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REVIEW

Cigarette Smoking-Induced Glucose Metabolic Reprogramming in Chronic Obstructive Pulmonary Disease: Mechanisms and Therapeutic Implications

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Abstract: Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous respiratory disorder that arises from interactions between genetic susceptibility and environmental exposures, with cigarette smoking being the primary modifiable risk factor. Cigarette smoke reprograms pulmonary glucose metabolism, a process recognized as an early molecular event driving disease progression. Prolonged exposure is associated with enhanced glycolysis, suppression of the tricarboxylic acid cycle and oxidative phosphorylation, mitochondrial dysfunction, and excessive production of mitochondrial reactive oxygen species. These metabolic disturbances converge to form a pathological axis linking metabolism, inflammation, and immunity, leading to immune dysregulation, chronic airway inflammation, and tissue remodeling. This review summarizes the characteristics and molecular mechanisms of cigarette smoke–induced glucose metabolic reprogramming in COPD while highlighting the therapeutic potential of targeting glucose metabolism. Particular emphasis is placed on comprehensive strategies aimed at restoring metabolic homeostasis. A deeper understanding of glucose metabolic reprogramming in COPD associated with smoking may provide novel insights into disease pathogenesis and contribute to the development of individualized therapies. Nevertheless, clinical evidence remains limited, underscoring the need for translational studies targeting glucose metabolism in COPD.

Keywords: chronic obstructive pulmonary disease, glucose metabolism reprogramming, cigarette smoke, mitochondrial dysfunction, targeted metabolic intervention

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and heterogeneous respiratory disorder characterized by irreversible airflow limitation and chronic respiratory symptoms, with primary clinical phenotypes including chronic bronchitis and emphysema.[1,2] In 2022, the Lancet COPD Commission categorized COPD into five types based on the major risk factors and emphasized that distinct pathophysiological mechanisms driven by these risk factors may translate into differentiated approaches to diagnosis, prognosis, and treatment.[3]

Cigarette smoking is the primary risk factor for COPD. Combustible cigarettes release substantial amounts of oxidants, tar, nicotine, and fine particulate matter during combustion, forming a complex mixture of harmful

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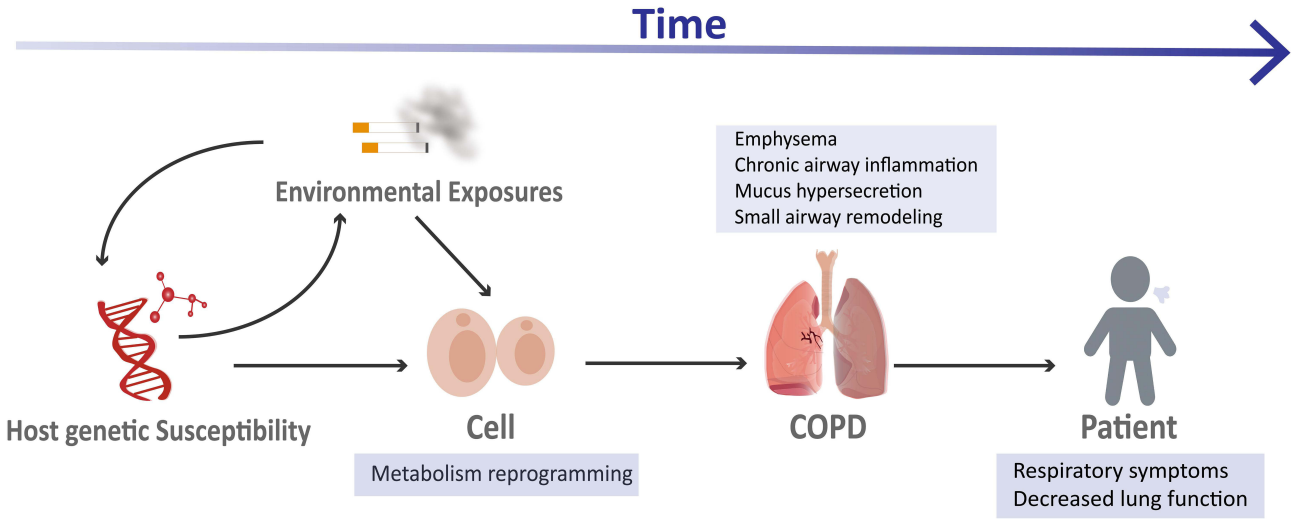

Figure 1 Metabolic reprogramming links genetic susceptibility and environmental exposures to COPD development.

