

OSEs have been identified in a host of different acute and chronic diseases. During lung infection and acute lung injury in humans and mice, OxPLs accumulate in the lung (Imai et al., 2008). OxPLs have a ubiquitous role in chronic inflammation and the pathophysiology of non-alcoholic steatohepatitis, ischemia-reperfusion injury, age-related macular degeneration, and atherosclerosis (Aredo et al., 2015; Que et al., 2018; Sun et al., 2020; Yeang et al., 2019). Furthermore, OSEs have been identified in tissues from individuals with hepatitis, multiple sclerosis, and Alzheimer's disease (Dei et al., 2002; Haider et al., 2011; Sánchez Pérez et al., 2006). In animal models of ischemia-reperfusion injury, hepatic steatosis, and acute lung injury, OSEs cause mitochondrial dysfunction, ROS accumulation, cell death, and inflammation (Imai et al., 2008; Sun et al., 2020; Yeang et al., 2019).

Levels of circulating OxPLs bound to apolipoprotein B-100, in particular those in the highest tertile of abundance, predicts the risk for cardiovascular disease and stroke (Tsimikas et al., 2012). Importantly, the pathophysiology of a number of chronic diseases in animal models can be prevented and reversed by neutralizing OxPLs with human E06 IgM antibodies. Transgenic LDL receptor deficient (*Ldlr*^{-/-}) mice that constitutively express the E06 variable fragment are resistant to steatosis, macrophage influx into the liver, liver fibrosis, and hepatocyte death caused by hyperlipidemic diet (Sun et al., 2020). Similarly, *Ldlr*^{-/-} mice expressing the E06 short variable fragment were resistant to atherosclerotic plaque formation caused by an obesogenic diet (Que et al., 2018). Transgenic mice that express the E06 variable fragment also develop significantly smaller infarcts following ischemia-reperfusion injury (Yeang et al., 2019). In vitro, exposure to exogenous E06 IgM prevents OxPL-induced cell death in cardiomyocytes (Yeang et al., 2019). Collectively, these preclinical data suggest that targeting and neutralizing OxPL OSEs holds some promise for developing therapeutics to combat and reverse chronic and acute inflammatory diseases.

