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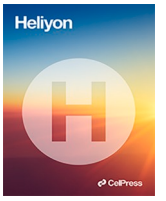

Review article

Glucocorticoids in lung cancer: Navigating the balance between immunosuppression and therapeutic efficacy

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ABSTRACT

Glucocorticoids (GCs), a class of hormones secreted by the adrenal glands, are released into the bloodstream to maintain homeostasis and modulate responses to various stressors. These hormones function by binding to the widely expressed GC receptor (GR), thereby regulating a wide range of pathophysiological processes, especially in metabolism and immunity. The role of GCs in the tumor immune microenvironment (TIME) of lung cancer (LC) has been a focal point of research. As immunosuppressive agents, GCs exert a crucial impact on the occurrence, progression, and treatment of LC. In the TIME of LC, GCs act as a constantly swinging pendulum, simultaneously offering tumor-suppressive properties while diminishing the efficacy of immune-based therapies. The present study reviews the role and mechanisms of GCs in the TIME of LC.

1. Composition and characteristics of tumor microenvironment (TME) in lung cancer (LC)

1.1. Composition of TME in LC

LC remains the leading cause of cancer mortality worldwide, with non-small cell LC (NSCLC) accounting for 80–85 % of cases, where adenocarcinoma represents the predominant pathological type [1]. Furthermore, the 5-year survival rate for patients with LC remains below 50 %. The tumor immune microenvironment (TIME) prominently influences the robustness of anti-tumor immune responses through the spatial interactions among immune cells and between immune cells and other cell types [2]. These interactions are critically linked to tumor progression and the prognosis of LC, underscoring the importance of TIME in the therapeutic landscape [3,4].

1.1.1. Role of tumor cells in TME

Tumor cells constitute the core component of the TME in LC, characterized by autonomous growth, unrestricted division, and evasion of immune surveillance [5]. LC cells can be categorized into several histological types, such as adenocarcinoma, squamous cell carcinoma, and small-cell LC [6]. These different types of tumor cells exhibit variations in gene expression, signaling pathways, and sensitivity to treatment. The tumor has been studied as a complex organ, indicating that the tumor constituents (tumor cells) are not

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inherently malignant. Instead, they require the involvement of the tumor stroma (non-tumor cells) to facilitate tumorigenesis, including continuous inflammation [7,8]. In their initial stages, tumor cells guide the formation of vasculature in the TME to recruit nutrients, cell-derived vesicles, and immune cells, thereby facilitating the development of many cancer characteristics [9,10].

1.1.2. Role of immune cells in TME

Immune cells, comprising both innate and adaptive immune cells, exert a critical regulatory influence on the TME, which is essential in the tumorigenesis, development, and treatment of tumors [11,12]. Innate immune cells mainly include dendritic cells (DCs), macrophages, and myeloid-derived suppressor cells (MDSCs) [13]. Their primary function in the TME is to recognize pathogens and tumor-associated antigens, thereby activating the adaptive immune response [14]. DCs, as essential initiators of the immune response, capture and present tumor-associated antigens to activate adaptive immune cells such as $CD8^+$ T cells [15]. Macrophages have a dual role in the TME, and they are capable of eliminating tumor cells while potentially augmenting tumor growth [16]. MDSCs, by secreting various suppressive molecules, repress the function of immune cells and affect the outcomes of tumor immune responses [17].

Adaptive immune cells primarily include $CD8^+$ T cells and regulatory T cells (Tregs) [18,19]. $CD8^+$ T cells, as the primary effector cells in the anti-tumor immune response, recognize and eliminate tumor cells [20]. However, their functional activity is notably diminished in the TME, undermining the efficacy of the immune response against tumors [21]. Meanwhile, Tregs impart immunosuppressive effects in the TME, curbing the immune response through suppressive cytokines or direct interaction with immune cells [22]. The critical involvement of Tregs in facilitating tumor immune evasion makes the reduction of Treg activity or blockade of their function a focal point of research in tumor immunotherapy [23]. In summary, the regulatory role of immune cells in the TME is indispensable, highlighting its potential as a therapeutic target in the ongoing battle against cancer.

