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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Editorial

Unraveling the Lung Immunometabolic Pathways in Airway Inflammation Driving Asthma Heterogeneity

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Received: March 31, 2023; **Published:** April 10, 2023

Abstract

Asthma is a common inflammatory airway disorder, affecting 350 million individuals worldwide, with the prevalence continuing to increase. At least two clinical heterogeneity exist among patients with asthma; those with increases in airway type2 cytokine activity (Th2-high eosinophilic asthma) and inhaled/systemic steroid-refractory (Th2-low non-eosinophilic) asthma. Although numerous immune pathways are being recognized increasingly to understand the development and disease progression, metabolic adaptations of the immune cells have provided new insights into the underlying mechanism of asthma pathogenesis. Here, we review recent insights into the metabolic adaptation and activation of the lung immune cells in the development and regulation of airway inflammation, with a particular focus on immunometabolic pathways in driving asthma heterogeneity. Our evolving understanding of immunometabolic pathways in regulating airway inflammation and asthma pathogenesis presents promising opportunities for novel therapeutic strategies.

Keywords: *Metabolic Reprogramming; Immune Cells; Asthma; Airway Inflammation*

Introduction

Asthma is an allergic airway inflammatory disease, affecting approximately 25 million individuals in the United States and over 350 million individuals worldwide, with the prevalence rate continuing to increase. Despite advancements in care, many individuals with asthma have poorly controlled disease, leading to significant morbidity. In addition, from a societal perspective, there are enormous direct and indirect costs for asthma care, which has been estimated to cost more than $900 billion in the next 20 years in the United States alone. Consequently, there is an urgent need for new therapeutic approaches for asthma.

It is now well appreciated that differences in airway inflammation and immune phenotype give rise to heterogeneity, including variability in symptom control, airflow limitation, treatment responses, and risk for acute exacerbations. However, the pathologic drivers of such differences between asthmatic patients remain unclear. Allergic asthma is the most common asthma subtype, affecting primarily children and approximately half of adults with asthma. The development of allergen-specific CD4+ T helper type 2 (Th2) cells represents a critical step in the onset of allergic asthma. Th2 cells are a dominant source of type 2 cytokines IL4, IL5, and IL13 that orchestrate allergic

airway inflammation in murine models and humans with allergic asthma. Mild asthma patients can shift into the severe category based on control. Some of the patients are prone to poor outcomes, including fatal asthma events, despite having a mild disease at baseline. Moreover, it is believed that lung infections in asthmatics develop a complex immune response and are associated with Th1/Th17 type instead of conventional Th2 immunity, in which neutrophils rather than eosinophils infiltrate the airways. This has led to an attractive hypothesis that neutrophil-rich Th1/Th17 cell-driven inflammation is the pathological correlate of steroid-resistant asthma. Despite recent therapeutic advances that aim to benefit patients with persistently elevated Th2 immune responses, many patients will not benefit, likely due to alternate or adjunct pathways of disease activation. Beyond host genetics, additional factors shape the immune mechanisms involved in asthma and other chronic inflammatory diseases. Accumulating evidence has highlighted links between altered human microbiota composition and metabolic states to asthma susceptibility and asthma phenotype in established diseases. Moreover, systemic markers of metabolic dysregulation and inflammation are prominent in many more severe, difficult-to-treat asthma patients. Advances in the immunometabolism field have highlighted that the cellular microenvironment modulates the effector properties of both innate and adaptive immune cells. Thus, there is an unmet need to understand the pathophysiologic mechanisms of asthma, identify asthma phenotypes and endotypes, and develop targeted approaches for these patients.

Metabolic adaptation of lung immune cells driving airway inflammation in asthma

Lung immune cells, including antigen-presenting myeloid dendritic cells (DC), macrophages as well as innate lymphoid cells (ILCs), natural killer cells (NK), and T cells, are crucial for the initiation, maintenance, and propagation of airway inflammation in asthma. DC can locally activate T effector cells in the airway wall by providing T-cell chemotactic cues and delivering MHC and costimulatory signals. In particular, the primary CD11b+ conventional DC subtype in the lung has been recognized to initiate and orchestrate T cell-mediated adaptive immune responses (Th1, Th2, and Th17) to inhaled aeroallergens in asthma. Under non- inflammatory conditions, these lung immune cells metabolically rely on mitochondrial oxidative phosphorylation (OXPHOS) and glucose utilization to meet their anabolic cellular demands. However, the lung immune cells undergo a rapid shift in metabolic requirements during inflammation, which drives the aerobic glycolysis pathway and fragments the tricarboxylic acid (TCA) cycle, thereby allowing citrate production from glucose. These metabolic adaptations in myeloid lung immune cells are utilized for acetyl CoA production and synthesis of fatty-acid. Recently, our lab and others have identified a novel mechanism of dimethyl fumarate (DMF) function in the lung, a derivative of TCA cycle intermediate fumarate, where it effectively interferes with DC migration to the draining mediastinal lymph node and subsequent induction of allergic sensitization and Th2 immunity to aeroallergen house dust mite (HDM). Moreover, it is increasingly recognized that not only the metabolic pathways drive the effector function(s) of these lung immune cells, but also the endogenous key metabolites regulate the cellular redox and inflammation, impacting the disease phenotype and outcomes. Here, we will review how metabolic pathways of the lung immune cells are interlinked with the heterogeneity of the disease and discuss whether these changes are attributed to distinct asthma phenotypes.

