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REVIEW ARTICLE

Immune metabolism in allergies, does it matter?—A review of immune metabolic basics and adaptations associated with the activation of innate immune cells in allergy

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Abstract

Type I allergies are pathological, type 2 inflammatory immune responses against otherwise harmless environmental allergens that arise from complex interactions between different types of immune cells. Activated immune cells undergo extensive changes in phenotype and function to fulfill their effector functions. Hereby, activation, differentiation, proliferation, migration, and mounting of effector responses require metabolic reprogramming. While the metabolic changes associated with activation of dendritic cells, macrophages, and T cells are extensively studied, data about the metabolic phenotypes of the other cell types critically involved in allergic responses (epithelial cells, eosinophils, basophils, mast cells, and ILC2s) are rather limited. This review briefly covers the basics of cellular energy metabolism and its connection to immune cell function. In addition, it summarizes the current state of knowledge in terms of dendritic cell and macrophage metabolism and subsequently focuses on the metabolic changes associated with activation of epithelial cells, eosinophils, basophils, mast cells, as well as ILC2s in allergy. Interestingly, the innate key cell types in allergic inflammation were reported to change their metabolic phenotype during activation, shifting to either glycolysis (epithelial cells, M1 macrophages, DCs, eosinophils, basophils, acutely activated mast cells), oxidative phosphorylation (M2 macrophages, longer term activated mast cells), or fatty acid oxidation (ILC2s). Therefore, immune metabolism is of relevance in allergic diseases and its connection to immune cell effector function needs to be considered to better understand induction and maintenance

Abbreviations: 2-DG, 2-deoxy-glucose; ACL, ATP citrate lyase; Ag, antigen; AIT, allergen immunotherapy; Akt, protein kinase B; Alum, aluminum hydroxide; Arg1, arginase 1; Atg, autophagy-related gene; BMMCs, bone marrow-derived mast cells; CHI3L1, chitinase-3-like protein 1; DC, dendritic cell; DCA, dichloroacetate; ECAR, extracellular acidification rate; ECRS, eosinophilic chronic rhinosinusitis; EoE, eosinophilic esophagitis; ERK, extracellular signal-regulated kinase; FA, fatty acid; FAO, fatty acid oxidation; FAS, fatty acid synthesis; FcεRI, high-affinity IgE receptor; GDH, glutamate dehydrogenase; GM-CSF, granulocyte-macrophage colony-stimulating factor; HA, hyaluronan; HDM, house dust mite; HIF-1a, hypoxia-inducible factor 1a; IDH, isocitrate dehydrogenase; IFN-γ, interferon gamma; ILC2, innate-like lymphocytes type II cell; IκKε, inhibitory κ B kinase-epsilon; Jmjd3, Jumonji domain-containing protein D3; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; LT, leukotriene; M2PK, M2-type pyruvate kinase; MAPK, mitogen-activated protein kinase; MS, mass spectrometry; mTOR, mammalian target of rapamycin; mTORC1/2, mTOR complex 1/2; NLRP3, NLR family pyrin domain-containing 3; NMR, nuclear magnetic resonance; NO, nitric oxide; NOX, NADPH oxidase; OCR, oxygen consumption rate; oxLDL, oxidized low-density lipoproteins; OxPhos, oxidative phosphorylation; PAMP, pathogen-associated molecular pattern; PDH, pyruvate dehydrogenase; PDHK(1), pyruvate dehydrogenase kinase (1); PG (D2), prostaglandin(D2); PGC-1β, peroxisome proliferator-activated receptor γ co-activator 1 beta; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase M2; PM, polymerized allergoids conjugated to mannan; PUFA, poly-unsaturated fatty acid; RBL-2H3, rat basophil leukemia cells; ROS, reactive oxygen species; SAM, S-adenosylmethionine; ß-hex, beta-hexosaminidase; ST-2, IL-33 receptor; STAT5/6, signal transducer and activator of transcription 5/6; TIM3, T-cell immunoglobulin and mucin domain-containing protein 3; TLR, Toll-like receptor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; VHL, von-Hippel-Lindau.

Goretzki and Lin equally contributed to this work

of allergic responses. Further progress in this field will likely improve both our understanding of disease pathology and enable new treatment targets/strategies.

KEYWORDS
allergies, glycolysis, immune metabolism, metabolism, oxidative phosphorylation, warburg effect

1 | INTRODUCTION

Allergic diseases are an increasing health and economic problem in developed countries with IgE-mediated type I hypersensitivity disorders reported to affect more than 25% of the population.[1,2]

Immunologically, onset and maintenance of type I allergies are caused by exaggerated type 2-mediated immune responses, directed against otherwise harmless environmental antigens. The main effector cells involved in establishment and elicitation of allergic reactions are antigen-presenting cells (dendritic cells (DCs) and macrophages), Th2 cells, IgE-producing plasma cells, eosinophils, basophils, mast cells, and innate-like lymphocytes type II cells (ILC2s). Additionally, lipid mediators derived from arachidonic acid such as prostaglandins (PGs, eg, PGD4, PGE2) and leukotrienes (LTs, eg, cysLT1), or the peptide hormone histamine (derived from histidine) are produced by activated immune cells within minutes, act locally through specific receptors expressed on many target cells, and are usually quickly metabolized.[3,4] These molecules are prominently involved in the hallmark features of allergic inflammation by inducing potent and bronchoconstriction/long-lasting bronchospasm, immune cell recruitment, airway inflammation, hyperresponsiveness, and remodeling.[3-5]

Activated immune cells can undergo extensive phenotypic changes in order to fulfill their effector functions. Therefore, activation, differentiation, proliferation, migration, and mounting of effector responses require metabolic reprogramming: For example, T cells, DCs, macrophages, or neutrophils were shown to undergo distinct metabolic changes upon activation.[6-9] To understand the mechanisms underlying these metabolic changes and their functional consequences is the aim of a new research field termed "immune metabolism." Box 1 summarizes the methods commonly used in immune metabolic studies Table 1.

This review will briefly introduce the fundamental principles of cellular energy metabolism, its connection to immune cell effector function, and then discuss the metabolic adaptations associated with the activation of allergy-related effector cells of the innate immune system.

2 | IMMUNE METABOLISM

2.1 | Cells can use glucose to generate energy either via oxidative phosphorylation or glycolysis

Exposure of immune cells to different stimuli may require cells to prioritize biosynthesis of certain molecules or reactive oxygen species (ROS) over the simple production of energy in the form of ATP.[10] To allow for this flexibility, cellular metabolism is a complex network of interconnected catabolic and anabolic pathways, most of which converge at the mitochondrion.[10]

Glucose, fatty acids, and amino acids are the main cellular energy sources which are used by the cell's metabolic pathways to generate both energy in the form of ATP or reduction equivalents and important biosynthetic intermediates needed for cellular function.

TABLE 1 Key methods used in immune metabolic analyses

Method	Application	Key publication
Single-cell genomics, transcriptomics, proteomics	Determination of the genome-wide gene-/RNA-/protein expression-/protein modification-levels to comprehensively characterize the investigated sample, find new target molecules, pathways, and establish novel relationships	14,15,38,41,44,55,56,81,91
Metabolomics	Molecular analysis of the overall metabolites (intermediate and final) in a biological system to determine the overall metabolic state and identify key metabolic pathways and interactions	15,41,44,81,142
Metabolic Flux Analysis	Determination of overall cellular metabolic state via real-time measurement of extracellular acidification rate (ECAR, glycolysis) and oxygen consumption rate (OCR, mitochondrial respiration)	14,44,81,83,84,142,145
Radioactive carbon tracing	Fate determination of exogenously applied nutrients	41,81,83,84,91,146
Colorimetric metabolite determination, mass spectrometry, lipidomics	Detection and/or quantification of single key metabolites to confirm findings obtained with the above-mentioned approaches	15,44,69,72,81,147

BOX 1 Methodological approaches to study immunometabolism

The recent breakthroughs in immune metabolic analyses have been made possible by a combination of both technological advances and established methods. "Omics" or system-level approaches such as metabolomics, single-cell genomics, transcriptomics, or proteomics have enabled a highly detailed understanding of global cellular responses to defined stimuli. Hereby, genomics describes the structure, function, evolutionary mapping, and editing of genomes, transcriptomics the sum of all RNA transcripts (messenger RNA, ribosomal RNA, transfer RNA, microRNA, and other non-coding RNAs), and proteomics the structure, function, interaction or modification of proteins (see also[148]). Relatively new in the field of omics, metabolomics characterizes both the intermediates and final molecules produced during the investigated sample's metabolic activity.[148] Metabolomic analyses are mainly based on nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS)-based techniques.[148,149] The results obtained from transcriptomics, proteomics, and metabolomics analyses are highly dependent on time point, cell type, treatment, and environmental factors and can therefore be used to describe changes associated with disease development and progression.[148]

Equally important, recent advances in computational high-throughput analyses have allowed to analyze and integrate the extensive datasets generated by the above-mentioned system-level approaches.

Another breakthrough technique, Metabolic Flux Analysis using Agilent Seahorse technology, has enabled researchers to monitor both the extracellular acidification rate (ECAR, as a proxy for lactate production and therefore glycolytic metabolism) and the oxygen consumption rate (OCR, as a measure of mitochondrial respiration) in real-time using relatively low numbers of living cells. Seahorse technology therefore allows studying both the overall metabolic state and response to exogenously applied stimuli and inhibitors even in rare cell populations.

These new technologies are complemented by established assays such as colorimetric determination of certain metabolites (eg, glucose, lactate, or amino acids), mass spectrometry, as well as radioactive carbon tracing studies (to determine the fate of exogenously applied nutrients) which allow for a detailed analysis of specific key molecules.