substances.[4] Because combustible cigarettes contain thousands of toxic chemicals with well-established health hazards, so-called "novel tobacco products" have been marketed as alternatives, but accumulating evidence indicates that they are far from harmless.[4] Among these, e-cigarettes produce inhalable aerosols by heating liquids containing propylene glycol, glycerin, flavorings, and nicotine.[5] Heat-not-burn products(HTPs), conversely, heat tobacco material itself at lower temperatures to release nicotine-containing aerosols.[4] Currently, there is insufficient epidemiological and mechanistic evidence to establish a link between e-cigarettes or HTPs and COPD, despite their capacity to induce oxidative stress, inflammatory responses, and lung function impairment.[6]

Compared with non-smoking-related COPD, the smoking-related subtype exhibits more pronounced differences in clinical phenotype, underlying mechanisms, and disease progression. Studies have demonstrated that individuals who smoke exhibit a higher prevalence of respiratory symptoms and pulmonary function abnormalities, a more rapid annual decline in forced expiratory volume in one second (FEV_1), increased frequency of acute COPD exacerbations, and elevated mortality rates.[7,8] Furthermore, genetic susceptibility plays a significant role in the onset and progression of COPD.[9] Exposure to cigarette smoke (CS) promotes the development of COPD by altering gene expression and signaling pathways, while emerging evidence suggests that dysregulated glucose metabolism may represent another key mechanism in this process[10,11](Figure 1). This review aims to outline a perspective that considers the metabolism–inflammation–immunity interplay under CS exposure. We systematically summarizes how CS alters pulmonary glucose metabolism and clarify its contribution to COPD pathogenesis. In addition, the potential of targeting glucose metabolic remodeling as a therapeutic strategy will also be discussed.

Glucose Metabolism in Lung

The concept of glucose metabolism reprogramming was first recognized in cancer biology, where it represents a hallmark metabolic alteration that distinguishes tumor cells from their normal counterparts.[12] This phenomenon, commonly referred to as the "Warburg effect", describes the propensity of cancer cells to favor glycolysis for lactate production even under normoxic conditions.[12]

Interestingly, despite sufficient oxygen availability, lung tissue demonstrates aerobic glycolysis, whereby substantial amounts of glucose are converted to lactate through the glycolytic pathway even under normoxic conditions.[13] On the one hand, this glycolysis-favored pattern may help reduce local oxygen consumption, thereby allowing greater oxygen distribution to peripheral tissues; on the other hand, lactate may act as a metabolic coupling factor, being taken up by neighboring lung cells via monocarboxylate transporters and subsequently converted to pyruvate for mitochondrial oxidation, thus facilitating intercellular metabolic cooperation within the lung microenvironment.[14,15] In addition to glycolysis, glucose can be metabolized via the pentose phosphate pathway (PPP) to generate nicotinamide adenine

dinucleotide phosphate (NADPH, reduced form) and ribose-5-phosphate, which are essential for maintaining redox homeostasis and synthesizing nucleic acids, respectively, thereby supporting antioxidant defense and cell proliferation.[16] Furthermore, pyruvate can be converted into acetyl-CoA by pyruvate dehydrogenase complex, entering the mitochondria to supply the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), providing an efficient energy source for alveolar epithelial cells, alveolar macrophages, and other immune cells.[17]

Importantly, aerobic glycolysis in the healthy lung represents a physiological adaptation that coexists with intact mitochondrial respiration and preserved redox homeostasis. This should be distinguished from a pathological Warburg-like program that emerges under injurious conditions and is characterized by reduced OXPHOS and disrupted cellular redox balance.

Clinical Impact of Glucose Dysregulation in COPD

Glucose dysregulation represents a clinically relevant but underrecognized feature of COPD. Clinical observational evidence has shown that patients with severe COPD had increased endogenous glucose production and clearance, along with elevated pyruvate flux and oxidation, suggesting dysregulated glucose metabolism contributes to pulmonary metabolic stress.[10] The triglyceride–glucose index has been strongly associated with all-cause mortality in patients with severe COPD.[18] In acute exacerbations complicated by ventilatory insufficiency, hyperglycemia correlates with worse clinical outcomes.[19] Subsequent studies have demonstrated that aberrant glucose metabolism may not only reflect comorbid conditions but also actively participate in COPD progression through metabolic and inflammatory crosstalk.[11,18] Importantly, such glucose-related disturbances are not limited to moderate or severe COPD. Large-scale population-based studies have shown that a higher dietary inflammatory index and the presence of diabetes are both significantly associated with reduced lung function.[20,21] A cross-sectional study conducted in a Japanese population undergoing medical examinations revealed that individuals with elevated glycated hemoglobin (HbA1c $\geq$ 5.6%) exhibited significantly lower FEV_1/FVC ratios, further underscoring the link between impaired glucose homeostasis and pulmonary dysfunction.[22]