Metabolic adaptations in Th2-high asthma

In the clinic, Th2-high asthma is manifested by the elevated level of blood and sputum eosinophils, fractional exhaled nitric oxide, serum IgE, and type 2 cytokines IL4, IL5, and IL13. The innate type 2 inflammatory response in the airways is orchestrated by natural killer cells and innate type 2 innate lymphoid cells, whereas the adaptive immunity, is developed by Th2 (T helper type 2) immune cells in the lungs. However, the Th2-mediated lung adaptive immune response leads to a phenotype of eosinophilic inflammation that accompanies IL-5, IL-13, and IL-4 cytokine productions.

Glycolytic enzyme pyruvate kinase M2

Allergen-induced Th2 inflammation is initiated by antigen-presenting DC that relies on mitochondrial oxidative phosphorylation (OXPHOS) in the immature state and is regulated via AMPK signaling. In the context of early Toll-like receptor (TLR) activation, DC undergoes metabolic reprogramming coupled with a glycolytic surge for ATP production. The immune- priming function, CCR7-dependent migration, and antigen-presentation capability of DC were strikingly reduced in the presence of 2-deoxyglucose (2-DG), a glucose analog. Fur-

thermore, hypoxia-inducible factor (HIF1α)-deficient DC has impaired CCR7 expression and oligomerization in the absence of glucose, suggesting the regulation of DC metabolic plasticity on effector function(s). Our lab and other groups have recently shown that pyruvate kinase M2 (PKM2) in CD11c+ APCs (a cytosolic enzyme responsible for converting phosphoenolpyruvate to pyruvate in glycolysis) is induced in acute asthma. Moreover, activation of PKM2 by small- molecule activator TEPP46 markedly decreased house dust mite (HDM)-induced eosinophilic airway inflammation, subepithelial collagen deposition, and mucous metaplasia via attenuation of STAT3 phosphorylation and IL-1β-mediated TSLP release (PMID 31924651). Interestingly, the redox regulation of the glycolytic enzyme PKM2 via glutathionylation regulates TSLP release and subsequent airway inflammation (PMID 33817836), indicating that metabolic modulations are an upstream event of Th2 inflammation in asthma.

Mitochondrial Irg1/itaconate axis as the regulator of Th2 inflammation

The uptake of allergens by antigen-presenting DC and cross-presentation are redox- dependent and linked with mitochondrial functions. The immune-priming and immune-presenting capability of DC are influenced by mitochondrial superoxide (reactive oxygen species; ROS) generation. Recently, we have shown that the mitochondrial metabolite itaconate, an intermediate of the TCA cycle, modulates DC effector function(s), thereby affecting the progression of HDM-induced allergic asthma in mice. Itaconate is produced from decarboxylation of the TCA cycle intermediate cis-aconitate and is encoded by immune responsive gene 1 (*Irg1*, also known as aconitase D1; *ACOD1*). In the absence of $_{Irg1}$, mitochondrial stress and ROS (mtROS) production are elevated by HDM stimulation, impacting the kinetic oxygen consumption rate (OCR) and metabolic genes, which impairs mitochondrial redox and associated immune-priming and immune-presentation capability of DC. These findings indicate that antigen uptake and priming are influenced by mitochondrial dysfunction and do not affect DC migration to draining LN. Moreover, the migration of DC is CCR7-dependent and is primarily controlled via glycolysis. Emerging evidence suggests that the cell-permeable octyl ester derivative 4-OI is metabolized intracellularly to itaconate, which exerts potent antioxidant and anti-inflammatory function via multiple mechanisms. Notably, itaconate and its derivative 4-OI exert the immunomodulatory functions via various mechanisms, including mitochondrial SDH inhibition, reducing mtROS production, and releasing Nrf2 from redox-sensing protein KEAP1 by posttranslational modification (2,3- dicarboxypropylation), blocking GAPDH enzymatic activity, and activating the transcription factor ATF3. Further studies on the Irg1/itaconate axis are awaited to explore the immunomodulatory role in DC effector function(s) and Th2 inflammatory pathways driving asthma pathogenesis.