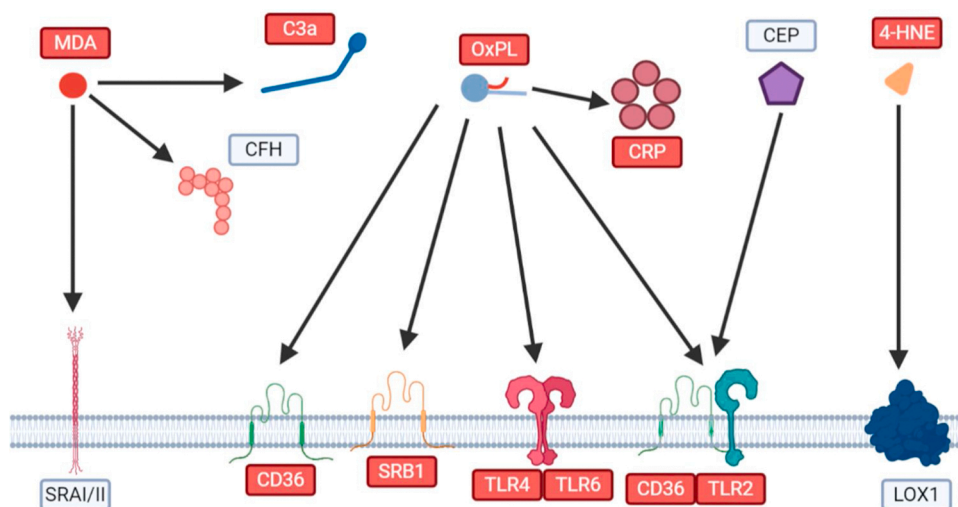


Fig. 1. Pattern Recognition Receptors for Oxidation Specific Epitopes. A variety of pattern recognition receptors (PPRs) recognize oxidation specific epitopes (OSEs). There are membrane bound receptors including scavenger receptor AI/II (SRBI/II), scavenger receptor BI (SRBI), CD36, toll-like receptors 2, 4, and 6 (TLR2, TLR4, TLR6), and lectin-like oxidized low-density lipoprotein receptor-1 (LOX1). There are also soluble PPRs including complement factor H (CFH), anaphylatoxin C3a (C3a), and C-reactive protein (CRP). These receptors bind a variety of OSEs including malondialdehyde (MDA), oxidized phospholipids (OxPL), 2-(ω -carboxyethyl)pyrrole (CEP), and 4-hydroxy-2-nonenal (4-HNE). Receptors and OSEs that have been identified or explored in the context of asthma are highlighted red. Arrows indicate interactions between OSEs and their receptors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