Diabetes itself may contribute to pulmonary impairment through several interrelated mechanisms. Chronic hyperglycemia promotes the accumulation of advanced glycation end-products, which trigger systemic and airway inflammation and enhance oxidative stress, thereby damaging lung tissue structure and elasticity.[23,24] Persistent inflammation exacerbates insulin resistance and metabolic imbalance, further weakening pulmonary metabolic homeostasis and repair capacity.[25] In addition, diabetes-related microvascular complications can involve the pulmonary circulation, leading to thickening of the alveolar–capillary basement membrane and impairment of gas diffusion, contributing to reduced lung function.[26]

Beyond disease-specific mechanisms, systemic factors also contribute to altered glucose metabolism in COPD. Insulin resistance and metabolic syndrome, which are common comorbidities in COPD patients, can exacerbate dysregulated glucose homeostasis and thereby confound the interpretation of metabolic findings.[27] Moreover, widely used pharmacological treatments such as systemic corticosteroids may induce hyperglycemia, while β-agonists and anticholinergics can influence glucose handling through effects on glycogenolysis, insulin secretion, and cellular uptake.[27,28]

Cigarette Smoke, Glucose Metabolism Reprogramming and COPD

CS exerts complex, multilayered effects on pulmonary metabolism and immune function in both active smokers and those with passive exposure, with such effects potentially varying by age, sex, and mode of exposure, thereby complicating the understanding of smoking-related COPD pathogenesis. Numerous observational clinical studies have indicated that patients with smoking-related COPD exhibit glucose metabolic dysregulation.[21,29] However, given the substantial heterogeneity across clinical populations and external factors, many studies have used cellular or animal models to minimize variability and elucidate the mechanistic role of smoking-induced alterations in glucose metabolism during COPD progression. These studies collectively suggest that CS induced glucose metabolic reprogramming serves as a critical node for amplifying inflammation and shaping immune adaptation, thereby contributing to the pathological progression of COPD through the axis of metabolism, inflammation and immunity.

Shift Toward Glycolysis: Impaired TCA Cycle and OXPHOS

CS exposure can induce alterations in glucose metabolism within pulmonary cells. In smoking-related COPD, a prominent metabolic feature is increased glucose uptake accompanied by enhanced glycolytic activity, whereas mitochondrial oxidative metabolism, including the TCA cycle and OXPHOS, is impaired.[30,31] It is noteworthy that this metabolic reprogramming occurs not only in airway epithelial cells but also in pulmonary immune cells, and is closely associated with persistent inflammation.

Clinical metabolomic studies have shown that lung tissues from COPD patients exhibit significantly elevated levels of glycolytic intermediates such as lactate and pyruvate, while key TCA cycle metabolites such as citrate and α-ketoglutarate are markedly reduced. These alterations suggest that glycolytic flux is enhanced whereas mitochondrial oxidative metabolism is impaired.[32,33] Such metabolic changes are closely linked to lung function decline and chronic inflammation in COPD.

Animal and cellular studies further corroborate these clinical observations. In a murine COPD model, prolonged CS exposure (12 weeks) markedly increased the expression of glucose transporter 3 (GLUT-3) in lung tissue, whereas GLUT-3 knockout significantly alleviated airway remodeling and lung function impairment, and inhibited epithelial–mesenchymal transition (EMT) in bronchial epithelial cells.[34,35] Consistently, mice subjected to long-term CS exposure exhibited substantial lactate accumulation in lung tissue accompanied by reduced activity of key TCA cycle enzymes.[36] In vitro, BEAS-2B bronchial epithelial cells exposed to cigarette smoke extract(CSE)(CSE: 1%-12.5%; 6-months) similarly showed GLUT-3 upregulation, along with enhanced glycolytic flux, decreased oxygen consumption rate (OCR), reduced ATP synthesis, and excessive lactate release.[34,37] To compensate for this energy deficit, cells further increased glucose uptake and reinforced glycolysis, accompanied by upregulation of glucose metabolism–related genes such as RPL13A and ATP5B.[32] In in vitro bronchial epithelial cell models, pyruvate kinase M2 (PKM2) upregulation is closely associated with enhanced inflammatory responses and EMT, whereas PKM2 knockdown significantly reduces the release of pro-inflammatory cytokines, lowers reactive oxygen species(ROS) levels, and suppresses EMT.[38]

Of note, the regulatory patterns of glucose metabolism differ depending on the duration of CS exposure. In a murine model subjected to whole-body CS exposure for 4 weeks, lung glycolytic flux exhibited a decreasing trend, accompanied by enhanced activity of the PPP and downregulation of key glycolytic enzymes such as glyceraldehyde-3-phosphate dehydrogenase. Concurrently, the expression and activity of electron transport chain(ETC) complexes were significantly upregulated, suggesting that acute CS exposure may induce a metabolic adaptation primarily driven by oxidative stress rather than by inflammation.[39] Short-term CS exposure may primarily trigger oxidative stress adaptation, whereas chronic exposure leads to inflammation-driven metabolic imbalance.