FAO pathway in Th2 inflammation

Type 2 innate lymphoid cells (ILC2) are regulators of Th2 inflammation and primarily rely on fatty acid (FA) metabolism for their development and effector function(s). Impaired FAO in Atg5-deficient mice resulted in increased ILC2 apoptosis associated with increased glycolysis, mitochondrial dysfunction, and excessive ROS production (PMID: 31738991). These metabolic adaptations in ILC2 lead to decreases in Th2 cytokine secretions and Th2-associated airway hyperreactivity. Interestingly, the inhibitory axis of programmed cell death protein-1 (PD-1) acts as a metabolic checkpoint to repress ILC2 proliferation and effector function(s), including proallergenic cytokine IL25 and IL33 secretions. Recent studies employing PD-1-deficient ILC2 and PD-1 agonists show that impaired FAO and glycolytic surge in ILC2 decreased airway hyperreactivity (AHR) in IL-33-induced airway inflammation, suggesting PD-1 as a potential therapeutic target in allergic asthma (PMID: 32778730). Furthermore, future research on ILC2 metabolism is warranted to address how metabolic adaptations in ILC2 regulate their effector function(s) and drive Th2 inflammation in asthma.

Arginine metabolism driving Th2 inflammation

Asthmatic patients manifest increased iNOS expressions and fractional exhaled NO (FeNO) productions, which drive airway inflammation and Th2 immune response. The substrate arginine is metabolized by inducible nitric oxide synthase (iNOS) in the cytosol and arginase (Arg2) in the mitochondria. The metalloenzyme arginase is primarily located in the cytosol (type I), whereas the type II isoform is mitochondrial and is expressed by various tissues, including the lung. Arginine is catabolized into NO and citrulline by iNOS, and is

a critical modulator of airway inflammation and asthma severity. Interestingly, Arg2 deficiency in mice demonstrates increased STAT6 phosphorylation, IL13 production, and higher eosinophilic airway inflammation in response to the OVA challenge (PMID: 27214549).

However, arginine metabolism does not seem to be limited just to epithelium, as arginase deficiency in ILC2s resulted in alleviated type 2 inflammation in a papain induced lung inflammation model via reduced type 2 cytokine secretion and regulation of glycolytic capacity of ILC2s [1]. Further, arginine metabolism via HIF has been shown to induce Th2 cytokines such as IL-5 and eotaxin-2. Eotaxin-2 is mainly expressed by alveolar macrophages (AM) and are key in an eosinophilic infiltration of the airways [2].

Macrophage polarization

Being the first line of defense for allergens and antigens, alveolar macrophages play a key role in asthma pathogenesis. Based on their activation status, they are classified as M1, a pro- inflammatory phenotype, and M-2 a pro-wound healing phenotype activated by IL-4 and IL-13. Both phenotypes of macrophages are increased in asthma patients underlining the heterogeneity of the disease [3]. Most strikingly, even in homeostasis, the metabolic profiles of the M1 and M2 AMs are different. While M1 macrophages primarily rely on glycolysis, M2 macrophages rely on FAO, OXPHOS [4,5]. This heterogeneity in AM populations can be attributed to polarization due to changes in local tissue environment, however it is important to note that M2 phenotype is predominant in asthmatic patients [6]. One of the pathways altered in AMs is the arachidonic acid pathway. Arachidonic acid is released in asthma [7], and its metabolism includes leukotrienes and prostaglandins. It has been shown that leukotrienes B_4 (LTB_4) and E_4 (LTE_4) are increased in AMs isolated from asthmatic patients [8] and this aberrant change in metabolism dictates asthma progression via the pro-inflammatory effect of LTB_4, which attracts neutrophils and eosinophils into the airways and the bronchoconstrictive role of LTE_4 to produce effects such as increased endothelial membrane permeability. Furthermore, metabolic stress in AMs induces reactive oxygen species (ROS) production in asthmatics directly contributing to their increased pro-inflammatory phenotype as shown by increased tumor necrosis factor (TNFα) and IL-6 secretion [9,10]. More recently, it was shown that AM phenotype was mediated by transcription factor FoxO1 via metabolic reprogramming. FoxO1 deficient AMs were shown to have a M2 like phenotype, and it was determined that the change in polarization was via downregulation of glycolytic capacity [11]. Additionally, AM polarization into M2 phenotype was also shown to be controlled by transcription factor GATA-3, where IL-33 induced uncoupling of the electron transport chain (ETC), and itaconate. This process was IL-4 independent and was abrogated in absence of GATA-3 [12]. The induction of itaconate in alternatively activated macrophages (AAMs), however, is inhibitory for M2 polarization as shown recently. It has been shown that itaconate and OI inhibit JAK1 and STAT6 polarization, which was not just limited to macrophages but also Th2 cells. Treatment of macrophages with octyl itaconate (OI) suppressed M2 polarization and JAK1 phosphorylation *in vivo* as well [13]. This data highlights the possibility of metabolic alterations determining AM phenotype via a variety of transcription factors and metabolic pathways and their intermediates such as itaconate. Together, the metabolic plasticity of AMs in different phenotypes suggests the importance of understanding mechanisms underlying this heterogeneity. It must be noted that the murine lung fails to mimic the microenvironment of a human asthmatic lung. For instance, the induction of Arg1 in AMs is only observed in murine models and not in human asthmatic AMs. However, the insight offered by murine models into the metabolic regulation of macrophage polarization is important, and paves way for the use of metabolic manipulation to drive changes in AM phenotype as a tool for therapy.