This combination of recent advances and established methods enables a comprehensive overall assessment of the metabolome that can be correlated to, for example, the overall transcriptome or proteome of the respective sample.[38,81] The key methods used in immune metabolic analyses are summarized in Table 1.

Under normal metabolic conditions, cells take up glucose via specialized glucose transporters from their surroundings. Inside the cell, glucose is activated by addition of an energy-rich phosphate group to generate glucose-6-P, which is subsequently cleaved in a multistep process in the cytoplasm to form two C3 bodies, finally resulting in the generation of two molecules of pyruvate[11] (Figure 1A). Pyruvate is then imported into the mitochondrion where it is metabolized in the Krebs (also called TCA) cycle as acetyl-CoA by pyruvate dehydrogenase (PDH).

The Krebs cycle itself is a sequence of biochemical reactions that is used by aerobic cells for the oxidative degradation of organic substances in order to generate both energy and biosynthetic intermediates (depicted in Figure 1A). Finally, pyruvate is degraded via the Krebs cycle, resulting in the generation of CO_2 and energy in the form of the reduction equivalent NADH.[12]

Besides the usage of glucose-derived pyruvate, the Krebs cycle can also be fueled by either fatty acids degraded into acetyl-CoA molecules or glutamate derived from amino acid metabolism, which is metabolized into α-ketoglutarate by the enzyme glutamate dehydrogenase[13] (GDH, Figure 1A). Finally, acetyl-CoA generated from citrate (via the ATP citrate lyase, ACL) can be used for either lipid production in the mitochondrion or epigenetic modification of selective genes via histone acetylation in the nucleus.[6,14-16]

NADH generated from the Krebs cycle is subsequently used in a process called oxidative phosphorylation (OxPhos) at the inner membrane of the mitochondrion.[12] Here, oxygen molecules are used as terminal electron acceptors to form a proton gradient over the inner mitochondrial membrane that drives the generation of ATP via the ATP synthase complex.[12] Therefore, mitochondrial activity results in the consumption of oxygen, which can be measured as oxygen consumption rate (OCR; Figure 1A). In addition, oxygen can be consumed independently of OxPhos or by certain enzymes in the cytoplasm.[17-19]

2.2 | Energy production via glycolysis in the cytoplasm is a hallmark feature of both cancer cells and activated immune cells

Under certain conditions, cells can decide to predominantly produce lactate from pyruvate via the consumption of NADH by the enzyme lactate dehydrogenase (LDH) in the cell's cytoplasm[20] (Figure 1B). Biochemically, this shift toward lactate production is mediated via hypoxia-inducible factor 1a (HIF-1a)-dependent upregulation of different pyruvate dehydrogenase kinases (PDHK).[21]

Inside the cell, the generated lactate cannot be further metabolized and is subsequently secreted out of the cell, acidifying the extracellular environment.[22] This pathway is common for anaerobic conditions, but was also detected nearly 100 years ago under aerobic conditions in cancer cells.[19,23,24] This "aerobic glycolysis," first detected by Otto Warburg, is therefore known as the Warburg effect.[24] It can be readily observed as yellow coloring of the culture

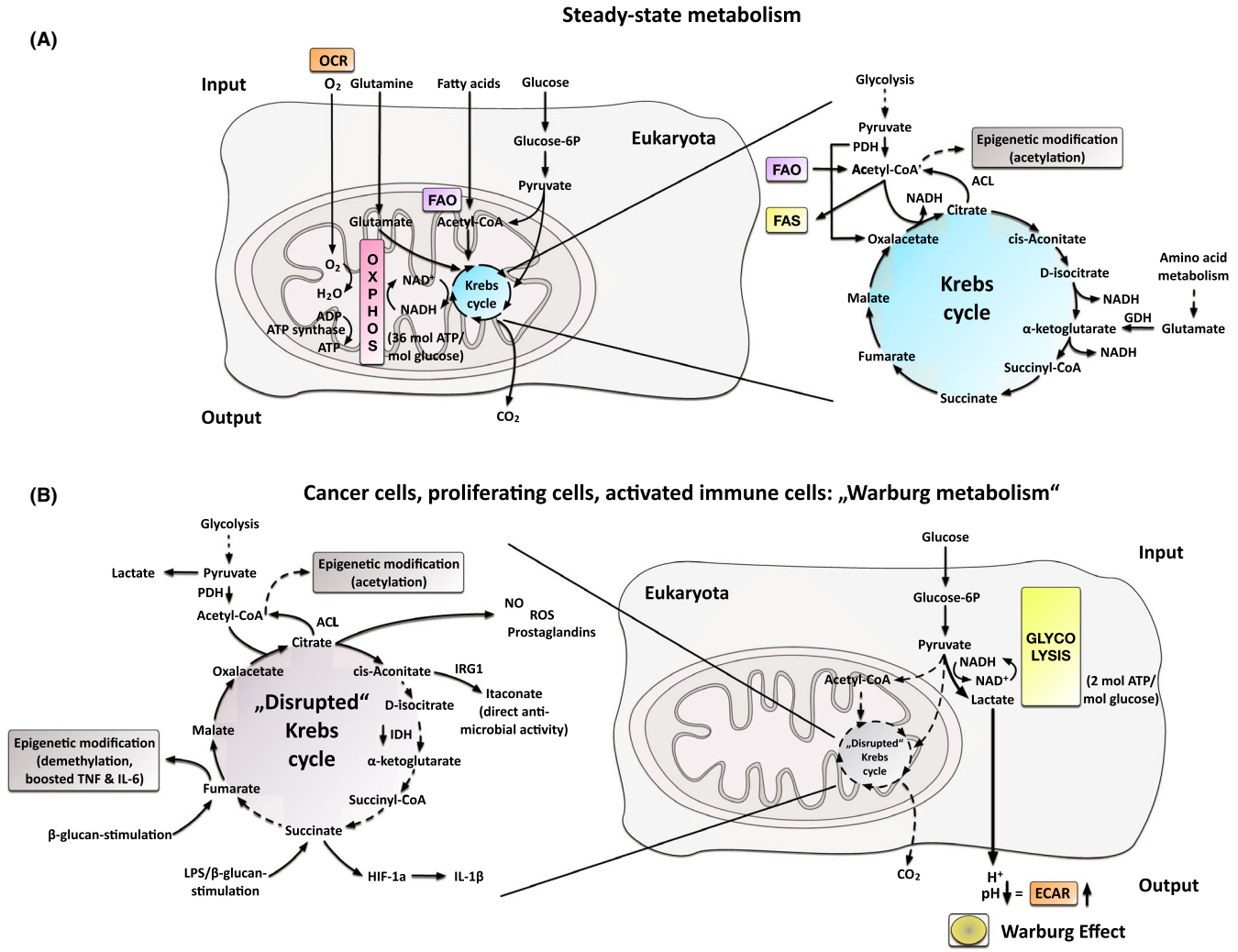

FIGURE 1 Major pathways contributing to cellular energy production and metabolic shift associated with the Warburg effect. Under normal conditions (A), cells take up glucose from their medium that degrade it in the cytoplasm into pyruvate. Pyruvate is subsequently imported into the mitochondrion where it is used in the Krebs cycle to generate reduction equivalents (NADH). These reduction equivalents are then used employing oxygen as terminal electron acceptor to generate a proton gradient over the inner mitochondrial membrane (measured as oxygen consumption rate (OCR)). This protein gradient drives the generation of ATP via the ATP synthase complex. Alternatively, the Krebs cycle can also be fueled by either fatty acids degraded into acetyl-CoA molecules or glutamate derived from amino acid metabolism. Under certain conditions, cancer cells, strongly proliferating cells, or activated immune cells can switch to predominantly producing lactate from glucose instead of fully oxidizing glucose into CO_2 in the mitochondrion (B, measured as extracellular acidification rate (ECAR)). While being energetically less efficient than OxPhos, glycolysis allows for a faster energy generation. In addition, the "disrupted" Krebs cycle, resulting from the lack of pyruvate, allows for the generation of important biosynthetic intermediates needed for immune cell effector function. Here, directly and indirectly antimicrobial molecules such as prostaglandins, NO, ROS, or itaconate are important immune effector molecules needed by the activated immune cells. Additionally, fumarate and acetyl-CoA (generated, eg, from citrate via the ATP citrate lyase, ACL) can be used for epigenetic modification. Abbreviations: OxPhos: oxidative phosphorylation, FAO: fatty acid oxidation, ROS: reactive oxygen species, NO: nitric oxide, FAS: fatty acid synthesis, PDH: pyruvate dehydrogenase, ACL: ATP citrate lyase, GDH: glutamate dehydrogenase, IDH: isocitrate dehydrogenase, IRG1: immune-responsive gene 1, HIF-1a: hypoxia-inducible factor 1a

medium and measured as extracellular acidification rate (ECAR; Figure 1B).

To date, it is known that the Warburg effect not only occurs in cancer cells, but also in either strongly proliferating cells or activated immune cells characterized by a high energy demand.[22,25] Therefore, this shift toward glycolysis is also used to fulfill the rapid energy demand of activated immune cells.