Mitochondrial Dysfunction and mtROS Accumulation

Mitochondria serve as the central site for cellular energy metabolism, hosting the primary locations for the TCA cycle and OXPHOS reactions. Exposure to CS significantly damages the structure and function of pulmonary cell mitochondria, leading to metabolic homeostasis disruption and excessive production of ROS. In particular, mitochondria-derived ROS (mtROS) play a crucial role in the development and progression of COPD.

Morphological analysis of bronchial epithelial cells in patients with COPD revealed typical mitochondrial morphological abnormalities, including loss of cristae, swelling, and fragmentation.[40] Animal studies and cell models have also yielded similar findings. In a CS-exposed mouse model (5 days/week for 4–6 months), genes associated with the TCA cycle, fatty acid oxidation, and redox regulation were compensatorily upregulated in pulmonary epithelial cells, accompanied by mitochondrial morphological and functional abnormalities including reduced cristae number, enlarged volume, decreased membrane potential, and reduced OCR.[39,41] In the BEAS-2B bronchial epithelial cell model, CSE stimulation (CSE: 1%-12.5%; 6-months or 24-hours) revealed characteristic ultrastructural alterations such as mitochondrial debranching, swelling, and cristae depletion.[32,42] Furthermore, CSE inhibits the activity of key complexes in the ETC, such as complexes I and II, leading to diminished NADH reoxidation capacity, disruption of the NAD^+/NADH ratio, and ultimately suppression of dehydrogenase reactions in the TCA cycle.[43]

These structural and functional abnormalities converge on impaired ETC efficiency and electron leakage.[44] When electrons combine with oxygen, they generate excessive mitochondrial mtROS, including superoxide anion ($O_2^{-}\cdot$),

hydrogen peroxide (H_2O_2), and hydroxyl radical (·OH).[44,45] These mtROS not only directly cause oxidative damage to DNA, lipids, and proteins but also act as signaling molecules to activate inflammation-related pathways such as the NLRP3 inflammasome and NF-κB.[44] Accumulating evidence further suggests that mtROS act upstream of signaling pathways such as STAT3 and PINK1-Parkin, thereby promoting EMT and small airway remodeling.[46,47] Together, these effects amplify chronic inflammatory responses in lung tissue and accelerate disease progression.[44–47]

Therefore, CS-induced mitochondrial structural disruption and dysfunction not only impair cellular energy metabolism but also drive chronic inflammation and lung tissue injury through mtROS-mediated signaling pathways, making it one of the key molecular events in the development of COPD (Figure 2).

Crosstalk Between Metabolism and Immunity in COPD

Disrupted glucose metabolism represents not only changes in cellular energetics but also a key driver of immune dysregulation. Metabolic intermediates and signaling molecules serve as "bridges" for immune regulation, establishing intricate metabolic-immune interaction networks between immune cells and structural cells (Figure 3). This interaction is particularly pronounced in the context of CS exposure, driving chronic inflammatory responses and airway remodeling.

Under chronic CS exposure, pulmonary macrophages exhibit a phenotypic shift predominantly toward classical activation (M1) polarization, regulated by an imbalance between glycolysis and mitochondrial metabolism.[48,49] M1 macrophages primarily rely on glycolysis for rapid energy production, promoting the release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6. In contrast, alternatively activated macrophages (M2) predominantly utilize OXPHOS and fatty acid oxidation to drive anti-inflammatory responses and tissue repair.[49] In a mouse COPD model, continuous exposure to CS for three months led to enhanced macrophage glycolysis, impaired mitochondrial function, and suppressed TCA cycle activity. This disrupts the metabolic equilibrium between M1 and M2 macrophages, promoting a shift toward the M1 phenotype.[50] Secondary metabolites like succinate stabilize HIF-1α expression, further enhancing glycolytic activity and pro-inflammatory factor production, thereby perpetuating chronic pulmonary inflammation and airway remodeling.[51,52]