mTOR has been implicated in T cell polarization through DC metabolism. mTOR ablation in the DCs induced a predominant Th17 response with HDM stimulation, which is known to have a dominant Th2 effect. The absence of mTOR altered DC metabolism by promoting FAO, inhibition of which using etoximir ablated the Th17 response and reversed the phenotype to a Th2 dominant one. This was shown to be mediated via IL-23 cytokine secretion, as neutralization of it also reversed the Th17 phenotype to confer Th2 polarity [14]. As mentioned above, the severe asthma endotype is marked by mixed granulomatous inflammation, which is neutrophil dominant, and is not responsive to steroid treatment. Therefore, FAO inhibition presents as an interesting target for the therapy of severe asthma to reverse its unresponsive steroid phenotype. The important role of mTOR becomes clearer in T cells, where it controls Th1, Th2, Th17, and Treg differentiation [15]. In the absence of mTOR, T cells differentiate into regulatory T cells (Tregs) instead of Teff cells. Furthermore, mTORC1

and mTORC2 induce differential STAT signaling in T cells, thus defining their cytokine secretion profile, which is responsible for skewing the effector cell subtype toward Th2 or Th1. Rheb is a protein important in mTORC1 signaling. In its absence, T-cells fail to induce STAT3 and STAT4 even in the presence of IL-6 and IL-12 that are known to induce Th1 effector cells. Further, in absence of Riktor, a protein important in mTORC2 signaling, T-cells fail to induce STAT6, for Th2 polarization.

Glycolytic reprogramming on T-cell polarization

IL-17 secreting Th17 cells are prominent in the severe asthma phenotype. RORγt is the transcription factor that mediates this effector function. HIF1 has been shown to transcriptionally activate RORγt and recruit a RORγt and p300 complex to the IL-17 promoter, thus enhancing Th17 cell development. Furthermore, HIF-1 has also been linked with Treg down regulation via Foxp3 proteasomal degradation, both under normoxic and hypoxic conditions thus making it relevant in conditions of lung inflammation with altered oxidative conditions [17]. Similarly, aerobic glycolysis has also been implicated in IFNη secreting Th1 cells, where lactate dehydrogenase (LDHA) maintains high acetyl-co-A levels and IFNη transcription levels through histone acetylation epigenetic mechanisms. Ablation of LDHA in T- cells prevents the progression of Th1 mediated immunopathology in autoimmune disease, however, can be translated to lung wherein LDHA has been shown to be induced under asthmatic conditions [18]. This can be further be linked to HIF-1 as HIF-1 has been shown to activate LDHA encoding genes.

Arginine metabolism and Th17 pathway

In DCs, with the increase in glycolysis after activation, the ETC is inhibited via the PI3-AKT and mTORC signaling dependent production of inducible nitric oxide synthase (iNOS) and nitric oxide (NO), levels of which correlate with severity of asthma and are regularly used as a biomarker to predict response to therapy [19,20]. As mentioned previously, iNOS deficient mice were shown to have lower eosinophilic inflammation compared with WT animals [21], however, in a mixed model of inflammation using HDM extract, the airway inflammation was comparable between the two groups, thus suggesting that arginine metabolism through iNOS does not affect IL-17 mediated airway inflammation. Arg2 deficiency on the other hand ameliorated both eosinophilic and neutrophilic airway inflammation in mice, suggesting the protective role of arginine metabolism through Arg2 [22]. Additionally, IL-17 secretion was increased in Arg2 deficient mice, however, Th17 cells were shown to be reduced, thus suggesting a cell specific effect of Arg2 on IL17 secretion and the importance of arginase in maintaining IL-17 balance in the airways to avoid an unfavorable phenotype containing a neutrophilic infiltration.

Effect of metabolic reprogramming in neutrophils

Neutrophils depend primarily on aerobic glycolysis for their energy needs. Despite having few mitochondria, OXPHOS is upregulated in neutrophils in response to stimulation and phagocytosis induction [23,24]. The studies on neutrophils in the lung however are limited, and studies in the human lung are even more scarce. However, it has been shown in lung neutrophils from patients of cystic fibrosis that enzymes such as PKM2 and HIF1α were upregulated suggesting metabolic reprogramming in neutrophils via glycolysis. Additionally, pro-inflammatory cytokines such as IL-1β were also shown to be induced in neutrophil cytosol. These effects were mediated via glycolysis as inhibition of it using 2DG in an *ex-vivo* study reversed IL-1β induction. The effect of glycolysis was shown to be via NLRP3 inflammasome, as its inhibition also reversed the pro-inflammatory signature [25].