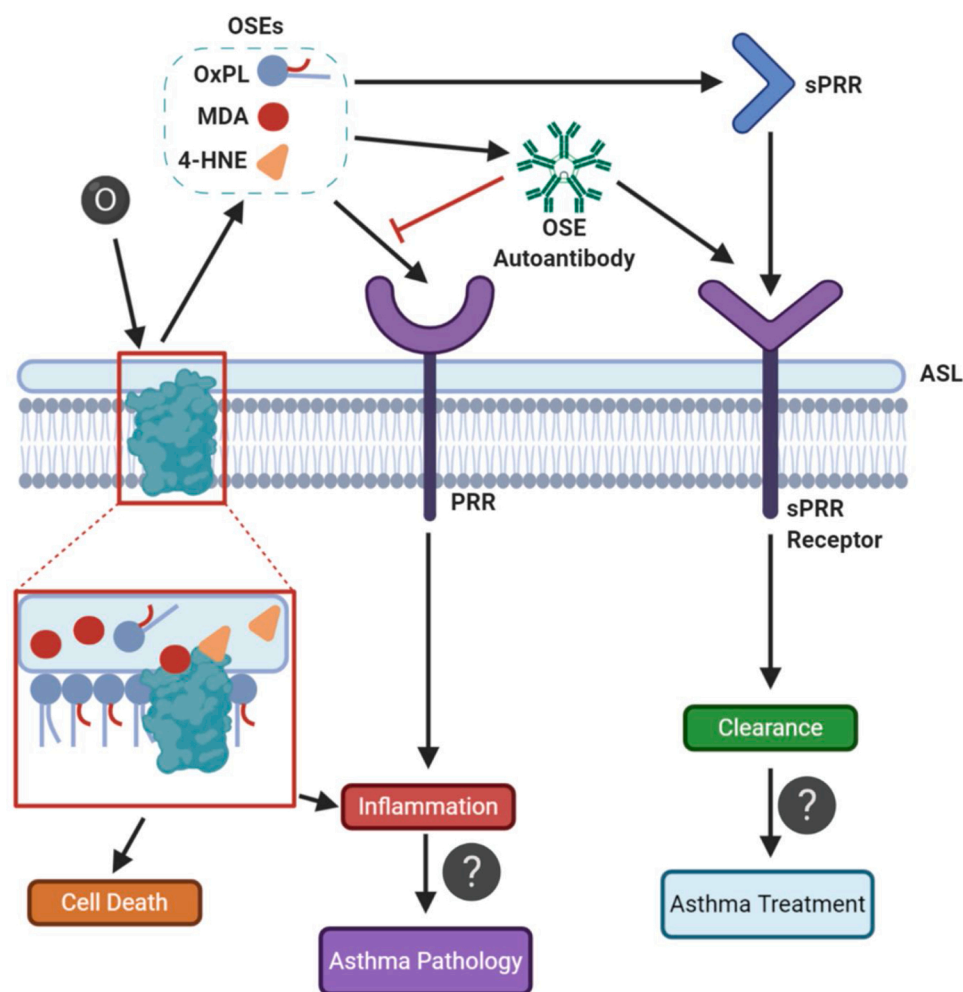


Fig. 2. The Role of OSEs in Asthma Pathophysiology and Treatment. Reactive Oxygen (O) oxidize phospholipids and lipids in the plasma membrane and the airway-surface liquid (ASL) to generate OSEs (inset). This includes oxidized phospholipids (OxPLs) and lipid cleavage products malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE). These OSEs can also form lipid-protein adducts with intracellular proteins and cell surface receptors. These OSEs, and their protein adducts, can trigger cell death through apoptosis and inflammation if left unchecked. A direct link between OSE derived inflammation and asthma pathology still needs to be explored. Soluble OSEs can act as damage-associated molecular patterns (DAMPs) and signal through cell surface pattern recognition receptors (PPRs) or soluble PPRs (sPPR). When bound to PPRs on the cell surface, OSEs can trigger inflammation, which could be linked with asthma pathology. sPPRs act to sequester OSEs and prevent chronic inflammation and tissue damage. These sPPRs can bind to sPPR receptors on the surface of phagocytic cells where they are neutralized and cleared. Alternatively, OSEs can bind to OSE IgM autoantibodies where they are neutralized and taken up by phagocytic cells for clearance. Binding of OSEs to IgM antibodies prevents them from binding to cell surface PPRs. The clearance of OSEs, through sPPRs or IgM, may provide a unique opportunity to target ROS and inflammation in asthma.

Table 1

Expression of OSE Pattern Recognition Receptors. Log₂ RNA counts from adult lung tissue presented as mean, with reference values provided for common cell type markers and housekeeping genes. En – Endothelial Cells, Ep: Epithelial Cells, Mes: Mesenchymal Cells, I: Immune Cells. LOD – Limit of detection. PRR – Pattern Recognition Receptor (cell surface). RNA abundance data obtained from data generated by the LungMAP Consortium [U01HL122642] and downloaded from (www.lungmap.net), on September 25, 2020. The LungMAP consortium and the LungMAP Data Coordinating Center (U01HL122638) are funded by the National Heart, Lung, and Blood Institute (NHLBI). LungMAP (Adult cells).

PRR	Endothelium	Epithelium	Mesenchyme	Immune
SRAI/II	6.17	6.08	9.25	10.73
CD36	12.63	10.79	9.48	12.30
SRBI	9.10	7.54	8.37	8.90
TLR4	10.10	4.90	8.61	11.73
TLR6	3.96	2.19	3.42	7.64
TLR2	7.81	10.21	6.82	11.62
LOX1	7.09	7.25	9.64	12.47
CFH	9.47	10.96	12.81	3.48
C3	8.62	13.77	15.36	8.38
Reference Genes				
GAPDH	12.76	12.69	13.50	14.55
CD45	6.70	7.83	9.94	13.17
EpCAM	6.19	12.60	4.91	0
CDH5	13.35	2.44	5.21	0.01
ACTA2	6.48	8.92	14.47	6.38

5. Current understanding of oxidative stress in asthma

The fundamental function of lungs is to facilitate gas exchange between the environment and bloodstream. Therefore, the lung is highly susceptible to oxidative stress from direct exposure to environmental oxidants. Chronic inflammatory diseases such as asthma are inextricably linked with the overproduction of ROS and reactive nitrogen species (RNS) that can overwhelm endogenous anti-oxidant systems (Al-Harbi et al., 2015; Erzurum, 2016; Mishra et al., 2018). There is substantial literature showing that ongoing oxidative stress is linked with the pathobiology of asthma including airflow obstruction, airway hyperactivity, and remodeling (Al-Harbi et al., 2015; Erzurum, 2016; Mishra et al., 2018). However, the cause-and-effect relationship between oxidative stress and asthma is unsettled and its potential as a therapeutic target remains controversial (Hubbard and Fogarty, 2004). Previous attempts to use antioxidants as interventions in asthma were unsuccessful (Holguin, 2013). This could be due to a lack of information on the cause-effect relationship between oxidative stress and asthma, the role of OSEs in mediating this effect, and the point in the cycle of oxidative stress-driven pathology that interventions have targeted. Production of ROS is multifaceted and is required for appropriate immune regulation and tolerance (Kraaij et al., 2010). OSEs, on the other hand, are produced when ROS is unconstrained and they directly disrupt cellular functions promoting inflammation and tissue damage. OSEs therefore may be a more specific marker of localized stress where they act as direct effectors of excessive ROS. In this way, OSEs provide both a more tangible target for limiting the damage caused by excessive ROS while potentially preserving the beneficial effects of low-level ROS. Therefore,

treatments targeting the OSEs generated by oxidative damage rather than targeting ROS themselves, could be effective in managing asthma symptoms.