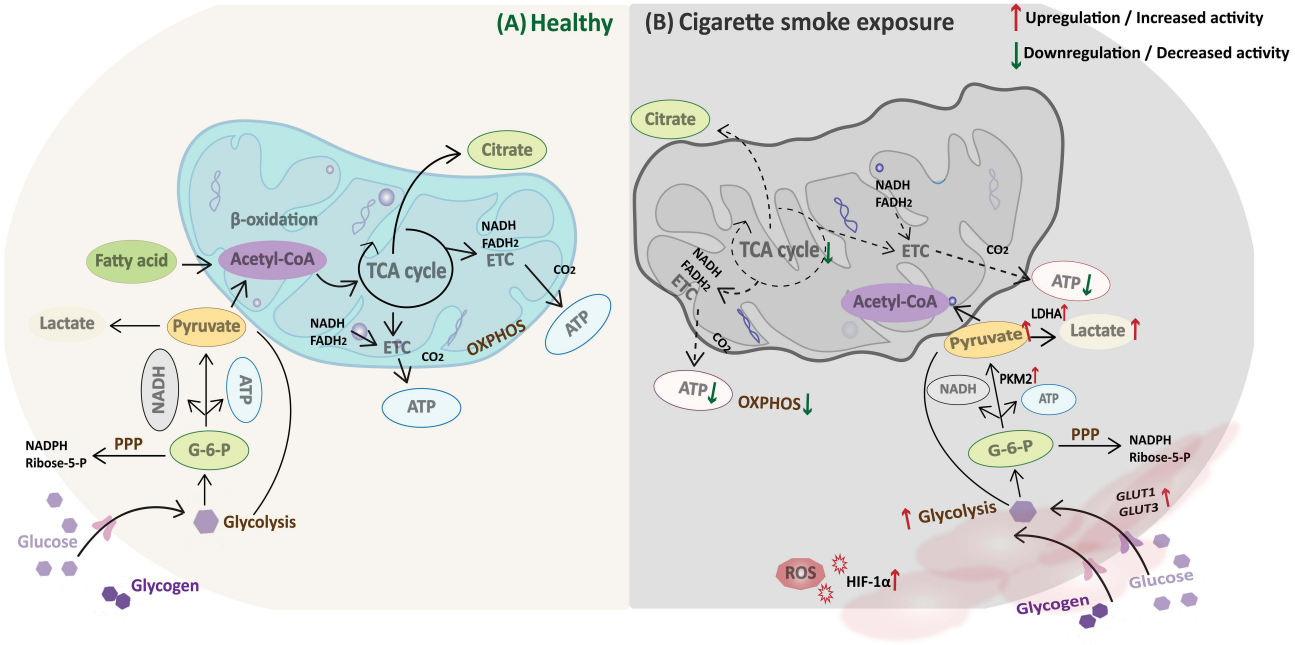

Figure 2 Altered glucose metabolism in lungs exposed to tobacco smoke.
Note: (**A**) In the healthy state, lung cells efficiently generate ATP via the glycolysis-TCA cycle-OXPHOS pathway, supplemented by the PPP to maintain metabolic homeostasis. (**B**) Under cigarette smoke exposure, GLUT1 and GLUT3 expression is upregulated and glucose uptake is increased. Activation of HIF-1α and PKM2 promotes a rise in glycolytic flux and an increase in lactic acid production, whereas TCA cycle flux and OXPHOS activity decrease. Mitochondrial dysfunction, decreased ATP production, and ROS accumulation promote a chronic inflammatory process.

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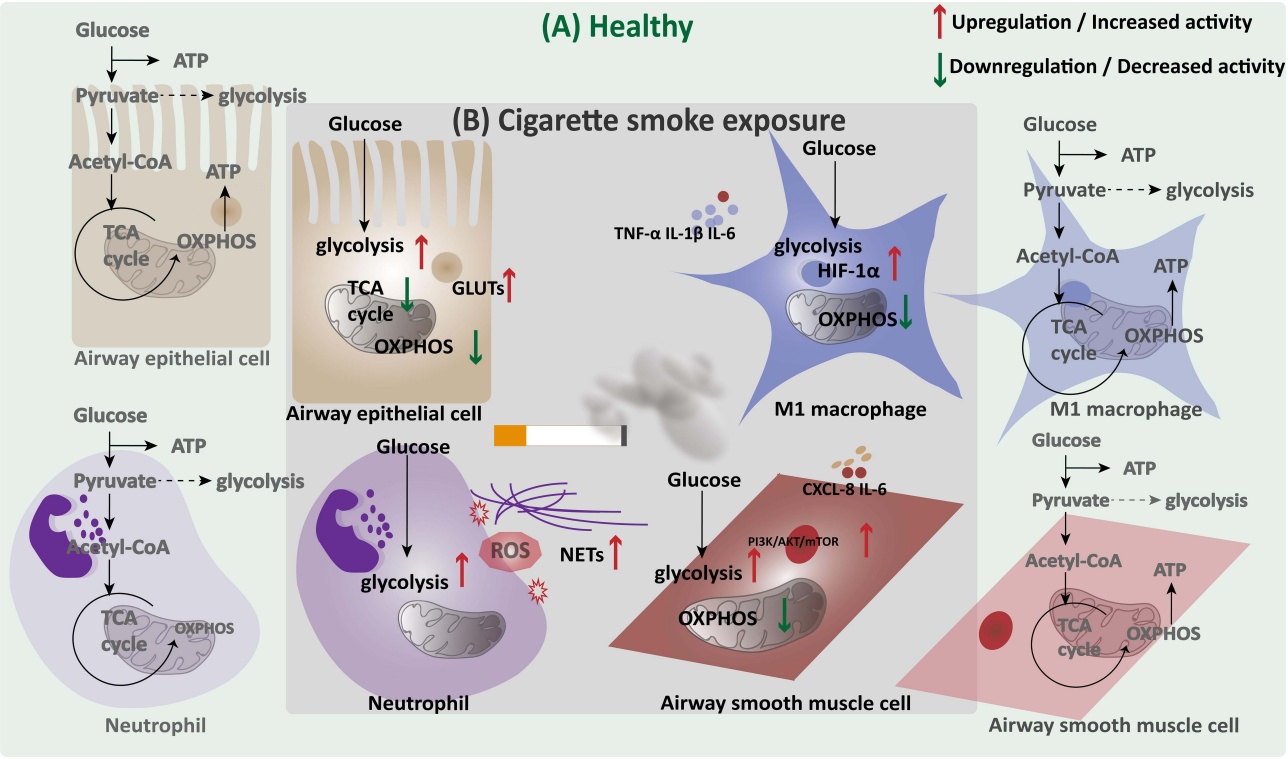