Indeed, a metabolic shift toward increased rates of glycolysis, often associated with reduced rates of OxPhos, was repeatedly described as an early step in the maturation, migration, differentiation, and pro-inflammatory activation of innate immune cells.[10] Of note, OxPhos and glycolysis have different energy yields: While complete oxidation of glucose in the mitochondrion results in the generation of 36 mol of ATP/mol glucose, glycolysis only generates 2 mol of

ATP/mol glucose[26] (Figure 1). However, glycolysis allows for a faster rate of energy generation while also providing important biosynthetic intermediates needed for immune cell effector function.[27-29] In addition, the speed of glycolysis is further increased by the induced upregulation of glycolytic enzymes via HIF-1a.[30] Thereby, while being less efficient, glycolysis can, for short periods of time, result in comparable energy production rates to full mitochondrial oxidation of glucose.[20]

Increased rates of glycolysis are likely also a relevant metabolic change in allergic patients: Ostroukhova and colleagues reported serum lactate to be increased in clinically stable asthmatic patients, suggesting an increase in glycolytic activity.[31] In line with this, activated T cells from asthmatic patients both expressed higher levels of the lactate-generating enzyme PDK1 and produced higher amounts of lactate compared to non-allergic controls.[31] Here, lower concentrations of lactate (up to 0.25 mM) promoted, while higher concentrations (>0.25 mM) inhibited T-cell proliferation.[31] Mechanistically, inhibition of lactate generation by the PDK inhibitor dichloroacetate (DCA) blocked T-cell proliferation as well as production of the cytokines IL-5, IL-17, and interferon gamma (IFN-γ), while stimulating production of IL-10 and induction of Foxp3.[31] In a mouse model of ragweed-induced asthma, DCA also suppressed both airway inflammation and hyperreactivity.[31] In summary, these data suggest aerobic glycolysis (promoting T-cell activation) to be increased in asthma. In line with these results, lactic acidosis is frequently reported in adult patients with acute severe asthma, particularly in an intensive care setting.[32-34]

2.3 | A shift toward aerobic glycolysis results in a "disrupted" Krebs cycle and the production of important immune cell effector molecules

In addition to working under conditions of low oxygen availability, the switch to Warburg metabolism also provides Krebs cycle intermediates which are critically needed in activated and proliferating immune cells[20,25,35-37] (Figure 1B).

Here, especially the accumulation of citrate, cis-Aconitate, and D-isocitrate (caused by a decreased expression of the enzyme isocitrate dehydrogenase (IDH, Figure 1B), which normally converts D-isocitrate to α-ketoglutarate[38]), resulting from a "disrupted" Krebs cycle, was suggested to facilitate the generation of both directly and indirectly antimicrobial molecules such as prostaglandins, nitric oxide (NO), ROS, or itaconate, all of which are important immune effector molecules (reviewed in[39]) (Figure 1B). Moreover, succinate accumulating in lipopolysaccharide (LPS)-stimulated macrophages was shown to promote glycolysis and IL-1β production via the stabilization of HIF-1a (reviewed in[40] (Figure 1B). Finally, fumarate was also shown to boost TNF and IL-6 production upon LPS re-stimulation of β-glucan-trained macrophages, potentially via inhibition of lysine-specific demethylase 5, resulting in increased levels of H3K4me3 at the promoters of Tnf and Il6[41] (Figure 1B).

Therefore, changes in the metabolic phenotype can have profound effects on the ability of the respective cell to fulfill its effector function.

2.4 | Metabolic adaptions in innate immune cell and trained immunity

Myeloid cells (monocytes/macrophages, NK cells, innate-like lymphoid cells) were shown to display an increased reactivity after restimulation with both the same or different stimuli, also well after the initial stimulation.[42-46] These results suggested that functional reprogramming of innate immune cells upon their initial activation can result in the development of innate memory-like responses which change the response of the respective cells toward a second challenge.[43] Here, compared to the initial response, subsequent immune responses to the second challenge can either be enhanced (termed "trained immunity") or suppressed ("trained tolerance").[43,47-49] This system allows innate immune cells to react differently to future infections.

Stimuli described to trigger trained immunity include among others β-glucan, the tuberculosis vaccine BCG, uric acid, oxidized low-density lipoproteins (oxLDL), parasites, or viral pathogens.[41,46,50-54] Moreover, in a model of atherosclerosis, Christ and colleagues showed sterile triggers in the form of a "Western Diet"(see also Box 2 for a summary of the connection between diet and inflammation) to activate innate immunity, NOD-like, and IFN signaling pathways, resulting in long-lasting, NLR family pyrin domain-containing 3 (NLRP3) inflammasome-dependent trained immunity in myeloid cells.[55] While systemic inflammation induced by a "Western Diet" was largely blunted by returning to a control diet, myeloid cell-induced innate immune responses, potentially contributing to the establishment and maintenance of inflammatory disease, remained augmented.[55]

Mechanistically, "innate immune memory" arises from both epigenetic (accumulation of H3K4me1, H3K4me3, or H3K27Ac modifications[46,50,56] and metabolic changes (including increased aerobic glycolysis, glutaminolysis, cholesterol metabolism, and fatty acid synthesis, reviewed in[46] in the respective cells that can last for prolonged periods of time and protect from secondary infections.[55,57,58] The long-lasting nature of epigenetic modifications allows cells to stay in the "trained" state characterized, for example, by an unfolded chromatin structure with exposed promoter and enhancer regions allowing for an easier activation of immune-related genes.[46]

In this context, the induced metabolic changes not only provide the energy needed for innate immune cell activation but also enzymes, cofactors, and substrates required for epigenetic modifications (eg, by providing acetyl-CoA via ATP citrate lyase (which converts citrate into acetyl-CoA) for histone acetylation, S-adenosylmethionine(SAM) for histone methylation, or α-ketoglutarate for activation of dioxygenases (reviewed in[46]).

BOX 2 Influence of diet on initiation and control of inflammation in allergy

Western lifestyle is associated with the increased consumption of calorie-rich diets high in refined starches, sugar, saturated, and trans-fatty acids, while at the same time being low in natural antioxidants and fiber (derived from fruits, vegetables, and whole grains) and omega-3 fatty acids (termed "Western Diet").[150] Combined with chronic overnutrition, a mostly sedentary lifestyle, higher levels of stress, and increased exposure to air pollution, "Western Diet" results in chronic low-level metabolic inflammation, which was termed "metaflammation" (reviewed in[151]). Risk factors for this chronic inflammatory state are summarized in the "metabolic syndrome" and include abdominal obesity, hypertension, insulin resistance, abnormalities in fat metabolism (hyperglycemia, hypertriglyceridemia, decreased high-density lipoprotein cholesterol), and aging.[150,152]

Mechanistically, consumption of a "Western Diet" was associated with activation of the innate immune system, resulting in both the production of excessive amounts of pro-inflammatory cytokines and formation of free radicals.[55,151]

Diet-induced inflammation was also suggested to contribute to allergy development: consumption of a "Western Diet," obesity, and high levels of low-density lipoprotein cholesterol were positively correlated with the risk of developing childhood asthma.[153-155]

In line with this, especially overconsumption of saturated fatty acids (FAs) was repeatedly reported to trigger inflammation and be associated with an increased risk of atherosclerosis, coronary heart disease, obesity, and "metabolic syndrome".[156-159] In this context, mouse studies showed high concentrations of saturated FAs to have direct cytotoxic effects,[160] contribute to TLR4-mediated inflammation,[161,162] induce endoplasmic reticulum-stress sensed by macrophages,[147] and induce mitochondrial ROS-dependent activation of the NLRP3 inflammasome via inhibition of adenosine monophosphate-activated protein kinase (palmitate[163]).

In contrast to this, unsaturated FAs (such as omega-3 FAs, eg, alpha-linolenic acid, docosahexaenoic acid, and eicosapentaenoic acid) are widely described as being anti-inflammatory.[150,164] Mechanistically, the beneficial effects of long-chain omega-3 FAs are likely mediated by (I) regulating hormone secretion and both (II) direct anti-inflammatory effects via GPR120-dependent inhibition of TNFR, TLR2, and TLR4 signaling and inhibition of NF-κB-dependent pro-inflammatory cytokine secretion[165,166] and (III) indirect anti-inflammatory effects via acting as substrates for the generation of potent anti-inflammatory molecules (resolvin, maresin, and protectin).[167] Accordingly, anti-inflammatory effects of poly-unsaturated FAs (PUFAs, having more than one double bond in their carbon backbone) were reported on epithelial cells (restoration of barrier function and reduction of pro-inflammatory mediators), macrophages (modulation of TLR-signaling), DCs (reduction of activation status and therefore T-cell activatory potential), neutrophils (restoration of balanced immune responses by decreasing pro-resolving functions), T cells (induction of Tregs, reduction of T-cell proliferation, T-cell activation, and T-cell differentiation into Th1/Th17 subtypes) (extensively reviewed in[168]).

Supplementation with/ consumption of fish oil rich in unsaturated omega-3 FAs was shown to suppress inflammatory immune responses in mouse food allergy models[169,170] and reduce allergy frequencies in children in the first four years of life.[171]

Furthermore, imbalances in the intake of PUFAs (higher intake of n-6 poly-unsaturated FA compared to n-3 PUFA), influencing the balance between Th1 and Th2 responses via inhibition of IL-13 production,[172] were shown to be associated with higher risks of obesity-related asthma[173,174] and uncontrolled asthma with severe clinical outcomes and frequent exacerbations.[175] Additionally, low intake levels of n-3 PUFAs were reported to result in worsening of asthma and pulmonary function,[176] while the prevalence of asthma is significantly reduced, for example, in Inuit populations[177-179] (which naturally have higher intake of n-3 PUFAs). Clinically, high intake of n-3 PUFA improved the prevalence of asthma symptoms, asthma control, lung function, airway hyperresponsiveness, and severity of exercise-induced bronchoconstriction (reviewed in[168]).