6. Evidence relating OSEs in asthma

Our understanding of the role of OSEs in lung disease, including asthma, is limited and requires further investigation. As already noted, OSE-specific inflammation is evident in acute and chronic inflammatory diseases, including acute lung disease (Imai et al., 2008). Moreover, in pre-clinical studies, OSE-directed therapy, specifically treatment with E06-IgM antibody, effectively reduces severity and the pathobiological underpinnings of smoking related disease in mice (Thayaparan et al., 2016). Finally, oxidative stress is an important determinant of steroid refractoriness and so targeting OSEs may promote resolution of steroid insensitivity (Adenuga et al., 2010).

A number of reports suggest that OSE abundance is increased in asthma. Recent studies have identified OxPLs as potential mediators in bronchoalveolar lavage (BAL) of atopic people with asthma and people without asthma but with airway hyperresponsiveness (AHR) after segmental allergen challenge (Pascoe et al., 2020a). Notably there is a correlation between the induction of OxPLs and a number of clinical indices of airway dysfunction. Moreover, phosphocholine-OxPL exposure in airway smooth muscle cells induces cyclooxygenase-2, biosynthesis of pro-inflammatory oxylipins, and release of interleukin-6, -8 and granulocyte-macrophage colony-stimulating factor (Pascoe et al., 2020a). Additionally, Calu3 epithelial cells exposed to phosphocholine-OxPL have significant impairments in barrier integrity, proliferation, and mitochondrial function (Pascoe et al., 2020b). This work complements ongoing studies with human subjects exposed to diesel exhaust, and in house dust mite (HDM) challenged mice that reveal environmental challenges induce significant OxPL accumulation in BAL (Jha et al., 2020b, c; Ryu et al., 2020). It is unclear where these OSEs originate from, however the lipid rich lining of the lung is a likely source. Whether inflammation drives OSE formation or vice versa is still unclear. Indeed, it is likely that inflammation promotes OSE formation which then perpetuates and promotes chronic inflammation in asthma.

MDA is elevated in serum from asthmatics, and positively correlates with disease severity and decline in lung function (Ozaras et al., 2000). Additionally, higher MDA levels are observed in exhaled breath condensate (EBC) and BAL fluid of asthmatics (Bartoli et al., 2011; Corradi et al., 2003; Schock et al., 2003). Interestingly, although inhaled steroid treatment can reduce MDA abundance in EBC from asthmatics, the levels of MDA still remains significantly higher than for non-asthmatics (Bartoli et al., 2011). This indicates that OSEs may be important factors contributing to steroid insensitivity that we can exploit to treat people with severe steroid refractory asthma. In mice, multiple studies exhibit increased levels of MDA in lung homogenates after environmental insult, and this effect is predictable enough that MDA measurements are often included as a marker of oxidative stress in animal models of asthma (Abdelaziz et al., 2018; Bao et al., 2017). 4-HNE has been reported to be increased in sputum of patients with asthma or mild HDM-allergy in parallel with decline in lung function (Lutter et al., 2015). Studies in animal models of allergic inflammation also show that exposure to pollen and ovalbumin causes elevation of 4-HNE in the lung homogenates and lavage (Almolki et al., 2004; Bol-dogh et al., 2005).

CD36 is a cellular scavenger receptor that recognizes OSEs and has an immunomodulatory role in diseases involving phosphocholine-expressing bacteria, and oxidized lipids (Febbraio et al., 2000; Ferracini et al., 2013; Greenberg et al., 2006). Epithelial cells and dendritic cells express CD36 (Silverstein and Febbraio, 2009), and its levels are elevated in asthmatic exosomes (Torregrosa Paredes et al., 2012). CD36 expression appears to localize to type-2 alveolar cells, where it could be theorized to play a role in clearance of oxidized surfactant molecules that participate in OSE mediated inflammation (Du et al., 2015, 2017).