Figure 3 Cell-specific glucose metabolic reprogramming in the lung under cigarette smoke exposure.
Note: (**A**) Under normal conditions, airway epithelial cells, macrophages, neutrophils, and airway smooth muscle cells mainly utilize OXPHOS through the TCA cycle for efficient ATP generation. (**B**) Cigarette smoke exposure disrupts this balance, promoting glycolysis while suppressing mitochondrial OXPHOS in multiple lung cell types. These metabolic shifts are accompanied by increased glucose uptake and inflammatory activation in epithelial and immune cells, as well as altered energy metabolism in airway smooth muscle cells.

Under physiological conditions, neutrophils are highly dependent on glycolysis to sustain effector functions such as chemotaxis, phagocytosis, and oxygen bursts.[53] Persistent CS exposure further enhances their glycolytic activity, leading to increased release of inflammatory mediators, elevated reactive ROS production, and excessive release of extracellular trap networks. This process amplifies airway inflammation while directly exacerbating epithelial injury and mucus secretion, thereby driving disease progression.[54] Furthermore, disrupted glycogen cycling mechanisms, including gluconeogenesis, glycogen synthesis and glycogen breakdown, in COPD neutrophils may contribute to unstable energy metabolism and imbalanced inflammatory responses.[55]

Beyond immune cells, airway smooth muscle cells (ASMCs) also participate in COPD airway remodeling through glycometabolic reprogramming.[40] In COPD animal models, CS disrupts mitochondrial structure in ASMCs and activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling pathway, and leading to oxidative stress and metabolic dysfunction. The PI3K/AKT/mTOR pathway serves as a central hub regulating cellular growth, survival, and metabolism by promoting glucose uptake, stimulating glycolysis, and inhibiting autophagy.[56] This ultimately leads to elevated glycolytic activity and mitochondrial dysfunction.[57,58] Hollins et al observed upregulation of NADPH oxidase 4 (NOX4) in bronchial biopsy specimens from COPD patients. In vitro stimulation models revealed that CS exposure to COPD-derived ASMCs induces excessive ROS production, partially reversible by NOX4 inhibitors.[59] These metabolic abnormalities enhance ASMCs contractility and further drive airway hyperresponsiveness and structural remodeling by promoting the release of inflammatory mediators such as IL-6 and CXCL-8.[59] Studies also indicate that metabolic reprogramming in ASMCs is not entirely dependent on exogenous CS exposure but may reflect intrinsic metabolic abnormalities inherent to COPD.[60,61]

Overall, immune cells and structural cells form a self-amplifying inflammatory loop in COPD through metabolic-immune interactions. This loop not only sustains chronic airway inflammation but also drives tissue injury and structural remodeling. This evidence currently derived primarily from animal and in vitro studies.