Effect of protein oxidation on immunomodulatory metabolites

Protein oxidation has been shown to be a key regulator of several diseases, specifically, S- glutathionylation (GSTP) where glutathione is conjugated to cysteine residues in proteins to alter protein structure and function [26]. GSTP polymorphisms have been linked to altered susceptibility of asthma development [27]. GSTP does so via metabolic reprogramming of the glycolysis pathway. One such glycolytic protein, PKM2, has been shown to be a target of GSTP oxidation, as it shown that in oxidated state, PKM2 dimerizes as returns from a canonical glycolytic pathway to a pro-inflammatory phenotype via IL-1β induction [28,29]. This offers new insight into the possible

inhibition of PKM2 dimer activity, thus limiting HIF1, pSTAT3 and glycolytic surge via GSTP inhibition. Most importantly, there is current lack of understanding of metabolic regulators that affect a shift to a neutrophilic endotype. Thus, it is pertinent to study how metabolic reprogramming causes this shift, and if it can be manipulated to provide therapeutic targets for the treatment of steroid resistant asthma. PKM2 has been shown to be requisite for Th1 and Th17 differentiation in models of experimental autoimmune encephalomyelitis (EAE). Serine/threonine kinase CaMK4 binds to PKM2 in order to stimulate its glycolytic activity and promote glycolysis for the differentiation of T-cells [30] thus offering a target for Th17 producing IL-17 cells, which is also relevant in obesity associated asthma, where glutathionylation of PKM2 has been shown to be pro-inflammatory as well [28].

Metabolic adaptations of obesity-associated asthma

Asthma is known to predispose to obesity. Clinically and experimentally however, obesity modifies asthma and it is known as obesity induced asthma [31]. In children and adults who are obese, a more severe phenotype of the disease is seen with approximately 4 - 6 fold higher risk of being hospitalized due to exacerbations [32]. Phenotypically, it manifests itself as different endotypes. Earlier-onset obese asthmatics have Th2 signature, with high severity, meanwhile, later-onset patients (primarily females) that do not have airway inflammation, but only adipose tissue inflammation and oxidative stress, somehow show a neutrophilic signature [33,34]. Attributing to this heterogeneity, obese asthmatics do not respond well to standard ICS therapy [35]. Several key metabolic anomalies were seen in obese mice, namely, arginine metabolism, mitochondrial dysfunction and insulin resistance [36,37]. As mentioned previously, mitochondrial dysfunction is a known early pathophysiological event in asthma, in obesity it presents itself similarly with increased ROS production and mitochondrial depolarization, thus reducing mitochondrial metabolism [38,39]. Further, metabolites such as asymmetric dimethyl arginine (ADMA) are increased thus affecting arginine bioavailability and nitro-oxidative stress through disrupted NO synthesis [40]. This is clinically similar to asthma as ADMA has been shown to be increased in IL-4 dominant Th2 asthma, where the cytokine was shown to produce ADMA via protein arginine methyl transferases and inhibited its degradation via dimethylarginine dimethylaminohydrolase 2 [41]. High dose of arginine exogenously increased arginine bioavailability and was able to attenuate the disease by reversing mitochondrial dysfunction [42-44]. This could prove useful as an intersection between both obesity and asthma, as well as obesity induced asthma. This highlights to the possibility of more complicated pathways as a link between the two diseases, and thus paves way for future research into how metabolism can be targeted to protect from obesity induced asthma.

Targeting metabolic reprogramming as a treatment for asthma heterogeneity

Accumulating experimental and clinical evidence demonstrates that metabolic regulators involved in various catabolic and anabolic pathways can be one of the most potential therapeutic targets for the treatment of asthma endotypes. For instance, alteration of energy metabolism in asthmatic lungs leading to upregulation of leukotriene synthetic pathway or increased utilization of L-arginine as substrate are widely addressed by using different therapeutic strategies to restore the balance. Apart from targeting catabolic and anabolic pathways, energy sensing metabolites such as AMPK, mTOR or Sirt1 are other attractive targets to manipulate the adaptive immune responses in allergic asthma. However, the contradicting findings as well as variable and incomplete responses by asthmatic patients to the current and potential therapeutics reflects that our understanding of the underlying pathogenic mechanisms in airway allergy is partially known.

