Metabolism of Epithelial Cells in Health and Allergic Disease: Collegium Internationale Allergologicum Update 2021

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Keywords

Metabolism · Epithelium · Allergy · Asthma · Atopic dermatitis · Obesity · Dyslipidemia · Mitochondria · Insulin · Glucose · Arginine · Nitric oxide · Arachidonate metabolism · Autophagy

Abstract

Concomitant dramatic increase in prevalence of allergic and metabolic diseases is part of a modern epidemic afflicting technologically advanced societies. While clinical evidence points to clear associations between various metabolic factors and atopic disease, there is still a very limited understanding of the mechanisms that link the two. Dysregulation of central metabolism in metabolic syndrome, obesity, diabetes, and dyslipidemia has a systemic impact on multiple tissues and organs, including cells of the epithelial barrier. While much of epithelial research in allergy has focused on the immune-driven processes, a growing number of recent studies have begun to elucidate the role of metabolic components of disease. This review will revisit clinical evidence for the relationship between metabolic and allergic diseases,

as well as discuss potential mechanisms driving metabolic dysfunction of the epithelial barrier. Among them, novel studies highlight links between dysregulation of the insulin pathway, glucose metabolism, and loss of epithelial differentiation in asthma. Studies of mitochondrial structure and bioenergetics in lean and obese asthmatic phenotypes recently came to light to provide a novel framework linking changes in tricarboxylic acid cycle and oxidative phosphorylation with arginine metabolism and nitric oxide bioavailability. New research established connections between arachidonate metabolism, autophagy, and airway disease, as well as systemic dyslipidemia in atopic dermatitis and ceramide changes in the epidermis. Taken together, studies of metabolism have a great potential to open doors to a new class of therapeutic strategies, better characterization of disease endotypes, as well as enable a systems biology approach to mechanisms of allergic disease.

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Edited by: H.-U. Simon, Bern.

Relationship between Metabolic and Allergic Diseases: Clinical Evidence

Concurrent dramatic rise of allergic and metabolic disorders is part of a modern epidemic afflicting industrialized societies [1–3]. Westernized lifestyle is linked to high calorie and carbohydrate dietary intake, obesity, sedentary lifestyle, and gut dysbiosis. Such factors promote systemic metabolic stress, which manifests itself in a number of metabolic conditions adversely affecting health outcomes, including metabolic syndrome (MetS), diabetes, insulin resistance, hypertension, and dyslipidemia. Dysregulation of central metabolism has a systemic impact on multiple tissues and organs. Disruption of epithelial metabolism has a special relevance to allergic disease since epithelial cells form a critical interface between internal (organismal) and external environments, and epithelial responses are thought of as key events in inception of allergic responses. This part of the review will revisit clinical evidence for the relationship between metabolic and allergic diseases, followed by highlights of potential mechanisms driving metabolic dysfunction of epithelial barrier.

MetS and Obesity

MetS is a complex disease, characterized by a generalized dysregulation of metabolites, glucose, and lipids. Clinical definitions of MetS include a number of factors including increased waist circumference, elevated fasting blood glucose, increased high cholesterol, and high triglycerides [4]. While only roughly 20% of US adults meet all of the requirements for MetS, over 56% have an elevated waist circumference, which may have metabolic consequences even in the absence of MetS. Multiple studies have demonstrated that patients with MetS have increased incidence of asthma and decreased lung function [5, 6]. Other studies concluded that obesity associates with allergic sensitization and allergic airway inflammation [7, 8]. Further studies have demonstrated that obesity is an even better predictor of asthma development, with overweight women having the closest correlation between obesity and asthma [8–10]. A Nigerian cross-sectional study showed a high prevalence of MetS among asthmatics (17.7%) and poorer asthma control in asthmatic patients with MetS [11]. A Norwegian prospective study demonstrated that MetS was a risk factor for incident asthma (OR: 1.57). Two components of MetS remained associated with incident asthma after mutual adjustment for the other metabolic components: high waist circumference (OR: 1.62) and elevated glucose or diabe-

tes (OR: 1.43) [5]. A meta-analysis of 7 independent studies showed that overweight and obesity are associated with increase in the odds of incident asthma, both in men and women [12]. A retrospective Korean study also showed that obesity is significantly associated with self-reported asthma (OR: 1.61) [13]. Moreover, asthmatics with metabolic disease and obesity are often resistant to traditional treatment with inhaled corticosteroids [14, 15]. The difficulty in treating these patients makes them a costly portion of the asthmatic population, accounting for over half of health-care costs in asthma [16].