Intervention Strategies for COPD Targeting Glucose Metabolism Regulation

Smoking Cessation and Glucose Reduction

Smoking cessation is the most fundamental and well-established intervention for slowing lung function decline in individuals with COPD.[62] As early as the 20th century, the Lung Health Study showed in a 5-year follow-up of 5,887 smokers with early COPD that the annual rate of decline in FEV_1 was −0.33% per year in complete quitters, significantly lower than that of intermittent smokers and continuous smokers.[63] Similar results have been obtained in subsequent studies.[64,65] In addition to reducing chronic inflammation and oxidative stress, smoking cessation may partially reverse smoking-induced disturbances in glucose metabolism. A meta-analysis involving 98,978 individuals with diabetes showed that HbA1c levels were 0.61% lower in non-smokers compared to smokers, and that HbA1c levels were similarly low among those who had quit smoking within the previous 10 years. Smoking cessation does not lead to an increase in HbA1c in the long term and may reduce the risk of vascular complications in diabetes by improving the lipid profile.[66] An observational study of 12 smokers also found a significant increase in insulin sensitivity and a decrease in fasting insulin levels immediately after 1–2 weeks of smoking cessation.[67] Together, these findings suggest that smoking cessation improves both pulmonary and metabolic health, thereby reducing COPD progression and enhancing quality of life.

Potential Therapeutic Agents Targeting Glucose Metabolism

In COPD patients with concomitant diabetes mellitus, rational glucose-lowering therapy is associated with improved prognosis. Classical hypoglycemic agents primarily consist of biguanides (eg, metformin), sulfonylureas (eg, glimepiride), glinides (eg, repaglinide), and α-glucosidase inhibitors (eg, acarbose), which exert glucose-lowering effects by inhibiting hepatic glucose output, facilitating insulin secretion, or delaying glucose absorption.[68] Novel hypoglycemic agents, on the other hand, include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and modified insulin analogs, which not only provide effective glycemic control but also confer additional benefits such as weight reduction and cardiorenal protection.[69] Specifically, DPP-4 inhibitors and GLP-1 receptor agonists enhance insulin secretion and suppress glucagon by amplifying the incretin effect. SGLT-2 inhibitors increase urinary glucose excretion by inhibiting renal glucose reabsorption.[70]

Multiple real-world studies have evaluated the role of novel antidiabetic drugs in COPD patients with concomitant diabetes. SGLT-2 inhibitors consistently demonstrate a reduction in the risk of acute exacerbations, hospitalizations, and mortality in COPD patients with diabetes, with their efficacy validated across large population studies in multiple countries.[71–73] Furthermore, retrospective cohort studies have further confirmed that SGLT-2 inhibitor use significantly reduces these risks of emergency department visits, hospitalizations, and mortality.[74,75] In contrast, GLP-1 receptor agonists offer limited benefits, while DPP-4 inhibitors show no significant improvement in most studies and even demonstrate increased acute exacerbation risk in some investigations.[71–73] A meta-analysis including nine observational studies demonstrated that, compared with sulfonylureas, SGLT-2 inhibitors were associated with a significantly reduced risk of COPD exacerbations (OR = 0.64, 95% CI: 0.52–0.79). Similarly, GLP-1 receptor agonists showed benefit (OR = 0.66, 95% CI: 0.49–0.89), whereas DPP-4 inhibitors did not provide consistent improvement.[76] However, meta-analyses of randomized controlled trials (RCTs) are still lacking for metabolic-targeted therapies in COPD and further studies are needed.[77–79]

However, it is worth noting whether glucose-lowering agents then benefit in COPD patients without diabetes? Animal models have shown that metformin inhibits epithelial sodium channel activity and significantly improves COPD-associated emphysema and lung dysfunction without adverse effects on non-pulmonary parameters.[80] However, metformin does not currently show clinical benefit in COPD patients without diabetes, and the results of a multicenter RCT that included 52 nondiabetic patients with acute exacerbations of COPD showed that metformin (up to 2 g/day for one month) failed to improve glycemia in hospitalized nondiabetic patients, and did not have a significant impact on validation metrics or clinical symptoms.[81] The primary endpoint was mean in-hospital blood glucose concentration, with secondary

Table 1 Potential Effects and Population-Specific Outcomes of Agents Targeting Glucose Metabolism in COPD Treatment