Hyaluronan (HA) is a major component of the extracellular matrix. It was reported to accumulate in both lung and serum of asthmatic patients and correlate with disease severity.[180] In this context, Sokolowska et al. demonstrated fragmented HA to increase the production of several classes of cPLA2a-dependent lipids (COX metabolites: thromboxane B2, prostaglandin E2, D2, and B2; metabolites from other pathways: 15-hydroxyeicosatetraenoic acid, 11,12-epoxyeicosatrienoic acid, and 14,15-epoxyeicosatrienoic acid; non-AA metabolites: 13-hydroxyoctadecatrienoic acid and 16(17)-epoxydocosapentaenoic acid) in patients with severe asthma.[181] In addition, low molecular weight HA treatment resulted in decreases in antiviral gene and protein expression (determined by whole-genome analysis) in patients with severe asthma, possibly caused by a reduced expression of genes involved in interferon-signaling, cell movement of lymphocytes, homing of T cells, and other canonical pathways.[181] Taken together, these results suggested a connection between extracellular matrix, global lipid mediator production, decreased antiviral responses, and asthma.[181]

Recent results suggest trained immunity to not only be relevant in infectious diseases, chronic inflammation, and cancer, but also in allergy and allergen immunotherapy. For example, aluminum hydroxide (Alum) was shown to influence the metabolic state of human DCs changing their responses toward immune-activating non-oxidized mannan in an allergen immunotherapy

setting: Benito-Vilalba and colleagues reported Alum to interfere with the allergy suppressing properties of allergoids conjugated to non-oxidized mannan.[59] Here, Alum suppressed polymerized allergoids conjugated to mannan (PM)-induced PD-L1 expression and IL-10 production from human DCs and impaired PM-induced functional Foxp3$^+$ Treg cells, while at the same time increasing Th1, Th2, and Th17 cytokine production.[59] Moreover, Alum suppressed the PM-induced induction of Tregs in mice.[59] Mechanistically, Alum inhibited PM-induced mammalian target of rapamycin(mTOR) activation thereby blunting glycolytic shift, ROS production, and DC capacity to generate functional Treg cells.[59]

Eljaszewicz et al. also showed subcutaneous allergen immunotherapy (AIT) for aeroallergens to result in dynamic changes in the systemic innate immune response, suggesting trained immunity to also contribute to the immunologic changes associated with successful AIT one year into the therapy.[49] In their study, AIT induced time-dependent changes in both composition and phenotypes of circulating ILCs, monocytes, and DC subpopulations: ILC2 cells displayed reduced frequencies in patients undergoing AIT, while ILC1 cells increased over time, suggesting that AIT limited the number of pathology-driving ILC2 in favor of ILC1 cells.[49] In addition, numbers of both plasmacytoid DCs and CD11c$^+$ myeloid cells increased and monocytes shifted from pro-inflammatory (non-classical) toward anti-inflammatory phenotypes (HLA-DR low, intermediate monocytes) during the course of AIT.[49] Therefore, AIT resulted in changes in the development of DC subsets with increased regulatory potential and the development of phenotypes, frequencies, and composition of immune cells with higher similarity to healthy controls.[49]

Taken together, cells undergo metabolic changes during both allergy and AIT. In the next section, we will go into more detail concerning the different cell types.

3 | METABOLIC CHANGES IN DIFFERENT TYPES OF IMMUNE CELLS

Our current understanding of the immune metabolic processes underlying allergic reactions is still limited. While the metabolic changes associated with activation of DCs and macrophages are meanwhile well described,[39] data about the metabolic phenotypes of the other innate immune cell types critically involved in allergic responses are limited. Therefore, this review will briefly recapitulate the current knowledge in terms of DC and macrophage immune metabolism and subsequently focus on the metabolic changes associated with activation of epithelial cells, eosinophils, basophils, mast cells, as well as ILC2s (the metabolic phenotypes and signaling pathways discussed in the review are illustrated in Figures 2–4).

Also, the acute activation and differentiation of T and B cells, as well as the formation of memory cells, which are not the focus of this review, are paralleled by distinct changes in cellular metabolism that are still not completely understood (reviewed in[60-62]).

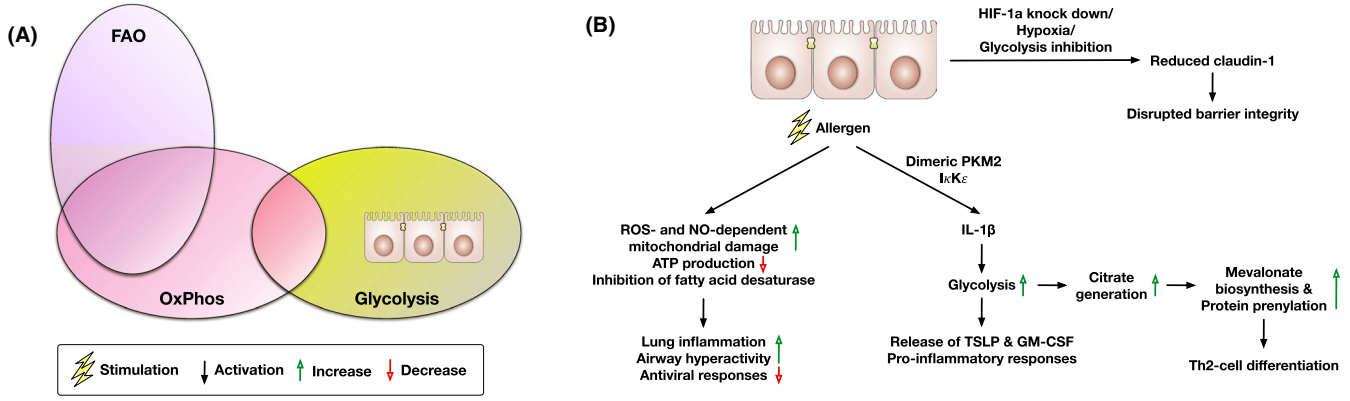

FIGURE 2 Metabolic phenotype and main signaling pathways associated with the allergen-mediated activation of epithelial cells. Epithelial cells are grouped within the metabolic pathways (glycolysis, oxidative phosphorylation (OxPhos), fatty acid oxidation (FAO), center) according to the published and discussed literature (A). Ovals represent the indicated energy pathway: violet: FAO; red: OxPhos; yellow glycolysis; In epithelial cells, allergen-induced activation results in mitochondrial dysfunction and reduced ATP production likely caused by reactive oxygen species (ROS)- and nitric oxide (NO)-dependent mitochondrial damage (B). This mitochondrial dysfunction was shown to contribute to lung inflammation, airway hyperreactivity, and reduced antiviral responses. Allergen contact also triggers a dimeric pyruvate kinase M2 (PKM2)- and inhibitory κ B kinase-epsilon (IκKε)-dependent production of IL-1ß and increased rates of glycolysis. Increased glycolysis was shown to contribute to the release of the Th2-promoting cytokines thymic stromal lymphopoietin (TSLP) and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as the induction of pro-inflammatory responses. Furthermore, via increased production of citrate, glycolytic metabolism results in increased levels of mevalonate biosynthesis and protein prenylation, which were shown to be important for Th2 differentiation. Finally, either HIF-1a knockdown, hypoxic culture conditions, or inhibition of glycolysis by 2-deoxy-glucose were shown to result in disrupted barrier integrity via a reduced expression of the tight junction protein claudin-1. For more detailed information, see text. Abbreviations: OxPhos: oxidative phosphorylation, FAO: fatty acid oxidation, ROS: reactive oxygen species, NO: nitric oxide, PKM2: pyruvate kinase M2, IκKε: inhibitory κ B kinase-epsilon, TSLP: thymic stromal lymphopoietin, GM-CSF: granulocyte-macrophage colony-stimulating factor, HIF-1a: hypoxia-inducible factor a