However, the relationship between MetS, obesity, and allergic disease extends beyond asthma. A cross-sectional retrospective study of 116,816 patients diagnosed with atopic dermatitis (AD) between 1998 and 2016 concluded that severely affected patients with AD may have 1 or more undiagnosed components of MetS [17]. Another cross-sectional population study of 8,217 US adults found significant association of AD with obesity, diabetes, and cardiovascular comorbidities [18]. A study of young adult males in Singapore found a significant association of metabolic and atopic conditions with moderate-to-severe AD [19]. A case-control study performed in pediatric dermatology practices in the USA found that moderate-to-severe pediatric AD may be associated with central obesity and high blood pressure [20]. A study by Agòn-Banzo et al. [21] has shown that pediatric AD patients have higher body mass index than healthy controls. A systematic literature review study found that central obesity is associated with AD, which was stronger for women than men [22]. Surprisingly, no studies report connections between metabolic disorders and food allergy, although it was reported that obese individuals with and without type 2 diabetes have significant changes in function and composition of gut microbiota [23]. Obesity and disease severity also magnify disturbed microbiome-immune interactions in asthma patients [24]. Importantly, such connections between metabolic and allergic conditions may develop in utero or in early life. For example, a study of 15,145 mother-child pairs in China found a significant association of maternal prepregnancy weight and gestational weight gain with children's allergic diseases [25].

Insulin Resistance and Diabetes

Multiple studies have brought to attention that insulin resistance correlates with asthma prevalence in both children and adults [6, 26]. Moreover, it appears that insulin resistance, prediabetes, and diabetes are linked to exacerbation-prone asthma and increase in exacerbation frequency [27–29]. A pediatric study in an obese population

at the Children's Hospital of Wisconsin found that higher insulin resistance was associated with asthma [30]. In addition, the authors showed that morbidly obese asthma patients have a higher degree of insulin resistance compared to morbidly obese nonasthmatic patients [30]. Another pediatric cross-sectional study linked asthma with abnormal glucose and lipid metabolism independent of body mass index [31]. Kozyskyj et al. [32] showed that, independent of puberty stage and progression, nonatopic asthma was 6-fold higher in adolescent girls who had insulin resistance but no central obesity 2 years earlier. Nonatopic asthma was 13 times more likely among girls with persistently high Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [32]. A pediatric study in Spain showed that HOMA-IR insulin resistance values were significantly associated with positive skin tests and allergic asthma diagnosis [26]. Another cross-sectional study demonstrated that insulin resistance and MetS are associated with worsened lung function in overweight/obese adolescents [6]. A pediatric study by Karampatakis et al. [33] showed that obese asthmatic children with confirmed insulin resistance have increased airway hyperresponsiveness compared to obese asthmatic children without insulin resistance. Authors suggest that obesity per se does not correlate to airway hyperresponsiveness unless it is accompanied by glucose intolerance and insulin resistance [33]. A study in Brazilian adolescents found that hyperinsulinemia, obesity, and MetS associate with severe asthma [34]. A Swedish birth cohort study of 1,284,748 children found evidence for co-occurrence, sequential appearance, and familial coaggregation of asthma and type 1 diabetes [35]. An Indonesian cohort study found that females but not males diagnosed with pediatric asthma had significantly higher risk of diabetes [36]. A retrospective birth cohort study of 97,554 children from a single integrated health care system in the USA found that maternal type 2 diabetes during pregnancy was a risk factor for development of childhood asthma in offspring [37].

In adult patients, British cross-sectional study in a female population found that FEV1 and FVC respiratory parameters were inversely associated with insulin resistance and prevalence of type 2 diabetes [38]. A Danish cross-sectional population-based study showed that insulin resistance was associated with aeroallergen sensitization and allergic asthma, but not nonallergic asthma [7]. A study in Turkey found that patients with asthma had higher insulin resistance (HOMA-IR), impaired fasting glucose, and impaired glucose tolerance when than the control group [39]. Danish population-based observa-

tional study found that insulin resistance was associated with incident wheezing (OR: 1.87) and asthma-like symptoms (OR: 1.61). The effect of insulin resistance was stronger than that of obesity and was independent of sex [40]. A South Korean study with patients that visited the hospital for a routine health check-up reported that subjects with airway hyperresponsiveness had higher insulin resistance than those without AHR [41]. An adult cross-sectional study from Elliot Israel's group at the Brigham and Women's hospital published that insulin resistance differentiates itself from other component of the MetS in that it is the only component that potentiates the obesity-asthma association [10]. Another article suggested that insulin resistance (a hallmark feature of polycystic ovary syndrome) might be the link between asthma and PCOS [42]. A very recent study by Yang et al. [43] of a cross-sectional cohort of 47,606 adult individuals with asthma but without physician-diagnosed diabetes found a positive association between glycated hemoglobin (HbA_{1c}) and lifetime odds of an asthma hospitalization, and an inverse association between HbA_{1c} and pulmonary function measured by FEV₁. HbA_{1c} relates to an individual's blood glucose concentration and is a marker of metabolic health, used to both diagnose prediabetes and diabetes. This was an important finding because it demonstrated that metabolic dysfunction may be a feature of allergic disease even in absence of endocrine diagnosis, which warrants additional investigation.