Leukotrienes: Even though glucocorticoids are the gold standards that are used to alleviate clinical symptoms of both stable and acute asthma, leukotrienes modifiers such as 5- lipoxygenase inhibitors and cysLT receptor antagonists are also widely used. The effect of leukotriene receptor antagonists (LTRAs) in combination with inhaled corticosteroids or as monotherapy has been investigated in asthmatic patients using meta-analyses and meta- regression of randomized controlled trials. This study revealed that LTRAs add-on use to inhaled corticosteroids improved some measures of asthma control, nonetheless, LTRA monotherapy displayed considerable improvement as compared to placebo control [45]. Pranlukast, montelukast, and zafirlukast are some of the currently available LTRAs which has been approved for the treatment of allergic inflammation since more than two decades [46]. In addition to LTRA, the 5-lipoxygenase (5-LO,

key enzyme in leukotriene synthesis) inhibitors are also reported to be effective in asthma control in experimental model. For instance, inhibition of 5-LO by an endogenous Vitamin E metabolite (α-T-13′-COOH) has been shown to limit the airway hyper-reactivity in the ovalbumin-induced asthma murine model by lowering the pulmonary leukotrienes levels [47]. Moreover, the repression of the action of nuclear-bound 5- LO-activating protein (FLAP), which activates lipoxygenase enzyme, leads to the inhibition of leukotrienes, and hence, negatively affects the lung inflammation in asthma development. For instance, MK-0591, a FLAP inhibitor, impeded the biosynthesis of allergen-induced leukotrienes in mild to moderate asthmatic patients leading to a significant reduction in early asthmatic reaction. However, MK-0591 showed decreased attenuation of AHR post 24 hours of histamine challenge [48]. Similarly, a broad spectrum of FLAP inhibitors such as GSK2190915, BAYx, GSK2190918 has entered clinical trials [49-51].

mTOR: The mammalian target of the rapamycin (mTOR) pathway is centrally positioned to integrate environmental cues to regulate the metabolism during lung inflammatory response. Many inhibitors of mTOR (endogenous and exogenous) are used to investigate the resolution of the clinical manifestation of acute and chronic pulmonary inflammation. For example, mTOR inhibitor, rapamycin, attenuates the HDM-induced increase in AHR, goblet cell metaplasia, and IgE by reducing the production of IL-13 cytokine and leukotrienes in the murine model of asthma [52]. In a subsequent study, the context-dependent role of rapamycin treatment at the later stages of the disease progression and on allergen re-exposure was investigated. The authors found that inhibition of mTOR during allergen re-exposure phase with concomitant rapamycin treatment led to reduction of Th2 cytokines, goblet cell metaplasia, and IgE. However, rapamycin treatment failed to reverse airway inflammation in chronic/established disease model and in fact augmented the levels of inflammatory cells and IL4 in the BALF [53]. Interestingly, these studies suggest an important role of the mTOR pathway in the early phase of allergic asthma, which is not the case in allergen re-exposure and disease progression.

Using the murine model of lung inflammation and remodeling, another group observed that the oral administration of novel rapamycin derivative, SAR943 (32-deoxorapamycin) attenuated ovalbumin-induced increased levels of IL4 and IL5, reduced eosinophil, neutrophil, and lymphocyte infiltration in lung, suppressed mucus hypersecretion and decreased bronchial hyperreactivity to methacholine [54]. Interestingly, in contrast to this study, the exogenous administration of SAR943 to ovalbumin-sensitized rats demonstrated inhibition of the proliferation of alpha-smooth muscle cells and epithelial cells in the rat airway without any effect on the bronchial hyperresponsiveness to acetylcholine or allergic inflammation [55,56]. These contradictory results reflect the species-specific differences of immunomodulatory compounds in mice and rats. Hence, treatment with rapamycin and its derivative is not just context-dependent, but also species specific.

In addition to the mTOR inhibitors, the role of upstream activator of mTORC1, small GTPase ras homolog enriched in brain (*Rheb*) in macrophage polarization was studied in the ovalbumin-induced asthma murine model system using myeloid cell-specific deletion of the *Rheb1* gene. The knock-out of the *Rheb1* gene in myeloid cells exhibited aggravated inflammatory response characterizing enhanced mucus production, airway hyperreactivity, and eosinophilia along with marked enhancement of M2 polarization and reduced M1 polarization of alveolar macrophages. This study suggests that *Rheb1* has an anti-inflammatory role in allergic asthma and is critical for the polarization of the macrophages [57]. Moreover, Rtp801, another endogenous inhibitor of mTORC1 (primary complex of mTOR) signaling, produced by alveolar type II epithelial cells suppresses anti-inflammatory epithelial mTORC1 responses in lung inflammation caused by endotoxin [58]. Overall, inhibition of mTOR pathway proves to restore the balances of Th17/Treg and Th1/Th2 cytokines and should be explored more.