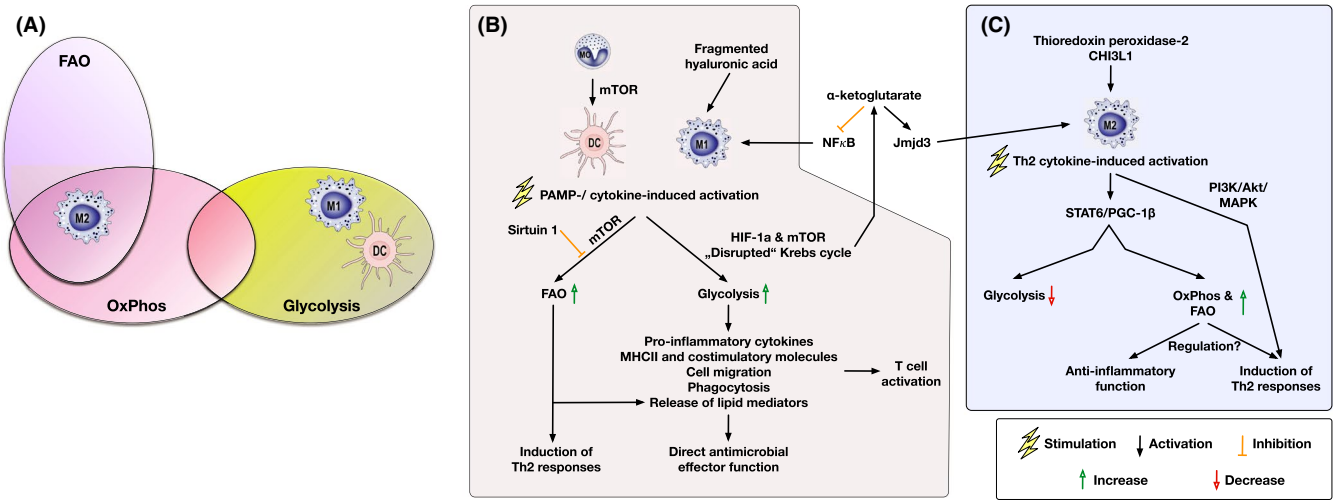

FIGURE 3 Metabolic phenotype and main signaling pathways associated with the activation of dendritic cells, M1, and M2 macrophages. Cell types are grouped within the metabolic pathways (glycolysis, oxidative phosphorylation (OxPhos), fatty acid oxidation (FAO), center) according to the published and discussed literature (A). Ovals represent the indicated energy pathway: violet: FAO; red: OxPhos; yellow glycolysis; activated DCs and M1-macrophages display a highly glycolytic phenotype. In both cell types, PAMP- or cytokine-mediated activation triggers a HIF-1a- and mTOR-dependent activation of glycolysis, paralleled by a disrupted Krebs cycle (B). Increased levels of glycolysis were shown to contribute to the production of pro-inflammatory cytokines, expression of MHCII and co-stimulatory molecules, phagocytosis, and cell migration, allowing these cells to activate T cells and fulfill their effector function. Moreover, mTOR signaling was shown to contribute to increased FAO in dendritic cells which promoted the induction of Th2 responses. Activation of FAO could be inhibited by Sirtuin 1(B). In M2 macrophages activation via Th2 cytokines triggers a STAT6- and peroxisome proliferator-activated receptor γ co-activator 1 beta (PGC-1β)-dependent activation of both OxPhos and FAO promoting their anti-inflammatory effector function (C). Concurrently, M2 macrophage activation is paralleled by a reduction in glycolytic metabolism. *Trichinella spiralis* thioredoxin peroxidase-2 and chitinase-3-like protein 1 (CHI3L1, via MAPK and PI3 K/AKT phosphorylation) were shown to promote M2 polarization and enhance Th2 responses. For more detailed information, see text. Consolidated signaling pathways involved in metabolic reprogramming are indicated for each cell type. Abbreviations: OxPhos: oxidative phosphorylation, PI3K: phosphoinositide 3-kinase, Akt: protein kinase B, STAT6: signal transducer and activator of transcription 6, PGC-1β: peroxisome proliferator-activated receptor γ co-activator 1 beta, HIF-1a: hypoxia-inducible factor 1a, PAMP: pathogen-associated molecular pattern, CHI3L1: chitinase-3-like, mTOR: mammalian target of rapamycin, FAO: fatty acid oxidation, Jmjd3: Jumonji domain-containing protein D3

3.1 | Epithelial cells

Epithelial cells are the first line of contact with allergens. Limited reports are describing the relationship between epithelial cell metabolism and different allergic diseases, such as asthma, house dust mite (HDM)-induced allergic airway inflammation, and eosinophilic esophagitis (EoE).[63,64]

Mitochondrial dysfunction and metabolic reprogramming are important for disrepair and fibrosis in lung disease.[65] Xu et al. reported increased mitochondrial numbers in bronchial epithelial cells and enhanced levels of OxPhos, partly driven by reprogramming of arginine metabolism, in the airway epithelium of patients with asthma.[66] Studies in in vivo animal models have suggested allergen-induced lung inflammation to be in part caused by ROS- and NO-dependent mitochondrial damage and reduced ATP production in the airway epithelium[67,68] (Figure 2B). Moreover, Rodriguez-Perez et al. demonstrated decreased fatty acid desaturase activity in humans with asthma.[69] Additional experiments using a HDM murine model and ex vivo bronchial epithelial cells from asthma patients suggested inhibition of fatty acid desaturase to promote both airway hyperresponsiveness and reduce antiviral responses[69] (Figure 2B), demonstrating fatty acid metabolism to be involved in asthma pathology.

Recently, Qian et al. reported the induction of glycolysis in the lungs of asthmatic mice.[70] Here, inhibitory κ B kinase-epsilon (IκKε)-dependent IL-1β production was shown to stimulate lactate generation via induction of glycolytic enzymes in primary mouse tracheal epithelial cells[70] (Figure 2B). Furthermore, enhanced glycolysis was required for IL-1β- or IL-1α-mediated pro-inflammatory responses, HDM-induced release of thymic stromal lymphopoietin (TSLP), and granulocyte-macrophage colony-stimulating factor (GM-CSF) from tracheal epithelial cells in vitro[70] (Figure 2B). In line with this, primary nasal epithelial cells from asthmatics were shown to express higher levels of LDHA and produce more lactate than cells derived from healthy controls.[70] A follow-up study from the same group suggested that the dimeric form of pyruvate kinase M2 (PKM2), an enzyme which converts phosphoenolpyruvate to pyruvate, was increased in a murine in vivo model of HDM allergy as well as nasal epithelial cells of asthma patients.[64] PKM2 was essential for IL-1β-induced pro-inflammatory signaling, which led to allergic airway pathogenesis[64] (Figure 2B). Another report showed that sputum lactate levels negatively correlated with lung function in asthmatics, suggesting that metabolic aberrations contribute to asthma development.[70] Additionally, Yagi et al. found mevalonate biosynthesis and subsequent protein prenylation (a posttranslational lipid modification) fueled by glucose-derived

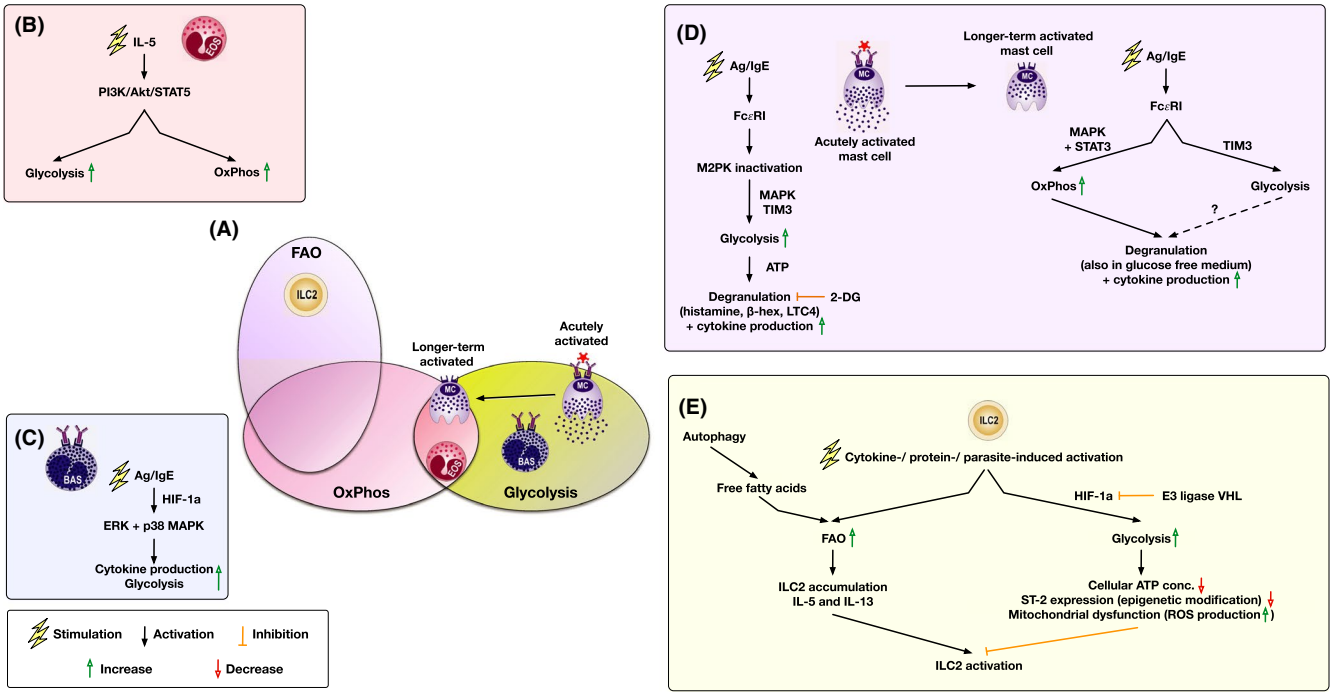

FIGURE 4 Metabolic phenotype and main signaling pathways associated with the activation of basophils, eosinophils, mast cells, and ILC2s. Cell types are grouped within the metabolic pathways (glycolysis, oxidative phosphorylation (OxPhos), fatty acid oxidation (FAO), center) according to the published and discussed literature (A). Ovals represent the indicated energy pathway: violet: FAO; red: OxPhos; yellow glycolysis; In eosinophils, IL-5-mediated activation results in a phosphoinositide 3-kinase (PI3K)-, Akt-, and signal transducer and activator of transcription 5 (STAT5)-dependent activation of both glycolysis and OxPhos, suggesting metabolic flexibility (B). Ag/IgE-dependent activation of basophils results in a HIF-1a-dependent activation of both ERK and p38 MAPK which mediate production of pro-allergic cytokines (C). In acutely activated mast cells, Ag/IgE stimulation via FcεRI triggers an inactivation of the M2-type pyruvate kinase (M2PK) which in turn promotes glycolysis via activation of MAPK and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM3). Glycolysis-derived ATP can then be used for mast cell degranulation and cytokine production. Upon longer term activation, mast cells can additionally employ MAPK- and STAT3-dependentOxPhos for energy generation allowing for degranulation and cytokine production also in glucose-free medium (D). In ILC2s activated by either cytokines, proteins, or parasites increased energy demand is met by FAO promoting ILC2 accumulation and production of effector cytokines (IL-5 and IL-13). The free fatty acids required for FAO in ILC2s are generated by autophagy. In contrast to this, HIF-1a-dependent glycolysis (which can be inhibited by the E3 ligase von-Hippel-Lindau(VHL)) results in ILC2 inhibition characterized by reduced cellular ATP concentration, mitochondrial dysfunction, and reduced ST-2 expression by epigenetic modification (E). For more detailed information, see text. Consolidated signaling pathways involved in metabolic reprogramming are indicated for each cell type. Abbreviations: OxPhos: oxidative phosphorylation, STAT5: signal transducer and activator of transcription 5, FAO: fatty acid oxidation, VHL: von-Hippel-Lindau, PI3K: phosphoinositide 3-kinase, Akt: protein kinase B, Ag: antigen, HIF-1a: hypoxia-inducible factor 1a, ERK: extracellular signal-regulated kinase, MAPK: mitogen-activated protein kinase, ROS: reactive oxygen species, ST-2: IL-33 receptor, FcεRI: high-affinity IgE receptor, ß-hex: beta-hexosaminidase, LTC4: leukotriene C4, TIM3: T-cell immunoglobulin and mucin domain-containing protein 3, M2PK: M2-type pyruvate kinase, 2-DG: 2-deoxy-glucose, ILC2: innate-like lymphocytes type II cell