Although an abundance of evidence points to a positive association between insulin resistance, diabetes, and asthma in multiple age-groups, association of diabetes and glycemic control with AD and other allergic diseases remains unclear. Despite positive associations between AD, MetS, and obesity reviewed above, there are conflicting reports in regard to the relationship between AD and diabetes. A retrospective cohort study of 3,386 patients with type 1 diabetes and 12,725 controls found that childhood type 1 diabetes may increase the risk of AD [44]. However, a study by Schmitt et al. [45] found an inverse relationship between these diseases. Other studies found normal insulin sensitivity, glucose tolerance, gut incretin, and pancreatic hormone responses in adults with AD [46]. A US study by Silverberg and Greenland [47] showed a higher prevalence of type 2 diabetes in adult patients with AD than in the general population [47]. However, a Danish study cohort of 30,079 adult patients with AD showed that patients with AD do not have an increased risk of new-onset type 2 diabetes compared with matched controls [48]. A cross-sectional analysis 259,119 participants between ages 30–74 from the Canadian Partnership

for Tomorrow Project also found no evidence of a positive association between AD and type 2 diabetes, but found an inverse relationship [49].

Dyslipidemia

One major facet of metabolic dysfunction is the presence of dyslipidemia, a disorder of lipid and lipoprotein metabolism [50]. Dysregulated lipid metabolism leads to the overproduction of certain lipids, decreasing levels of high-density lipoproteins and increasing levels of low-density lipoproteins, contributing to imbalanced cholesterol. A growing body of literature suggests that dysregulated lipid metabolism is related to presence and severity of AD. AD is characterized by decreased barrier function in the epidermis and defects in epithelial differentiation. In patients with AD, the epidermis often has a deficiency in ceramides and other lipids, commonly resulting in increased transepidermal water loss and lower barrier function [51, 52]. Studies from the skin of AD patients have shown that disrupted lipid metabolism within the atopic epidermis closely resembles systemic dyslipidemia. Samples from human patients have shown decreased expression of enzymes involved in lipid metabolism and ceramide synthesis including stearoyl CoA desaturase, fatty acid elongase 1 and 3 (ELOVL1 and ELOVL3), ceramide synthase 3 (CerS3), and glucocerebrosidase [53, 54]. In addition to decreased expression of these crucial enzymes, skin from AD patients has shown abnormal localization of lipid metabolizing enzymes and disturbed lipid content in the stratum corneum [55]. Furthermore, the presence of Th2 cytokines in AD has been shown to decrease the presence of long-chain ceramides and sphingolipids responsible for healthy barrier function in the epidermis [54]. While the altered lipid content of epidermis in AD patients has been characterized, the relationship between systemic lipid metabolism and AD severity is an emerging area of study. Patients with severe AD have higher BMI than AD patients as a whole, with significantly higher levels of total cholesterol and triglycerides. In a pediatric cohort, the onset and severity of AD, measured by the SCORAD index, significantly correlated with an abnormal blood lipid profile, including increase in total cholesterol and triglycerides [56]. In a study of 5,007 Korean adults central obesity and high triglyceride levels correlated positively with the presence of AD in women [57]. These studies suggest that systemic dyslipidemia, hypertriglyceridemia, and general lipid dysregulation are risk factors for AD that can potentially influence lipid content and regulation in the epidermis.

Key Epithelial Metabolic Pathways with Relevance to Allergic Disease

Balanced metabolism is key to normal barrier function of the epithelium. The airway epithelium is the first defense barrier encountered by an inhaled allergen [58]. Disruption of the epithelial barrier is thought to make it more susceptible to allergic sensitization [59, 60]. Epithelial barrier dysfunction is now thought of as a central event in the initiation and progression of allergic diseases [60, 61]. Despite the growing appreciation of critical role for metabolism in homeostasis and chronic disease, there are surprisingly few studies of its contribution to allergic disease pathogenesis. The clinical evidence reviewed above illustrates the complexity of relationships between allergic and metabolic conditions, likely complicated by clinical endophenotypes of disease and multifaceted and context-dependent nature of systemic metabolic dysfunction. While clinical evidence points to clear associations between various metabolic factors and atopic disease, there is still a very limited understanding of the mechanisms that link the two. In this part of the review, we are going to highlight several metabolic pathways in epithelial cells with relevance to allergy that is linked to processes of barrier deficiency, inflammation, and allergic sensitization.

Insulin Signaling and Glucose Metabolism

Epithelial cells express insulin receptor (INSR) and depend on insulin signaling for proliferation, differentiation, and upstream regulation of glucose transport mechanisms and bioenergetics pathways (summarized in Fig. 1). The critical role for insulin in maintenance of epithelial homeostasis has long been appreciated. The first efforts to culture bronchial epithelial cells from human lungs, dating back to the 1980s, demonstrated that insulin is essential for epithelial culture [62–64]. Today, insulin is a necessary supplement in all commercial growth and differentiation media for primary epithelial cultures. Multiple studies show that signaling defects in INSR or INSR substrate molecules impair the differentiation and function of the epithelium and other cell types [65–67]. This may directly translate to the human condition, as insulin resistance is linked to multiple skin diseases [47, 68]. Insulin resistance in diabetes is directly linked to deficiencies in wound healing and epithelial dysfunction [69].