Interestingly, CD36 positive extracellular vesicles are increased in abundance in BAL from asthmatics, and further induced following cigarette smoke exposure (Hough et al., 2018). Additionally, the lipid composition of exosomes is altered in asthmatic subjects; however, no studies have specifically profiled OSEs in these exosomes (Hough et al., 2018). CD36 expression is increased in airway epithelial secretory cells after exposure to IL-13, where the cells take on a metaplastic/pro-inflammatory phenotype (Jackson et al., 2020). In response to allergen challenge, CD36 KO mice are refractory to airway hyperresponsiveness, and exhibit lower abundance of alveolar macrophages, CD4 + T cells, eosinophils and neutrophils in the lungs (Patel and Kearney, 2020). Future research is required to determine whether OSEs and/or OSE receptors associated with lung exosomes contribute to local inflammation, oxidative damage, and tissue injury.

Polymorphisms in TLR2 and TLR4 have been associated with asthma risk (Zhao et al., 2017) and play an important role in mediating airway inflammation induced by HDM allergen (Hammad et al., 2009). Specifically, TLR4 mediates HDM induced epithelial production of inflammatory cytokines IL-13, IL-33, and chemokine GM-CSF (Hammad et al., 2009). In a mouse model of acute lung injury, OxPL can signal through TLR4 in the lung to promote IL-6 production (Imai et al., 2008). Furthermore, TLR2 mediates OxPL induced production of IL-1 β and KC/Gro (IL-8) in murine bone marrow derived macrophages (Kadi et al., 2011). Therefore, allergen induced inflammation in the lung may be in part mediated by OxPL signaling through TLRs. It is important to note, that at low concentrations, OxPL may act as an antagonist of LPS-TLR signaling and may represent an important homeostatic mechanisms in the lungs that goes awry during asthma exacerbations, specifically when anti-oxidant systems are compromised (Erridge et al., 2008).

CRP is elevated in asthma, negatively correlated with lung function, and positively correlated with sputum eosinophil number (Allam et al., 2009; Takemura et al., 2006). Furthermore, C3a, which can bind to and sequester MDA, is elevated in the plasma of asthmatics upon hospital admission for asthma symptoms (Nakano et al., 2003). Elevated serum CRP and C3a in asthma may indicate an increase in OSE burden, especially during exacerbations. This suggests that treating the OSE burden may be a unique opportunity for better treatment of asthma symptoms and exacerbation. Finally, SRB1 deficient mice have increased neutrophil and lymphocyte lung infiltrates following allergen challenge (Reece et al., 2017). Of note, SRB1 null mice have elevated levels of serum MDA (Muthuramu et al., 2018). Collectively, these data provide evidence from both animal and human studies that OSEs are present and associate with severity of lung dysfunction and airway inflammation. Nonetheless, the role of OSEs in asthma pathophysiology and their potential as therapeutic targets has largely been unexplored. Steroid-resistant asthma is a significant problem that requires new ideas to advance treatment. OSEs, as mediators induced by, and that contribute to oxidative stress, could play a role in controlling steroid responsiveness, but no research has been done to date in this area.

7. Can limiting and neutralizing OSEs be a novel therapy for asthma? Future research directions

The formation of OSEs, including MDA and 4-HNE, is increased in asthma, yet no therapies specifically target OSE accumulation or their effects. As the biological effects of OSEs are diverse, and the nature and breadth of receptors that may mediate these effects are broad, a feasible strategy for therapeutic development could be to prevent accumulation of OSEs by enhancing clearance or diminishing generation and/or neutralize their biological impact (Fig. 2). Given that oxidative stress and oxidized biomolecules are a common feature of asthma, regardless of phenotype, it is possible that targeting the clearance of OSEs may be a therapeutic strategy that provides effectiveness across asthma phenotypes/endotypes.