PPAR-γ: Pioglitazone is a thiazolidinedione-type diabetic drug that activates the transcription factor involved in the glucose and lipid metabolism, named peroxisome proliferator-activated receptor gamma (PPAR-γ). It has been long established that the peroxisome proliferator- activated receptors, PPAR-α and PPAR-γ, are involved in the regulation of the antigen-induced airway inflammation, eosinophil influx, Th2 cytokine production, and AHR in the experimental model of asthma [59]. The intratracheal sensitization of mice with ovalbumin-pulsed DCs treated with agonists of PPARγ such as rosiglitazone revealed that PPARγ activation strongly prevents the activation of

Th2 cells in draining mediastinal lymph nodes and hamper recruitment of eosinophils in the BALF by suppressing the antigen-presenting capabilities of dendritic cells. This finding has been further confirmed by using other PPARγ agonists like ciglitazone, and antagonist, GW9662 [60]. In addition, rosiglitazone and pioglitazone treatment of ovalbumin-induced allergic airway disease in mice indicated decreased bronchial inflammation, airway hyperresponsiveness, ROS production, and HIF1α levels in lung tissue [61,62]. However, clinical trials of PPAR-γ activator on asthmatic patients demonstrated varied results. A 4-week rosiglitazone treatment study of smokers with asthma and on the late asthmatic reaction in two randomized controlled trials showed moderate improvement in the airway obstruction [63,64]. On the other hand, the difference in airway reactivity of a subset of obese patients with poorly controlled asthma post pioglitazone treatment showed its limited efficacy in measures of asthma control in a randomized 12-week controlled trial [65]. The participants assigned to pioglitazone in this study even gained significant weight during the trial which may further negatively influence the asthma control. In a subsequent study, [66] 12- week treatment of pioglitazone to mild asthmatic patients also showed no improvement in markers of airway inflammation in mild asthma in a double-blind randomized controlled trial.

Hence, despite multiple evidence of anti-inflammatory effects of PPARγ agonists in pre-clinical studies, the evaluation of clinical application points to the contrary.

Sirtuin1 or SIRT1: Sirtuin1 or NAD-dependent deacetylase sirtuin-1 is regarded as an important metabolic sensor which influences the immune response. Histone acetyltransferase activity and histone deacetylase activity are found to be reduced in the asthmatic lungs. Hence, activation of sirtuin1 by synthetic activators such as SRT1720 and resveratrol have been shown to decrease the amount of eosinophil infiltration in lung tissue, as well as reduced levels of IL-5 and IL-13 cytokines in the BAL fluid of the ovalbumin-challenged mice [67]. In agreement with these findings, *in vitro* experiments with different cell lines (A549 cells) also showed that SIRT1 enhancers such as myricetin significantly reduced the TNF-α triggered- inflammatory response by inhibiting NF-Kβ activation, and hence, in turn leading to the significant reduction of the secretion of pro-inflammatory cytokines, IL6 and IL-8 cytokine [68]. Similarly, bergenin, which is an antitussive and anti-inflammatory polyphenol compound also augmented the TNF-α induced pro-inflammatory response by inhibiting SIRT1 activity [69]. However, in contrast to the previous anti-inflammatory role of SIRT1, sirtuin inhibition by pharmacological compound has been shown to inhibit allergic inflammation and adaptive Th2 immune response by repressing the PPARγ receptor activity of lung dendritic cells in the mouse model of airway allergy. This leads to enhanced effector function of lung dendritic cells and thereby, pro-Th2 phenotype [70]. The intriguing nature of sirtuins as both pro- and anti- inflammatory can probably be explained by its varied effect on T cell-dependent inflammations such as airway allergy (promotes Th2 response) and T cell-independent inflammatory conditions which are mainly driven by innate inflammatory mechanisms related to aging, oxidative stress, and metabolic dysfunction.

Arginine: The enzymes arginase and nitric oxide synthase are the key players in the metabolism of L-Arginine for the maintenance of airway health. Dysregulation in the L-arginine metabolism contributing to the allergic airway inflammation can occur either through increased arginase activity or inhibition of nitric oxide synthase by endogenous inhibitors such as asymmetric dimethylarginine (ADMA). In an ovalbumin induced-allergic inflammation murine study, high dose L-arginine treatment (250 mg/kg X2) decreased not just bronchial hyperresponsiveness, Th2 cytokines, goblet cell metaplasia, but also the pulmonary arginase activity and inducible NOS in bronchial epithelia [44]. Clinical studies related to supplementation of L-arginine have shown that long-term intake of the amino acid by asthma patients may lead to the enhanced production of ADMA [71]. However, treatment with L-arginine in addition to the standard asthma medications to a cohort of 50 patients with severe asthma demonstrated no significant reduction in asthma exacerbations [72]. Inhibition of arginase enzyme is another widely studied strategy which attenuates the cardinal features of the asthma. For instance, systemic treatment of mice with N-omega-hydroxy-nor-l-arginine (nor-NOHA), a competitive inhibitor of arginase resulted in significantly reduced ovalbumin induced-pulmonary inflammatory response [73].

Dysregulation of arginine metabolism and increased formation of advanced glycation end- products (AGEs) associated with obesity-related asthma, which leads to inflammation and bronchoconstriction, is shown to be regulated by glucagon-like peptide 1 (GLP-1) [74].