In mouse models, systemic hyperinsulinemia promotes airway hyperresponsiveness, collagen deposition, and airway remodeling, which may be due to decreased

Fig. 1. Insulin signaling and epithelial barrier function in asthma. Insulin signaling maintains barrier homeostasis via balancing biosynthetic and bioenergetics reactions in epithelial cells. Signaling partners of insulin with relevance to allergic processes include IGFs, IL-4/IL-13 cytokines, glucose transporters, and protease-activated receptor signaling. Insulin resistance and loss of insulin signaling lead to impaired epithelial differentiation, barrier function, and upstream availability of glucose for mitochondrial bioenergetics reactions. Imbalanced insulin signaling and glucose metabolism in asthma may promote barrier deficiency, allergic sensitization, and inflammation. IGF, Insulin-like growth factor.

pathogen clearance across the strengthened epithelial barrier [70]. Increased insulin in cultures of primary human nasal epithelial cells results in increased expression of MUC5AC at the mRNA and protein level [71]. MUC5AC is the mucin responsible for the viscoelasticity of mucus, which is produced to protect the airway epithelium from pathogens and dehydration. Decreasing insulin supplementation in epithelial culture (which aligns with cellular effects of insulin resistance) has been shown to increase expression of PAR2 on human airway epithelial cells, which is a proteinase-activated receptor linked to allergic sensitization [72, 73]. We previously published a comparative study of epithelial gene expression patterns convergent across several transcriptomic studies of human adult asthma [74]. This computational study revealed that the downregulation of insulin signaling in epithelial cells represented a surprisingly conserved and most consistent feature across multiple studies of mild, moderate, and severe asthma. This was overrepresented by the downregulation of insulin target genes INSR, IRS2, FGFR1, and FGFR2, which progressed with asthma severity [74]. Our validation of data mining results in primary human bronchial epithelial cells grown in submerged and air-liquid interface conditions revealed that gene expression of healthy epithelial cells grown without insulin closely matched gene signatures of asthmatic epithelial cells at normoinsulinemic baseline [74]. Our fur-

ther interrogation of insulin pathway genes in asthma revealed that this pattern of dysregulation is more specific to the Th2 high molecular endotype of asthma previously described by Woodruff et al. [75]. Moreover, both INSR and insulin receptor substrate 2 (IRS2) showed significant negative association with markers of Th2 high inflammation (POSTN and SERPINB2) (unpublished data). These results indicate that the downregulation of INSR and its proximal signaling targets is a conserved feature in asthmatic epithelium closely associated with Th2 high inflammation.

Insulin has several important interacting partners at the level of cellular membrane and downstream signaling (Fig. 1). Among them, glucose transport proteins are differentially regulated by insulin, which determines rates of uptake and utilization of glucose in cellular biosynthetic and bioenergetics pathways. There are 14 glucose transporters (GLUT or SLC2A) encoded by the human genome, which are membrane proteins that facilitate the transport of glucose across the plasma membrane. Class I transporters (GLUT1-4) are best characterized with GLUT4 traditionally studied as an insulin-dependent transporter [76]. It is currently unknown whether glucose transporter biology is altered in allergic disease. At the level of downstream signaling, Molina et al. [77] demonstrated that insulin regulates glucose uptake and barrier function in human airway epithelial cells via PI3K/Akt

signaling pathway. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase signaling pathway that is responsive to changes in PI3K/Akt pathway and controls insulin signaling [78]. mTOR controls a wide range of cellular processes, including cell growth, differentiation, and glucose and lipid metabolism [79, 80]. Dysregulation of mTOR leads to a number of metabolic pathological conditions, including obesity and type 2 diabetes [80]. Moreover, mTOR proteins are regulatory for epithelial morphogenesis and regulate epithelial barrier formation [81]. mTOR activity was found to be decreased in airway epithelium from asthmatic patients, which was associated with downstream increase in autophagy [82]. Multiple studies of the mTOR pathway in mouse models of allergic inflammation converged on the common finding that acute activation of the mTOR signaling is required for asthma onset; however, mTOR may have a protective effect during established allergic inflammation [83–86]. Consequently, rapamycin (mTOR inhibitor) ameliorates acute inflammatory response in these models but exacerbates inflammation when administered during established chronic response [83]. Therefore, we speculate that mTOR signals in asthmatic epithelium are reflective of metabolically reprogrammed chronic phenotype of these cells rather than driven by direct Th2 cytokine stimulation.

With immediate relevance to allergic inflammation, it is well documented that Th2 cytokines IL-4 and IL-13 signal through INSR substrates IRS1 and IRS2 for activation of PI3K and other downstream pathways [87]. Originally discovered by Dr. William E. Paul in 1990s, signaling interactions between IL-4/IL-13 receptors and INSR substrates have been studied for over 25 years [88]. Although many facets of this interaction have been described in terms of cellular proliferation and survival, it is still not clear whether IRS2 is a positive or negative regu-

lator of IL-4 and IL-13-induced responses, the potential of which is hardly explored in allergic diseases. Why Th2 cytokine signaling is so closely and proximally intertwined with key mediators of insulin signaling and metabolism remains an enigma.