citrate generation to play an important role in Th2 cell differentiation[30] (Figure 2B). Taken together, these studies indicate that the upregulation of glucose metabolism in epithelial cells during allergic disease and mediators derived from the activated epithelial cells could promote allergic inflammation (Figure 2A,B).

In general, allergic diseases are characterized by a dysfunctional epithelial barrier. Several studies also indicate the importance of epithelial cell metabolism on maintenance of barrier integrity: Masterson et al. showed either HIF-1a knockdown or prolonged hypoxia leading to the suppression of both claudin-1 expression (a tight junction control protein) and epithelial barrier function by using in vitro 3D organotypic epithelial cultures[63] (Figure 2B). Clinically, esophageal biopsies from EoE patients also showed a repressed HIF-1a and claudin-1 expression.[63] Although limited reports are describing the metabolism of intestinal epithelial cells in food allergy, it was shown that glucose metabolism was critical to preserve the structure of the intestinal epithelial barrier.[71] In vitro, ATP depletion in CaCo2 intestinal epithelial cells using either 2-deoxy-glucose (2-DG) or hypoxia conditions increased epithelial permeability associated with a loss of tight junction structure with derangements of perijunctional actin[71] (Figure 2B).

In summary, the available studies suggest that changes in mitochondrial function, fatty acid metabolism, and glycolysis of epithelial cells are involved in allergic disease progression.

3.2 | Platelets

In order to understand the pathomechanism and metabolic changes associated with allergic diseases, Obeso and colleagues investigated material from profilin allergic patients ex vivo that were grouped into either non-allergic controls, mild, moderate, or severe allergics.[72]

In this study, the progression to the severe allergic phenotype was characterized by a decrease in both carbohydrates (hexoses, pentoses) and pyruvate while lactate levels were increased in plasma.[72] Furthermore, concentrations of lysophospholipids, sphingosine-1-phosphate, sphinganine-1-phosphate, and lauric, myristic, palmitic, and oleic acids also increased with disease severity.

In contrast to this, significantly down-regulated transcripts in the severe allergic group were found to be associated with coagulation, platelet function, protein synthesis, histone modification, and fatty acid metabolism.[72] Especially, in severe allergics, platelets displayed a downregulation of transcripts associated with formation of adhesion complexes (GP1BA, GP9, GP6, and SELP), platelet activation (P2RY12, ALOX12, and PTGS2), aggregation of complexes (ITGB3, ITGA2B), synthesis of 12-hydroxyeicosatetraenoic acid and thromboxane A2 (ALOX12, PTGS2), and both shape change induction and granule secretion processes (MYL9, SDPR, RAB27B).[72]

Therefore, the results obtained by Obeso et al. suggest the transition to severe allergic phenotypes/inflammation to be either caused or accompanied by alterations in platelet function, reduced protein synthesis, and the switch to glycolytic Warburg metabolism.[72]

3.3 | Dendritic cells and macrophages

As part of the innate immune system, DCs and macrophages need to quickly react to invading pathogens in order to induce and orchestrate protective immune responses. In response to inflammatory signals, macrophages polarize into two cell types: (1) inflammatory M1-macrophages, driven by bacteria-derived pathogen-associated molecular patterns (PAMPs) such as LPS and IFN-γ, and (2) anti-inflammatory M2 macrophages activated by type 2 cytokines IL-4 and IL-13.[73-75]

Several studies repeatedly reported the ability of DCs and M1-macrophages to switch their metabolism toward glycolysis, resulting in a "disrupted" Krebs cycle[76-80] (Figure 3A). This tendency enables these two cells to efficiently execute their particular effector functions, such as producing pro-inflammatory cytokines,[81] phagocytosis in macrophages,[82] cell migration,[83] and $CD4^+$ and $CD8^+$ T-cell activation[84] in DCs (Figure 3B). Mechanically, HIF-1a is important for glycolytic metabolism in both cell types: HIF-1a-deficient macrophages lack both lactate and ATP production after LPS stimulation, and impaired glycolysis was shown to profoundly reduce the clearance of bacteria and fungi in vitro and in vivo.[85,86] In DCs, HIF-1a-deficiency leads to decreased expression of MHCII, CD80, and CD86, resulting in impaired T-cell stimulatory capacity[87,88] (Figure 3B). Moreover, succinate and succinyl-CoA were shown to induce IL-1β production via stabilization of HIF-1a in vitro[81] (Figure 1B).

Besides HIF-1a, Krebs cycle-derived metabolites also play an important role in macrophage-mediated inflammation: Fumarate was shown to induce TNF and IL-6 production, citrate to induce ROS, NO, and prostaglandin production in vitro[89] (Figure 1B). Furthermore, the mTOR network was also reported to be involved in DC differentiation, glycolysis, and mitochondrial respiration both in vitro and in vivo, which all contribute to the regulation of immune responses by DCs[90] (Figure 3B). In contrast to M1-macrophages and DCs, M2 macrophages show decreased glycolytic activity, paralleled by a higher basal mitochondrial OCR in vitro[38] (Figure 3C). This metabolic reprogramming is mediated by the signal transducer and activator of transcription (STAT6)-dependent peroxisome proliferator-activated receptor γ co-activator 1 beta (PGC-1β) signaling pathway[91] (Figure 3C). Knockdown of PGC-1β results in inhibition of fatty acid oxidation (FAO) and anti-inflammatory functions in vitro.[91] In addition, α-ketoglutarate, both an intermediate of the Krebs cycle and the product of glutaminolysis (Figure 1A), was shown to suppress NF-κB activation and restrict M1 polarization, while promoting M2 polarization via Jumonji domain-containing protein D3 (Jmjd3)-dependent epigenetic reprogramming in vitro[92] (Figure 3C).

Although the metabolic profiles of activated DCs and macrophages are well reported, studies on the contribution of DC and macrophage immunometabolism in allergic diseases are still limited. Since M2 macrophages are activated by Th2 cytokines, they have been suggested to be involved in allergic diseases such as asthma.[93,94] Jin et al. found that in vivo, recombinant *Trichinella spiralis* thioredoxin peroxidase-2, a protein that belongs to a family of antioxidant enzymes, could both promote M2 polarization and enhance Th2 responses[95] (Figure 3C). Another in vivo study by Kim et al. showed that chitinase-3-like protein 1 (CHI3L1), a glycoprotein that hydrolyses chitin, was secreted from intestinal macrophages.[96] Via mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) phosphorylation, CHI3L1 led to M2 macrophage polarization and contributed to Th2-associated inflammation in food allergy in vivo[96] (Figure 3C).

In contrast to these findings, Otobe et al. showed the induction of a M2 macrophage-phenotype to protect from local Th2 responses in a mouse model of 2,4-dinitrofluorobenzene-induced contact hypersensitivity.[97] In CX3CR1-deficient mice, 2,4-dinitrofluorobenzene challenge resulted in decreased ear swelling and dermal edema, paralleled by an increased expression of M2 macrophage markers (eg, arginase-1) in peritoneal macrophages isolated ex vivo.[97]

Besides M2 macrophages, the release of pro-inflammatory cytokines and lipid mediators by M1-macrophages also plays a role in allergy. Tiotiu et al. analyzed macrophages in the sputum and found that in severe asthma patients, both macrophage number and their activation status were reduced compared to healthy controls. However, three gene modules involved in the regulation of inflammatory response (TNF, TLR, and NF-κB pathways) were found to be enriched in severe asthmatics, suggesting these cells to closely resemble a M1-phenotype.[98]

Moreover, fragmented hyaluronic acid, which plays a role in the pathogenesis of asthma,[99] can polarize macrophages toward a M1-phenotype through cytosolic phospholipase A2 group IVA activation and arachidonic acid release in vitro[100] (Figure 3B), indicating a link between allergic inflammation and lipid metabolism in macrophages.

In DCs, during metabolic stress, Elesela and colleagues found Sirtuin 1, an NAD^+-dependent deacetylase, to activate AMPK, resulting in phospho-acetyl-CoA carboxylase-mediated inhibition of fatty acid synthesis in vitro (Figure 3B). This process altered the T-cell differentiation induced by the respective DCs from Th2/Th17 toward Th1-responses both in vitro and in vivo, suggesting Sirtuin 1-regulated metabolism to have an important role in DC function.[101] Besides, Sinclair et al. reported that mTOR-deficient $CD11b^+$ DCs showed metabolical reprogramming, resulting in disrupted FAO. When intranasally challenged with HDM in vivo, mTOR-deficient $CD11b^+$ DCs induced a neutrophilic Th17 response instead of eosinophilic Th2 inflammation[102] (Figure 3B).