Drug	Main Mechanism	Population	Outcome	Ref
Metformin	Inhibition of mitochondrial complex I; activation of AMPK; suppression of hepatic gluconeogenesis	COPD	No significant effects on blood glucose, inflammation, or clinical recovery	Hitchings AW et al[81]
		Diabete with COPD	Reduced risk of acute exacerbations	Kimura Y et al[73]
Sulfonylurea	K_ATP channels Binding to SUR1 subunit of β-cell K_ATP channels; stimulation of insulin secretion	Diabete with COPD	Reduced mortality, cardiovascular events, invasive ventilation, and bacterial pneumonia	Yen FS et al[84]
SGLT-2 Inhibitor	Inhibition of renal SGLT-2; reduced glucose reabsorption; increased glycosuria	Diabete with COPD	Lower risk of acute exacerbations, hospitalization, and death; no mortality difference vs DPP-4 inhibitors	Pradhan R et al[71,72,75]
GLP-1 Receptor Agonist	Activation of GLP-1 receptor; glucose-dependent insulin secretion; suppression of glucagon; delayed gastric emptying	Diabete with COPD	Reduced risk of acute exacerbations; Reduced risk of exacerbations, pneumonia, oxygen dependence, and mortality; improved cardiorespiratory health	Pradhan R et al[71,73,85–87]
		Obesity with COPD	Weight loss; increased FVC, DLCO, and CAT score; no change in FEV_1 or FEV_1 /FVC	Altintas Dogan AD[88]
DPP-4 Inhibitor	Activation of GLP-1 receptor; appetite regulation; delayed gastric emptying	Diabete with COPD	No significant reduction in COPD exacerbations; poor control of acute episodes	Pradhan R et al[71,72,85]

endpoints including fructosamine, C-reactive protein, and COPD Assessment Test scores. These negative results may reflect the short exposure period, the acute disease setting, and potential confounding from comorbidities and concomitant medications such as systemic corticosteroids and inhaled bronchodilators, all of which could obscure metabolic or clinical signals. Novel hypoglycemic agents, SGLT2i and GLP1RA have also shown anti-inflammatory, antioxidant, mucus secretion reduction and airway remodeling effects in animal models, but there are no clinical studies to demonstrate their role in COPD patients without diabetes.[82,83]

In COPD management, combining smoking cessation, dietary intervention and metabolic homeostasis regulation to construct an integrated intervention strategy is expected to delay disease progression more effectively. A summary of the main glucose metabolism–targeting agents and their population-specific effects in COPD is provided in Table 1.

Conclusions and Challenges

In recent years, much attention has been paid to the role of metabolic reprogramming in the pathogenesis of COPD, and in particular, abnormalities in glucose metabolism, characterized by enhanced glycolysis and impaired OXPHOS, have been recognized as an important metabolic remodeling phenomenon driven by CS exposure. In this review, we summarize the specific alterations of glucose metabolism in different cells of the lung and how they are involved in airway remodeling, mucus secretion disturbances, immune imbalance, and structural damage in COPD by affecting cellular energy homeostasis, autophagy regulation, immune responses, and inflammatory signaling. Our review highlights that smoking-induced glucose metabolic reprogramming should not be regarded as isolated abnormalities in glycolysis, the TCA cycle, or OXPHOS. Instead, these changes converge into a pathological metabolism–inflammation–immunity axis, which serves as a central mechanism linking energy imbalance with chronic inflammation, immune

dysfunction, and structural damage in COPD. Moreover, when interpreting associations between glycemic markers or dietary indices and lung outcomes, potential confounding factors should be considered. Comorbid metabolic diseases, systemic corticosteroid use, bronchodilator therapies, as well as BMI and physical activity may all influence glucose metabolism and lung function, and could partly account for the heterogeneity across studies.

However, current research still faces several challenges. First, metabolic alterations across different COPD subtypes remain poorly characterized, highlighting the need for subtype-specific investigations. Second, although experimental studies provide strong evidence linking altered glucose metabolism to COPD pathogenesis, the causal relationship with clinical phenotypes has not been fully established, and clinical validation remains limited. Third, while some glucose-lowering agents have shown protective effects in COPD patients with comorbid diabetes, their potential application in non-diabetic COPD populations requires well-designed, large-scale randomized controlled trials. Finally, most available metabolomic data are derived from tissue samples, lacking single-cell resolution and spatial mapping. Future studies integrating multi-omics approaches, including metabolomics, transcriptomics, epigenomics, proteomics, and single-cell technologies, will be essential to build a more precise framework of "metabolic typing," capture cellular heterogeneity and individual variability, and ultimately guide personalized interventions.

Abbreviations

COPD, chronic obstructive pulmonary disease; HTP, Heat-not-burn product; FEV1, forced expiratory volume in one second; CS, cigarette smoke; PPP, pentose phosphate pathway; NADPH, nicotinamide adenine dinucleotide phosphate; TCA, tricarboxylic acid; OXPHOS, oxidative phosphorylation; GLUT-3, glucose transporter-3; EMT, epithelial–mesenchymal transition; CSE, cigarette smoke extract; OCR, oxygen consumption rate; ETC, electron transport chain; ROS, oxygen species; PKM2, pyruvate kinase M2; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1β; ASMC, airway smooth muscle cell; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; NOX4, NADPH oxidase 4; T2DM, type-2 diabetes mellitus; GLP-1, Glucagon-like peptide 1; DPP-4, Dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2; RCT, randomized controlled trial.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, design, literature search, analysis, or interpretation; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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