Insulin-Like Growth Factor Signaling

Insulin-like growth factors (IGFs) are signaling hormones that share signaling with the INSR signaling pathway. IGFs are predominately produced in the liver but can also be produced by many types of peripheral cells and have autocrine and paracrine functions. IGF-1, the primary IGF implicated in allergic airway inflammation, binds to IGF-1 receptor (IGF-1R) [89]. IGF-1 shares considerable homology with insulin and can bind to INSR [90]. IGF-1 binds to IGF binding protein 3 (IGBP3) and forms a complex that transports IGF-1 through the blood to target tissues. When bound to IGBP3, IGF-1 is not bioavailable and cannot activate signaling mechanism downstream of its receptor. Interestingly, IGF-1, IGF-1R, and IGBP3 have multiple roles in the promotion and exacerbation of allergic inflammation. In mice sensitized to chicken-egg ovalbumin (OVA), treatment with an IGF-1 neutralizing antibody inhibited elevation of airway resistance, inflammation, and airway wall thickening in response to ovalbumin challenge [91]. A study in human asthmatics demonstrated a correlation between IGF-1 expression and collagen thickening in bronchial biopsies [92]. Treatment with inhaled corticosteroid beclomethasone dipropionate decreases epithelial IGF-1 expression in bronchial biopsies of asthmatic patients [92]. Expression of IGF-1 and IGF-1R can also be regulated by Th17 cytokines [93] and eosinophils [94]. Lee et al. [95] provide an excellent review on the diverse roles of IGF-1 and IGBP3 in allergic airway disease and discuss the potential for therapeutic targeting of IGF-1 signaling.

Fig. 2. Mitochondrial metabolism in asthmatic epithelial cells. Ultrastructural changes in mitochondria from asthmatic airway epithelial cells associate with biochemical features of mitochondrial dysfunction as well as increase in oxidative phosphorylation. Upstream defects in insulin-regulated glucose uptake may favor downstream glucose availability for biosynthetic rather than bioenergetics reactions in TCA cycle (unpublished data, based on metabolic flux, and untargeted metabolomics analysis). Increased mitochondrial respiration in asthmatics is attributable specifically to enhanced arginine metabolism to ornithine by upregulated arginase, which drives the production of alternate substrates for the TCA cycle. Airway inflammation is also characterized by increased expression of iNOS, which results in elevated production of FENO

in nonobese allergic asthmatics. A key consequence of the increase in oxidative phosphorylation is the generation of ROS. The primal ROS made by the mitochondrial electron transport chains is O_2^- , which is catalyzed by SOD2 to yield H_2O_2 . Mitochondrial ROS activates NLRP3 inflammasome which promotes airway inflammation. Gene expression changes in enzymes associated with altered metabolism in asthmatic epithelium (based on published RNA-seq dataset [74]) are mapped out along with corresponding metabolic reactions. Blue and red highlights indicate potential downregulation and upregulation, respectively, in asthmatic metabolic pathways. SOD, superoxide dismutase; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase.

(For figure see next page.)

Mitochondria

It is well established that chronic inflammation accompanies insulin resistance, in part due to increases in oxidative stress in insulin-resistant cells [96–98]. Allergic asthma is also characterized by increased oxidative state [98], although mechanistic links between oxidative stress and asthma remain poorly explored. Recent work by our group and others suggests that changes in mitochondrial

function may play significant roles in the pathogenesis and exacerbation of asthma (summarized in Fig. 2). Electron microscopy has revealed ultrastructural changes in airway epithelial mitochondria in mouse models of asthma or biopsies from human subjects with asthma, associated with biochemical features of mitochondrial dysfunction such as increased oxidative damage or activation of apoptotic pathways [99, 100]. Xu et al. [100] have found

that mitochondria in asthmatic bronchial epithelial cells have increased expression of inducible nitric oxide synthase (iNOS), ARG2, and mitochondrial respiratory complexes III and IV. The study also reports a marked increase in oxygen consumption rate and glycolysis measured by extracellular acidification rate in asthmatic epithelium [100]. A study by Winnica et al. [101] also found an increase in oxygen consumption rate parameters in cells from both lean and obese donors, and increase in extracellular acidification rate in cells from obese asthmatic donors. Moreover, these increases were documented not only in epithelial cells but also platelets from asthmatic donors, which suggests a systemic-level metabolic dysfunction in these patients [101]. A key consequence of increase in oxidative phosphorylation is the generation of reactive oxygen species (ROS). The primal ROS made by the mitochondrial electron transport chains is $O^{\cdot -}$, which is catalyzed by superoxide dismutase to yield H_2O_2 , the ROS most relevant to cell signaling [102]. A large body of evidence indicates that ROS plays a vital role in airway signaling and inflammation by modulating cytokine transcription [102, 103]. Moreover, increased mitochondrial respiratory and glycolytic activity could explain the increased extracellular ATP commonly found in asthmatic exhaled breath condensate [104].