Multiple reports show that OSEs can be neutralized and their clearance enhanced using natural IgM antibodies such as E06 (Chou et al.,

2009; Shaw et al., 2000). Witzum and colleagues developed an E06 monoclonal IgM based on the human natural antibody, and it is in use as diagnostic probe for OSE related inflammatory conditions in pre-clinical research (Hörkkö et al., 1999; Palinski et al., 1996). Pre-clinical studies using E06-IgM to neutralize OSEs are revealing potential therapeutic benefits in animal models for atherosclerosis, aortic stenosis, hepatic steatosis and non-alcoholic steatohepatitis, and inflammatory pain control (Oehler et al., 2017; Que et al., 2018; Sun et al., 2020). Two studies have addressed the capacity of E06 IgM to mitigate inflammation and injury in the lung. In a mouse model of acute lung injury induced by lung-instilled OxPL, E06 significantly inhibits production of IL-6 by pulmonary macrophages (Imai et al., 2008). Cigarette smoke exposure of mice triggers the selective accumulation of antibodies for oxidized low-density lipoprotein in the lung (Thayaparan et al., 2016). Moreover, intranasal instillation of E06 was sufficient to prevent smoking-induced IL-1 α production, and promoted lipid uptake and the internalization of cigarette smoke particles by macrophages. To our knowledge, there are no studies that investigate the effects of lung-instilled E06 in animal models of asthma. Nonetheless, the advances that we have noted establish some promise to investigate the therapeutic benefit of E06 antibody in asthma, an approach that would neutralize OxPL-increasing OSE clearance from lung. OSE accumulation results in neutrophil recruitment (Binder et al., 2016). In asthma, the persistence of OSEs, in part due to potential deficits in clearing mechanisms, may contribute to neutrophilic inflammation. In this way, promoting the clearance of OSEs in the lung via macrophages could help resolve neutrophilic inflammation.

There is evidence from meta-analyses for an association between asthma and reduced serum levels of HDL cholesterol and elevated LDL cholesterol (Peng and Huang, 2017). Lipid components of lipoproteins, primarily LDL, are a major source of soluble OSEs. Therefore, statins, which inhibit hyperlipidemia, can limit the availability of substrates for phospholipid peroxidation in the circulation (Nou et al., 2016; Tsai et al., 2014). Epidemiological and pre-clinical studies reveal that statin use for cardiovascular indications is associated with improved control of asthma symptoms, including fewer ER visits, and reduced use of oral corticosteroids (Wang et al., 2018a). The mechanisms for these effects are unclear, but statins do appear to have pleiotropic effects that include immunomodulatory, anti-inflammatory and oxidative stress-mitigating impact. However, short course clinical trials using oral statins have not revealed any significant effects on asthma symptoms, and very high dose systemic delivery of statins has no-to-modest effects on allergen challenge-induced airway hyper-responsiveness in mice (Jha et al., 2018; Zeki et al., 2015). High dose, systemically delivery of simvastatin is not sufficient to produce measurable levels of pharmacologically active simvastatin in the lungs, which may explain the lack of beneficial effects of oral statins in asthma trials (Bews et al., 2014; Jha et al., 2018). On this basis, inhaled statin formulations have been investigated and are shown to mitigate lung inflammation and airway hyperresponsiveness (Jha et al., 2020a; Wu et al., 2017; Zeki et al., 2015). Ongoing work has begun to reveal a mechanism for this effect, as published preliminary data indicates that very low dose inhaled simvastatin is sufficient to prevent accumulation of OxPLs in BAL from HDM challenged mice (Jha et al., 2020b, c). Coupled with data that indicates OxPLs are sufficient to induce a pro-inflammatory response in human airway smooth muscle cells (Pascoe et al., 2020a), additional pre-clinical studies that specifically investigate the impact of neutralizing and promoting turnover of OxPLs with reagents such as lung-delivered statins or E06 IgM are needed. This could be highly revealing, and may be a platform to assess interventions that can overcome the hurdles of steroid refractory asthma.

8. Conclusion

OSEs are present in a host of acute and chronic inflammatory conditions, including asthma, and cause cell death, inflammation, and tissue

dysfunction. Pre-clinical research indicates that targeting OSEs and their accumulation could be an effective treatment for a host of human diseases. The undeniable presence of OSEs in asthma suggest that they could be involved in disease pathology and that limiting their accumulation or neutralizing them may be a novel avenue for asthma treatment.

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