Taken together, metabolic pathways impact both DC and macrophage function and fate, which also influences induction and maintenance of allergic reactions.

3.4 | Eosinophils

Data describing the immune metabolic status of eosinophils are sparse. Early on Sher et al. reported polyhydroxyalkanoate S-stimulated eosinophils to increase both hexose monophosphate shunt activity and glycolysis in vitro.[103] Recently, Porter and colleagues compared human eosinophils and neutrophils in terms of metabolic phenotype in vitro[104] : While eosinophils and neutrophils displayed similar glycolytic capacity, eosinophils exhibited significantly greater basal mitochondrial respiration, ATP-linked respiration, maximum-and spare respiratory capacity.[104] These results suggest that (compared to neutrophils) eosinophils display a greater metabolic flexibility, with the ability to use either glycolysis, glucose oxidation, or OxPhos[104] (Figure 4A). Concordantly, Peachman et al. have calculated the number of mitochondria in neutrophils to range from 5–6 mitochondria per cell while this number was 5 to 6 times higher in eosinophils (24–36 mitochondria/eosinophil).[105]

Interestingly, eosinophils from atopic and non-atopic subjects were shown to have comparable OCR upon priming in vitro with IL-5 and stimulation with the chemotactic factor N-formyl-methionyl-leucylphenylalanine.[104]

Accordingly, Jones et al. confirmed human eosinophils to display metabolic plasticity.[19] Here, human eosinophils stimulated in vitro with either IL-5, IL-3, or GM-CSF increased glycolysis while also enhancing glutaminolysis with subsequent degradation via the Krebs cycle[19] (Figure 4B). Interestingly, IL-5-driven activation of both increased glycolysis and mitochondrial activity in eosinophils was dependent on STAT5/PI3K/Akt-signal transduction (Figure 4B), resulting in NADPH oxidase(NOX)-dependent ROS production.[19] This ability of eosinophils to compensate for reduced ROS production and Krebs cycle intermediates by increasing glycolysis confirms their metabolic plasticity.

Increased glycolytic activity by cytokine-stimulated eosinophils was accompanied by accumulation of both intra- and extracellular lactate and therefore the generation of a local acidic microenvironment.[19] Eosinophils and T cells were shown to efficiently fulfill their effector functions in acidic environments,[106,107] suggesting that metabolic changes can also induce, maintain, or boost the function of other immune cells.

Autophagy (Greek for "eating of self") is a both highly conserved and regulated catabolic process responsible for the turnover of macromolecules and organelles via the lysosomal degradative pathway.[108] In mammals, it is regulated by mTOR (mTOR activation results in autophagy inhibition), PI3K, and numerous autophagy-related (Atg) proteins.[108]

The contribution of autophagy to eosinophil development and activation is largely unknown (reviewed in[108]). Interestingly, eosinophil development seems to be differentially regulated by the mTOR complex: while autophagy induction by rapamycin-induced inhibition of mTOR complex 1 (mTORC1) effectively blocked eosinophil differentiation and attenuated OVA-induced allergic airway inflammation with reduced numbers of eosinophils (in local airways, peripheral blood, and bone marrow),[109] application of the mTORC1/2 inhibitor torin 1 resulted in accelerated eosinophil differentiation and elevated levels of eosinophil infiltration in an experimental mouse model of allergy.[110]

Additional studies suggest that autophagy levels in eosinophils may regulate the severity of allergic inflammation.[111] Higher levels of autophagy were reported in human sputum and peripheral blood eosinophils from patients with severe asthma compared to non-severe asthma and healthy controls which were further increased by stimulation with IL-5 in vitro,[112] suggesting that autophagy could play a role in eosinophil activation and pathogenesis of severe asthma.

Using genetically modified mice that lack Atg5, a protein essential for autophagosome formation (specifically in eosinophils or neutrophils), Germic and colleagues reported in vitro, both ROS production and extracellular trap formation in eosinophils and neutrophils to be independent of autophagy.[113] In contrast, Silveira et al. reported the autophagy inhibitor, 3-methyladenine to reduce extracellular trap formation in the airway, decrease the number of eosinophils, eosinophil peroxidase activity, goblet cells hyperplasia, pro-inflammatory cytokines, and NFκB p65 content while at the same time improving oxidative stress, mitochondrial energy metabolism, and Na^+, K^+-ATPase activity in a mouse experimental asthma model.[114] However, in this model indirect effects of 3-methyladenine on eosinophil activation cannot be excluded.

Indeed, Choi et al. suggested impaired autophagy to indirectly promote eosinophilic inflammation and pathogenesis of eosinophilic chronic rhinosinusitis (ECRS): In their model, myeloid cell-specific deletion of Atg7 aggravated eosinophilia, epithelial hyperplasia, mucosal thickening, and increased production of PG D2 in mice with ECRS via macrophage-derived IL-1β.[115] Furthermore, myeloid deficiency for autophagy was associated with gene expression profiles

favoring eosinophilic inflammation, Th2 responses, PG D2 dysregulation, and mast cell infiltration in vivo.[115]

In summary, the observed metabolic flexibility and shifting toward glycolysis may allow eosinophils to both efficiently fulfill their function in inflammatory environments with limited availability of oxygen and quickly adapt to different microenvironments. This speculation is in line with their function in both immune effector responses as well as establishment and maintenance of immune homeostasis.[104]

3.5 | Basophils

As for eosinophils, data describing the immune metabolic phenotype of basophils are limited and also the role of autophagy in basophil function is currently unknown. Sumhayev and colleagues showed the IgE-mediated activation of primary human basophils to result in an extracellular signal-regulated kinase (ERK)- and p38 MAPK-dependent accumulation of HIF-1a in vitro[116] (Figure 4C). HIF-1a mediates cellular adaptation to hypoxic conditions by regulating glycolysis, angiogenesis, and cell adhesion.[117-119] In the study of Sumhayev et al., HIF-1a activation and the induced glycolysis supported IgE-mediated inflammatory basophil responses by providing the ATP necessary for IL-4 and VEGF production[116] (Figure 4C).

In a follow-up study, Sumbayev and colleagues examined the contribution of HIF-1a to the synthesis of angiogenic and inflammatory cytokines from either primary human basophils, LAD2 human mast cells, or THP-1 human myeloid cells in vitro.[120] As was already observed for IgE-stimulated human basophils, TLR ligand–induced cytokine secretion from HIF-1a knockdown LAD2 mast cells was markedly reduced while degranulation was unaffected.[120] Moreover, either LPS, PGN, or IgE stimulation of THP-1 cells resulted in HIF-1a accumulation and release of TNF-α, VEGF, and IL-6.[120]

Taken together, these results suggest that HIF-1a and the induced immunologic and metabolic changes (increased glycolysis) are important determinants of basophil effector function.[120]

3.6 | Mast cells

While information about the immune metabolism in eosinophils and basophils is limited (see above), more data are available for mast cells. Several studies suggest that ATP generation via glucose metabolism plays an important role in acute, FcεRI-mediated mast cell activation (Figure 4).

Already 55 years ago, Chakravarty and colleagues reported increased glycolytic rates in ex vivo-isolated rat mast cells.[121] Inhibition of glucose metabolism by 2-DG had no effect on compound 48/80-induced histamine release from rat mast cells while anaphylactic (IgE-mediated) mediator release was inhibited by high concentrations of 2-DG (20–80 nM resulting in 30 to 55% inhibition)[122] (Figure 4D). These early results suggested both glucose transport and utilization via glycolysis to support histamine release from mast cells. In line with an increased glucose metabolism, the concentrations of both pyruvate[123] and ATP[124] were lower in mast cells after antigen challenge.

Concordantly, Takei and colleagues reported depletion of glucose from the culture medium of rat peritoneal mast cells to time-dependently decrease anti-IgE-induced histamine release in vitro.[125] This reduction of mediator release was suggested to be due to the inhibition of ATP-dependent Ca^{2+}-release from intracellular calcium stores.[125] Moreover, mast cells isolated from rats infected with the parasite *Nippostrongylus brasiliensis* as well as rat peritoneal mast cells ex vivo-stimulated with either compound 48/80, polymyxin B, or melittin were reported to both secrete histamine and produce lactate.[126]

In accordance with the mainly glycolysis-driven activation of mast cells, inhibiting glycolytic ATP production in bone marrow-derived mast cells (BMMCs) in vitro was shown to attenuate IL-33-mediated mast cell function while inhibiting OxPhos had little effect on cytokine production.[37] Moreover, inhibition of mast cell glycolysis also inhibited IL-33-induced neutrophil recruitment and cytokine production in vivo.[37]

FcεRI-meditated activation of rat basophil leukemia cells (RBL-2H3) in vitro resulted in reduced activity of the glycolytic enzyme M2-type pyruvate kinase (M2PK) which regulates the terminal step of glycolysis.[127] Interestingly, FcεRI-meditated inactivation of M2PK, likely resulting in the accumulation of glycolytic intermediates, was shown to be required for mast cell degranulation in vitro, suggesting a link between mast cell metabolism and effector function[127] (Figure 4D). Moreover, these glycolytic intermediates are also used for the synthesis of, for example, phospholipids or diacylglycerols, molecules that play important roles in mast cell degranulation.[128,129]

Concordant with the above-described glucose-dependency of mast cell degranulation, long-term in vitro culture of BMMCs with 33 mM glucose increased the FcεRI-dependent release of β-hexosaminidase and leukotriene C4 while having no effect on mast cell viability, surface expression levels of FcεRI, intracellular ATP levels, calcium signaling, or IL-6 secretion.[130] These results suggest glucose availability to act as a regulating factor for FcεRI-mediated mast cell responses. Mechanistically, long-term culture with glucose was shown to induce a FcεRI-dependent phosphorylation of cytosolic phospholipase A2 at residue Ser505 in vitro.[130] Since mast cells cultured with glucose also showed increased degranulation upon stimulation with suboptimal antigen concentrations, prolonged high-glucose culture may increase mast cell sensitivity to low antigen doses and therefore have profound effects on the threshold with which allergic reactions are induced.[130]

In accordance with the results by Kitahata, culture of the human mast cell lines HMC-1 and LAD2 in high-glucose medium (25 mM) increased the levels of intracellular ROS and phosphorylation of ERK-, c-Jun N-terminal kinase (JNK), and p38-MAPK, which in turn promoted production of pro-inflammatory (TNF-α, IL-1β, IL-6) and pro-allergic cytokines (IL-13).[131] Of note, β-hexosaminidase

production was increased in LAD2 cells, while its release was independent of glucose concentration.[131] These findings indicate that ROS induced by in vitro culture in high-glucose medium activate pro-inflammatory and pro-allergic cytokine production in mast cells via MAPK-signaling (Figure 4D).