Hence, targeting GLP-1 have also led to novel treatments of allergic airway. GLP-1 analog liraglutide potently ameliorated the ovalbumin-induced chronic airway inflammation, mucus hyper- secretion, and compromised the raised content of IL-4, IL-5, and IL-13 cytokines in BABLB/c mice through inactivation of NF- κB in a PKA-dependent manner [75]. Subsequently, comparative studies on the rates of asthma exacerbations and symptoms revealed a trend of reduced counts of asthma exacerbations in type 2 diabetic patients with asthma who were prescribed glucagon-like peptide-1 receptor (GLP-1R) agonists [76] as well as improved lung function in diabetic patients [77]. The beneficial role of GLP-1R agonist beyond type-2 diabetes and obesity control and preclinical studies have led to significant interest in the investigation of its potential use in chronic inflammatory pulmonary disease treatment.

AMPK: Moreover, metformin (antidiabetic drug), an AMPK activator, is reported to hamper the exacerbation of allergic eosinophil response in a high-fat diet (HFD) fed obese mice post ovalbumin challenge. The high influx of eosinophils in BALF and lung tissue, increased levels of eotaxin, TNF-α, NO, and increased expression of iNOS protein displayed by obese mice after the ovalbumin challenge were all normalized by metformin [78]. These observations were in line with a subsequent report which studied airway hyperactivity and asthma in rats with dietary obesity. Concomitant treatment of metformin to rats on a HFD for 5 weeks demonstrated that metformin was not just able to inhibit weight and fat gain, but also prevented the development of obesity-associated airway hyperreactivity [79]. In addition, cigarette smoke induced cardinal features of emphysematous chronic obstructive pulmonary disease like pulmonary inflammation, lung injury, and mitochondrial dysfunction were also ameliorated by metformin in the murine model [80].

PD1: Another study has suggested the beneficial immunomodulatory role of the PD1 agonist treatment which exploits the PD1 inhibitory signaling to elicit efficient repression of the activated ILC2s. PD1-agonist was found to improve ILC2-mediated lung inflammation and airway hyperactivity in IL-33 and HDM-induced asthma in a humanized mouse model. The PD1 agonist demonstrated both a therapeutic and preventive role in the clinical context of asthma treatment in a humanized mouse model [81].

Adenosine: The role of adenosine and adenosine receptors in asthma pathogenesis has been a subject of conflicting observations. The pro-inflammatory effects of IL-13 in lung inflammation imparted by adenosine accumulation have been long established. Degradation of adenosine by adenosine deaminase (ADA) enzyme therapy was found to significantly diminish the IL-13- induced inflammation and alveolar destruction in IL-13 transgenic mice [82]. However, in a more recent study, adenosine signaling via A2A adenosine receptor present on the pulmonary ILC2s is identified as a negative regulator of allergic airway inflammation. Perturbation of adenosine metabolism by adenosine-A2A axis on ILC2 is mediated by the accumulation of intracellular cAMP and NF-κB pathway downregulation. Murine airway inflammation when challenged with papain or IL-33 was significantly improved upon treatment with an adenosine analog, NECA via reduction in ILC2 response [83].

Conclusion and Future Perspectives

It is evident how actively cell metabolic reprogramming shapes immune responses both via energy supplementation and immunomodulation in diseases including asthma. Different phenotypes of asthma are regulated differentially via various metabolic pathways, where in glycolysis mediators such as HIF1a and PKM2 control not just DC and T-cell effector function in type2 high asthma, but also mediate neutrophil effector function in type 2 low asthma. Additionally, while arginase 2 supports type2 cytokine secretion from ILC2s, it inhibits Th17 cells and IL-17 production. This ability of metabolic reprogramming to affect immunogenicity of immune cells highlights its pivotal role in disease pathomechanism.

The use of animal models for lung inflammation, such as asthma are particularly tricky as different animal models such as OVA, papain, obesity and HDM are used, but do not exactly replicate the complexity and heterogeneity of human disease. It does however offer otherwise difficult to obtain unique insight into disease progression. It also helps pave way for further research into cell specific metabolic reprogramming and how it drives phenotypic expression. In light of ICS being the cornerstone of asthma therapy for many years, and the

resistance of mixed granulomatous inflammation to such therapy, all insight into manipulating metabolism to favorable phenotypes is pertinent. One current knowledge gap is the lack of understanding of the role of antigen presenting cells in neutrophilic inflammation, the molecular changes that control such phenotypes, and the metabolic reprogramming that drives these changes. Thus, future research into exploring the link between metabolites and asthma phenotypes would possibly help expose new targets for controlling asthma progression despite its phenotype.

Financial Support

Research reported in this publication was supported by the National Institutes of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health under Award number RO3A1153794-01A1 to A.M.

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