Mitochondrial products such as ROS, excessive ATP, and mitochondrial DNA are capable of initiating inflammation via potent activation of the nod-like receptor 3 (NLRP3) inflammasome, a group of proteins responsible for promoting an IL-1 mediated response [105–107]. In human tracheal epithelial cells, inhibition of mitochondrial ROS has been shown to downregulate expression and activation of NLRP3, its effector enzyme caspase-1, and pro-inflammatory cytokine IL-1 β [108]. NLRP3 activation plays important roles in both type 1 and type 2 inflammations. Mouse models have demonstrated that activation of NLRP3 is necessary for allergic sensitization and establishment of allergic airway inflammation [108]. A mouse model of *Aspergillus fumigatus* induced airway inflammation demonstrated that inhibition of mitochondrial ROS in mouse epithelium through calcium signaling decreased AHR, eosinophil recruitment, NLRP3 activation, and NF- κ B activation [109]. Another mouse study similarly demonstrated that epithelium mitochondrial inhibition through ubiquinol-cytochrome c reductase II core protein (UQCRC2) deficiency increased airway eosinophil infiltration, mucin, and AHR in response to ragweed challenge in sensitized mice [110]. In human airway epithelial cells, inhibition of mitochondrial Ca^{2+} uniporter protected cells against IL-13-induced apoptosis and

maintained mitochondrial membrane potential [111]. These human and mouse mechanistic studies demonstrate both that mitochondria in epithelial cells regulate the type 2 immune response, and suggests that mitochondrial dysregulation in epithelial may underlie and exacerbate type 2 inflammation. Mitochondria also play a key role in the airway remodeling [111, 112]. For example, mitochondrial ROS in airway epithelium has been shown to regulate collagen production [113]. Mitochondrial ROS in airway epithelium is necessary activators of TGF- β , which drives airway remodeling and collagen deposition commonly seen in asthma and allergic airway disease [112]. The importance of mitochondria in lung disease is also supported by genetics, for example, by associations of the mitochondrial haplogroup U with increased IgE and asthma [114, 115].

Mitochondrial Bioenergetics and Nitric Oxide Production

Several recent studies linked altered mitochondrial function to enhanced arginine metabolism as well as changes in nitric oxide (NO) bioavailability in the asthmatic airway. Studies of both lean and obese asthmatics demonstrated increased metabolism of arginine to ornithine due to the upregulation of arginase [100, 115, 116]. Increased mitochondrial respiration in asthmatics [100, 117] (described in the section above) has been specifically attributed to enhanced arginine metabolism to ornithine by upregulated arginase, which leads to generation of glutamate through catalysis by ornithine aminotransferase and drives the production of substrates for the tricarboxylic acid (TCA) cycle [100]. Airway inflammation is also characterized by increased expression of iNOS [118, 119], which results in elevated production of FENO in allergic asthmatics [119, 120]. NO is metabolized from arginine and is produced constitutively in the airways of healthy individuals. In patients with allergic airway inflammation, elevated FENO is a biomarker for the presence and severity of asthma [118, 119, 121]. Increased epithelial iNOS activity and expression is commonly reported in type 2 allergic disease [100, 118, 119, 122, 123]. Expression and activity of iNOS can be induced by a number of inflammatory mediators and cytokines, including LPS, IFN- γ , and IL-13 [123–125]. Increased NOS activity can lead to an uncoupling from its substrate, arginine, which leads to the generation of superoxides and reactive nitrogen species (RNOS). iNOS uncoupling and subsequent RNOS induction in the epithelium have been shown to promote downstream inflammation and may be a contributing factor in allergic airway inflammation.

Therefore, suppressing arginase activity to lessen its impact on arginine availability and NO production, as well as supplementation with citrulline and arginine substrates, are being explored as therapeutic approaches to balance arginine-dependent metabolic pathways and restore homeostatic NO activity.

Notably, there are qualitative differences between arginine metabolism in epithelium from lean and obese asthmatics [126]. The airways of obese asthmatics have been shown to be NO deficient, which contributes to airway dysfunction and reduced response to inhaled corticosteroids. FENO has been observed to be much lower in such asthmatic phenotypes despite iNOS upregulation, and this is thought to be due to deficiency of L-arginine, a critical substrate for NO synthase (NOS), as well as accumulation of asymmetric dimethylarginine (ADMA). This leads to decreased iNOS activity and uncoupling of the enzyme, which prevents NO synthesis [116, 127, 128]. In cultured human bronchial epithelial cells, L-citrulline, a precursor of L-arginine and NO formation, has been shown to prevent ADMA-mediated NO synthase (NOS2) uncoupling, restoring NO and reducing oxidative stress [126, 129]. In a short-term pilot clinical study, L-citrulline treatment improved asthma control and FENO levels in obese asthmatics with low or normal FENO [126]. Publications by Winnica et al. [101] and Holguin [130] further detail differences in this pathway between lean and obese asthmatics.

Although we are reaching greater mechanistic understanding of pathways and biomarkers downstream of arginine metabolism in asthma, increased mitochondrial respiration and alternative fueling of TCA cycle by amino acid metabolism suggest compensation due to significant changes in upstream bioenergetic processes. Such upstream mechanisms are not yet known; however, changes in insulin and glucose metabolism in asthmatic epithelial cells (detailed above) represent one plausible candidate. Arginine metabolism, glucose metabolism, and insulin signaling are intimately connected. It has been shown that in type 2 diabetes plasma arginase activity correlates with the degree of hyperglycemia and is reduced by physiologic elevation in insulin levels [131]. Moreover, in type 2 diabetes insulin resistance is associated with impaired NOS in skeletal muscle [132]. Arginase inhibition was found to improve insulin resistance in obese rats [133]. mTOR complex 1 (mTORC1) is another important upstream regulator of mitochondrial biogenesis in lung epithelium [134]. The impact of mTORC1 on the mitochondrial activity of lung epithelial cells has not been extensively studied within the context of allergic

inflammation and asthma, but it is likely that the increased mitochondrial activity observed in allergic epithelium involves changes in mTOR signaling.