Erlich and co-authors described mitochondrial-, MAPK-dependent-, and STAT3-driven OxPhos to contribute to IgE-antigen-mediated degranulation of human and mouse mast cells in vitro[132] (Figure 4D) suggesting that not only glycolysis but also ATP production by OxPhos in the mitochondrion is involved in fulfilling the energy demands of activated mast cells. In contrast to the beforementioned studies, in vitro mast cell degranulation occurred even in glucose-free medium.[132] However, in accordance with the abovementioned studies, Erlich and colleagues also found MAPK-signaling to be a pivotal pathway connecting mast cell function and metabolism[132] (Figure 4D).

Phong et al. also reported FcεRI-mediated activation of mouse BMMCs in vitro to result in a rapid, T-cell immunoglobulin and mucin domain-containing protein 3 (TIM3)-dependent induction of glycolysis, while OxPhos was mostly unchanged[133] (Figure 4D). These changes are reminiscent of immediate reprogramming observed upon lymphocyte activation.[133] Interestingly, at later time points, IgE/Ag-stimulated mast cells displayed a broader metabolic potential in vitro with increases in both mast cell capacity for glycolysis and OxPhos, determined by increased OCR and spare respiratory capacity, and both higher ECAR and glycolytic reserves, respectively[133] (Figure 4D). In this experimental setting, inhibition of OxPhos also decreased both degranulation and cytokine production.[133] The observed time-dependent differences in mast cell mitochondrial respiration were suggested to result from more complex, transcriptional reprogramming events which have longer lead times and are therefore not observed in "acute" mast cell stimulations.[133] Of note, FAO was found to be dispensable for mast cell activation in vitro since the FAO inhibitor etomoxir neither inhibited IgE/Ag-induced mast cell activation, IL-6 production, nor degranulation.[133]

To investigate the role of autophagy in mast cell development and effector function, Ushio et al. generated BMMCs from mice lacking the essential autophagy-inducing protein Atg7.[134] While autophagy was constitutively induced in BMMCs, even under full nutrient conditions, deletion of Atg7 neither impaired BMMC-development, Ca^{2+} mobilization, induction of early signaling molecules, activation of MAPK and NFκB, nor cytokine production upon FcεRI crosslinking.[134] However, Atg7-deficent BMMCs showed a strongly impaired ability to degranulate in vitro.[134] Moreover, cellular ATP content of Atg7-deficient BMMCs was increased compared to controls, suggesting that the observed disruption of degranulation was not caused by energy limitations.[134] In vivo, reconstitution of mast cell-deficient mice with Atg7-deficient BMMCs strongly impaired passive cutaneous anaphylaxis reactions, demonstrating the in vivo relevance of autophagy for mast cell function.[134]

In contrast to this, Nian et al. reported the inhibition of IL-33-receptor (ST2)/PI3K/mTOR-mediated autophagy in mast cells to induce degranulation and release of inflammatory mediators in vitro.[135]

In summary, the available data suggest short-term mast cell activation to mainly rely on increased glycolysis while OxPhos also contributes to mast cell metabolism upon longer stimulation (Figure 4A).

3.7 | ILC2s

In contrast to either basophils, eosinophils, or mast cells, ILC2s were shown to predominantly depend on FAO for their effector function in the context of either helminth infection or malnutrition[136] (Figure 4E). Here, ex vivo-isolated ILC2s displayed constitutive fatty acid uptake,[136] and both ILC2 accumulation and ILC2-derived IL-13 production in mice were shown to depend on fatty acid uptake and oxidation while being independent of glucose[136] (Figure 4E). In vivo, blockade of FAO in a model of *Trichuris muris* infection significantly reduced ILC2 accumulation, IL-5, and IL-13 production.[136] This dependency of ILC2 function on fatty acids rather than glucose may be the evolutionary result of their need to function in the locally nutrient (and glucose)-deprived environments created by parasites at sites of infection.[137]

In addition to the subordinate role of glycolysis in ILC2 function, Wagner et al. reported tumor-derived lactate to suppress local ILC2 proliferation, ILC2 survival, and ILC2 effector function in vivo.[138] This suppression of the IL-33/ILC2/eosinophil tumor surveillance axis resulted in enhanced tumor growth.[138]

Galle-Trager et al. also showed FAO to be critical for ILC2 function.[139] Lack of autophagy, which has been described as a major pathway for lipid breakdown by targeting lipids to autophagosomes[140] in Atg5-deficient mice, impaired FAO resulting in increased levels of glycolysis as well as apoptosis in activated ILC2s.[139] This shift toward glycolytic metabolism disrupted ILC2 homeostasis and Th2 cytokine production, resulting in reduced ILC2-mediated airway hyperreactivity in vivo.[139] Moreover, induction of glycolysis was paralleled by reduced cellular ATP concentrations and accumulation of dysfunctional mitochondria producing excessive amounts of ROS in ex vivo-isolated lung ILC2s[139] (Figure 4E). Taken together, these results confirm the importance of FAO for ILC2 function while also showing autophagy to provide free fatty acids through lipid droplet degradation in order to maintain ILC2 energy balance (Figure 4E).

In line with these results, Li et al. reported a critical role for the E3 ubiquitin ligase von-Hippel-Lindau (VHL) in ILC2 maturation by preventing HIF-1a-mediated induction of glycolysis and inducing IL-33 receptor (ST2) expression[141] (Figure 4E). Here, in ex vivo-isolated ILC2s, reduced ST2 expression was caused by HIF-1a-driven expression of the glycolytic enzyme M2PK, resulting in epigenetic modification of the ST2[141] (Figure 4E). Based on their results, Li et al. proposed a model in which imbalances in the equilibrium between glycolysis and OxPhos alter epigenetic modifications of genes important for ILC2 function (eg, ST2).[141]

Contradictory to the above-mentioned studies, ILC2s were also shown to partly depend on aerobic glycolysis driven by the urea cycle enzyme arginase 1 (Arg1), which metabolizes L-arginine.[142] Monticelli showed both mature human and mouse ILC2s to constitutively express Arg1, generating the downstream metabolites proline and polyamines, which in turn drive collagen-synthesis and other bioenergetic pathways critical for cell proliferation.[142-144] Genetic deletion of Arg1 in ILC2s resulted in reduced ILC2 function with abrogated papain-induced type 2 lung inflammation in vivo due to disrupted ILC2 proliferation and strongly reduced Th2 cytokine production.[142] Arg1 inhibition was shown to disrupt amino acid metabolism in ex vivo-isolated ILC2s, thereby preventing the generation of L-arginine-derived polyamines which reduced rates of aerobic glycolysis.[142]

In summary, the currently available studies suggest that ILC2s (in contrast to, eg, basophils, eosinophils, and mast cells) mainly require FAO for proper development and effector function, while a metabolic shift toward glycolysis may impair ILC2 function (Figure 4A,E).

4 | CONCLUSION

Type I allergies are the result of complex interactions between different immune cells. In order to fulfill their effector function, the key cell types of allergic inflammation were reported to change their metabolic phenotype during activation, shifting to either glycolysis (epithelial cells, M1 macrophages, DCs, eosinophils, basophils, acutely activated mast cells), OxPhos (M2 macrophages, longer term activated mast cells), or FAO (ILC2s).

In addition to these cell-intrinsic changes in metabolic phenotypes, the local microenvironment in which immune responses are initiated and maintained can change the metabolism and therefore the functional properties of the infiltrating immune cells. For example, barrier surfaces are metabolically distinct from the rest of the body with both decreased oxygen tension and lower nutrient levels, especially at sites of inflammation.[133]

Therefore, immunometabolism clearly is of importance in allergic diseases. Understanding the metabolic changes associated with the activation of the key immune cell types involved in the induction and maintenance of allergic responses will likely result in a more complete understanding of the disease pathology as well as the identification of novel target molecules and strategies for the treatment of allergic diseases. Indeed, immune metabolic analyses have already identified glycolytic ATP production[37] and STAT3[132] in mast cells, as well as Arg1,[142] VHL,[141] and autophagy[139] in ILC2s as potential targets to modulate allergic responses (see above). Further studies can only improve our understanding of the complex and fascinating connections between immune cell metabolism and effector function.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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