It remains to be resolved which mitochondrial fuels are preferentially used by epithelial cells in allergic disease. The canonical pathways that are able to fuel mitochondria are glycolysis via import of pyruvate into mitochondria, fatty acid oxidation via acetyl-CoA, and glutaminolysis via conversion of glutamine into alpha-ketoglutarate (alpha-KG). Using [U-¹³C]glucose metabolic flux analysis, which allowed us to trace metabolism of glucose in downstream metabolic pathways, we found that glucose conversion to glycolytic intermediates for energy production is significantly decreased in asthmatic bronchial epithelial cells past the glucose 6-phosphate step in glycolysis (unpublished data). Rather, we found higher utilization of glucose in lipid and amino acid biosynthetic reactions upstream of arginine metabolism. The abundance of alpha-KG is also increased in asthmatic mitochondria, which may be due to glutaminolysis (independent of ornithine conversion). In conjunction with observed decreased pyruvate import into mitochondria, there is a possible switch from glycolysis towards glutaminolysis as another main process fueling mitochondria in asthma. Figure 2 summarizes key metabolic pathways and highlights some of our recent findings in regard to metabolic changes in asthmatic epithelium. In lieu of connection of asthma to insulin resistance and obesity, utilization of glucose in bioenergetics versus biosynthetic reactions and its upstream impact on arginine and NO metabolism warrants further investigation.

PPAR-γ

Peroxisome proliferator-activated receptor gamma (PPAR-γ) belongs to a family of nuclear hormone receptors that regulate lipid, fatty acid, and glucose metabolism. In its canonical signaling role, activated PPAR-γ sequesters transcription factor NF-κB, which prevents the transcription of NF-κB and therefore prevents inflammation [135]. PPAR-γ is constitutively expressed in airway epithelial cells, and expression can be further induced by IL-4 administration [136]. Expression of PPAR-γ is elevated in the airway epithelium and airway smooth muscle of asthmatics [137], as well as in the nasal polyps of patients with seasonal rhinitis [138]. The function of PPAR-γ in airway epithelia specifically remains a point of contention. While PPAR-γ is increased in asthmatic epithelium and correlates with decreased lung function [137], mouse studies suggest a protective role of PPAR-γ in the pathogenesis of allergic airway inflammation. Multiple studies

have used PPAR- γ agonists to demonstrate that activation of PPAR- γ in mice ameliorates allergic symptoms including IgE, lung IL-4, IL-5, IL-13, mucus, AHR, and lung eosinophils [139–142]. A mouse study in which PPAR- γ was deleted specifically in airway epithelial cells in vivo showed a significant worsening of allergic airway inflammation and also demonstrated that PPAR- γ regulated MUC5AC and inflammatory cytokine production in cultured human bronchial epithelial cells in vitro [142]. Studies suggest that PPAR- γ is likely protective during the pathogenesis of allergic airway inflammation, and a less effective regulator of established inflammation [140]. PPAR- γ can also be regulated by a number of confounding factors including corticosteroid use and inhaled particulate matter [137, 143]. PPAR- γ is a regulator of lipid, fatty acid, and glucose metabolism, and the effect of inflammation on PPAR- γ 's metabolic functioning remains yet to be investigated. It is likely that while inflammatory cytokines and mediators increase PPAR- γ expression, they may also contribute to increase metabolic activity through PPAR- γ . Further studies in airway epithelial cells are needed to determine the role of epithelial PPAR- γ at various stages of allergic airway inflammation. For further information, Nobs and Kopf [144] have written an excellent review of PPAR- γ biology and its role in airway inflammation.

Arachidonate and Fatty Acid Metabolism

Arachidonic acid (AA) is a fatty acid that can be metabolized into a number of lipid mediators called eicosanoids through the arachidonate metabolic pathway. Arachidonate enzymes and eicosanoids form a large, diverse family of mediators such as prostaglandins and cysteinyl leukotrienes that have both pro- and anti-inflammatory roles in atopic disease [145, 146]. Within the human airway, epithelial cells are the major source of airway eicosanoids with some contribution from airway infiltrating eosinophils [147–149]. Arachidonate 15-lipoxygenase (15-LO1 or ALOX15) and AA metabolite 15(S)-hydroxyeicosatetraenoic acid are prominent in human airways and are increased in asthma [147, 148, 150]. A study by Zhao et al. [149] demonstrated that 15-lipoxygenase-1 (15-LO1) and 15-hydroxyeicosatetraenoic in human airway epithelial cells induced production of MUC5AC, a major mucous protein overproduced during airway inflammation. Multiple studies have also implicated AA metabolites in aspirin sensitivity disorders such as aspirin-sensitive asthma/rhinosinusitis and aspirin-exacerbated respiratory disease [151, 152]. A number of other AA metabolites and enzymes have been associated

with asthma including secreted phospholipase A2 group X and 15-Oxo-ETE [152, 153]. Upregulation of these AA metabolites and enzymes has been largely associated with airway inflammation. However, some epithelial-derived AA metabolites, such as prostaglandin E2, have roles in wound healing and airway regulation [154]. The rich study of eicosanoids in airway inflammation has revealed a number of therapeutic targets, including inhibition of cyclooxygenase 1 and 2 by dexamethasone [154, 155]. Fatty acid beta-oxidation is the most powerful way to produce ATP and fuel cellular energy. There is evidence that fatty acid oxidation plays a critical role in fueling asthmatic bronchial smooth muscle remodeling [156]. However, there is no consensus on the balance of fatty acid synthesis versus oxidation in epithelial cells during allergic inflammation. While analysis of airway epithelial cells generally reveals increased expression of enzymes involved in metabolism of arachidonic acid [147, 148, 150], patients with AD exhibit decreased expression of enzymes involved in fatty acid metabolism in the epidermis [53, 54]. These data suggest that utilization of fatty acids may be tissue dependent, which warrants further investigation.

Autophagy

Autophagy ("self-eating") is the fundamental cellular process by which cells degrade cellular components to provide material for the generation of new components. This metabolism-interconnected process provides a way for unnecessary or misfolded proteins to be degraded and prevents downstream processes such as apoptosis. The dysfunctional autophagy process in both structural and immune cells has been implicated in pathogenesis of various inflammatory diseases including asthma [157]. Genetic associations between autophagy genes and asthma have been documented, including correlation of autophagy-related gene 5 (ATG5) polymorphisms with reduced lung function [158, 159]. Autophagy plays different roles in lymphoid and myeloid compartments in allergic airway inflammation. Impaired autophagy in lymphoid compartment decreases inflammation in asthma and mouse models of allergic airway inflammation [160]. On the other hand, inhibition of autophagy in myeloid cells seems to promote inflammasome activation and inflammation [161]. Within the structural compartment and airway epithelial cells, autophagy largely promotes tissue remodeling and exacerbates airway inflammation [162–164]. In normal human bronchial epithelial cells, inhibition of autophagy blocked alternaria-induced IL-18 production, suggesting that autophagy plays a pivotal role in

the initiation of airway inflammation [165]. IL13 activates autophagy to regulate mucus secretion and superoxide production in airway epithelial cells [166, 167]. mTORC1 signaling has upstream regulatory roles in autophagy. MTOR suppresses autophagy-mediated production of IL25 in allergic airway inflammation [82]. Particulate matter promotes autophagy in human bronchial epithelial cells by inhibiting Pi3K/Akt/mTOR pathway [168]. For detailed reviews on autophagy and allergic disease, we further refer our readers to reviews by Zeki et al. [169] and Painter et al. [161].

Summary and Future Directions

Mechanistic and clinical study of epithelial metabolism in allergy represents a new frontier in the field that comes with multiple challenges. Studies of the epithelium in allergic diseases traditionally focus on physical and immune causes of barrier dysfunction, such as direct exogenous insult by allergens, proteases, injury, and inflammation [61]. Metabolic pathways reviewed here represent an entire suite of less appreciated but potent endogenous disruptors of epithelial homeostasis with key relevance to disease [60]. Several key questions remain to be answered in this regard. Complex interactions between systemic and cellular effects of obesity, MetS, insulin resistance, and inflammation in different disease contexts illustrate necessity to control for different aspects of systemic metabolic dysfunction in clinical and translational studies. Understanding metabolic underpinnings of clinical endophenotypes may bring us one step closer to personalized medicine and a systems biology level understanding of allergic disease. More studies are necessary to bridge metabolic biomarkers and systemic metabolic dysfunction measured in clinical studies with mechanisms at the cellular level, as illustrated by studies connecting FENO biomarker levels with changes in arginine metabolic pathway. In particular, metabolic processes upstream of mitochondrial dysfunction and significance of insulin pathway in allergic asthma are still in their infancy. Although strongly supported by an ever-growing number of mechanistic murine and in vitro studies, causality of metabolic dysfunction in promoting allergic inflammation is not yet understood. Longitudinal studies of maternal, in utero, and postnatal metabolism hold great promise in elucidating gene-environment interactions, epigenetic reprogramming, and early life susceptibility to allergic disease. Importantly, understanding early life factors may lead to new intervention and prevention strategies with

upstream potential to target the development of allergy. Whether drugs used to treat metabolic disease can be repurposed to target allergic inflammation also remains to be investigated. Collectively, studies of metabolism have a great potential to reach different levels of understanding of pathogenesis of allergic diseases and a new class of therapeutic approaches to target them.

Acknowledgements

We would like to thank Dr. Navdeep Chandel (Northwestern University) for sharing his expertise in mitochondrial biology and thoughtful discussions of metabolic processes occurring in asthmatic epithelial cells.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Funding Sources

Berdnikovs S. was supported by the National Institutes of Health (NIH/NIAID) (R01AI127783) and the Ernest Bazley Foundation (Chicago, IL, USA).

Author Contributions

All the authors participated in literature searches and outlining and structuring the concepts in this review. A.M.Q. and S.B. wrote and edited the manuscript. M.E.C. and S.B. designed and prepared figures. Final version of the manuscript was approved by S.B.

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