1.1.3. Role of extracellular matrix (ECM) in TME

The ECM, another critical component of the TME, comprises various proteins such as fibronectin, elastin, and matrix metalloproteinases (MMPs) [24]. The ECM provides physical support to tumor cells and actively participates in signaling, cell migration, and angiogenesis [25,26]. In LC, abnormal expression and distribution of ECM are closely associated with tumor progression and an unfavorable prognosis [27,28]. The proteins in the ECM can be categorized into fibrillar proteins (fibronectin, collagen, laminin, and elastin) and glycosaminoglycans (chondroitin sulfate, hyaluronic acid, heparan sulfate, and keratan sulfate) [29]. Through cross-linking mechanisms, these molecules are distributed abundantly in the ECM, contributing to the formation of a net-like tissue structure crucial for providing mechanical support to tumor cells [30]. Additionally, they are implicated in intercellular communication, cell proliferation, and metastasis [31]. ECM, as a pivotal component of the TME, undergoes continuous remodeling, and ECM stiffening is a notable characteristic of tumors [32–34]. In a stiffened ECM, the deposition of collagen and hyaluronic acid leads to high solid stress within the tumor, causing vascular collapse. This condition results in insufficient perfusion of tumor tissue, inhibits immune cell infiltration, and hinders drug delivery and distribution. ECM stiffening can induce the activation of certain ion channels and cell signaling pathways, ultimately influencing tumor growth, angiogenic potential, metastatic capacities, immune escape, and resistance to therapeutic agents [35].

During tumor progression, immune cells respond to signals from the ECM. ECM stiffening inhibits the perivascular infiltration of T cells, causing them to migrate along the ECM-rich tumor capsule [36,37]. This phenomenon, observed in various cancers, such as colorectal cancer and LC, can adversely affect the immune response [38]. ECM stiffening also leads to hypoxia, induces glycolytic metabolism, creates an acidic environment, and inhibits the activation of T lymphocytes [39]. Concurrently, it increases the production of immunosuppressive mediators such as transforming growth factor-beta (TGF-β), affecting Treg differentiation, promoting abnormal angiogenesis, and diminishing the expression of cell adhesion molecules and surface glycoproteins [40]. This further impacts the infiltration of T cells [41]. Additionally, ECM components regulate macrophage polarization, with studies reporting that collagen and hyaluronic acid can drive macrophage M1 polarization *in vitro* [42,43]. Collectively, ECM modulation can enhance the effectiveness of anti-tumor therapy by regulating the TME, improving drug permeability, and enhancing the immune response, thereby providing new opportunities for the development of personalized treatment strategies.

1.1.4. Dynamics of angiogenesis in tumor progression

Angiogenesis in the tumor context is crucial for the sustained survival and proliferation of cancer cells, critically influencing their ability to grow, invade, and metastasize [44]. The TME, composed of tumor cells, adjacent cellular entities, and a milieu of secreted cytokines, orchestrates a favorable setting for oncogenic growth and survival [45]. The interplay of multiple factors in the TME imparts critical effects on shaping tumor development [46]. This review provides insights into the regulatory influence of the microenvironment on the angiogenic process in tumors. The pronounced expression of angiogenic factors and inflammatory cytokines, coupled with hypoxic environments in the TME, underscores the unfavorable effectiveness of existing anti-angiogenic medications [47]. Strategic combinations of anti-angiogenic agents with drugs targeting tumor-promoted inflammation or hypoxia may enhance therapeutic efficacy [48].

Tumor angiogenesis also affects the TME, enabling cancer cells to migrate along the walls of newly formed vessels and initiating the growth and the genesis of new tumors at specific sites [49]. Tumor angiogenesis triggers immune suppression in the TME through various mechanisms, including the repression of DC maturation and antigen presentation, recruitment of immunosuppressive cells, and suppression of cytotoxic T cell function mediated by angiogenic factors [50]. Furthermore, tumor-induced neovascularization is characterized by immature development, wherein inadequate adhesion of endothelial cells results in excessive vascular permeability, poor perfusion, and minimal amelioration of hypoxia [51]. The escalation of hypoxia in solid tumors further intensifies both tumor

growth and metastatic potential [52]. Concurrently, the TME promotes the production of numerous factors that enhance tumor angiogenesis, thereby creating a vicious cycle of malignant tumor growth [53].

1.1.5. *Role of cancer-associated fibroblasts (CAFs) in the TME*

CAFs play crucial roles in the TME, influencing tumor initiation, progression, and treatment outcomes through interactions with cancer cells, matrix components, and immune cells [54]. The interplay between CAFs and tumor cells facilitates tumor development through various pathways. On the one hand, CAFs can secrete a multitude of cytokines, growth factors, and chemokines *via* paracrine actions, thereby stimulating tumor cell proliferation, invasion, and metastasis [55]. On the other hand, CAFs can adhere to tumor cells through direct contact, influencing tumor cell growth and differentiation [56].

In the context of TME remodeling, CAFs assume a central role by secreting various proteases, such as MMPs, to degrade ECM components, thereby promoting tumor cell invasion and metastasis [57]. Additionally, CAFs can alter the structure and function of the ECM by secreting enzymes like fibrinolysins and collagenases, creating favorable conditions for tumor cell growth [58,59].

CAFs are key players in tumor angiogenesis, releasing pro-angiogenic molecules such as vascular endothelial growth factor (VEGF) to foster the development of tumor vasculature [60]. Simultaneously, CAFs interact directly with endothelial cells to promote their migration and proliferation, thus further driving tumor angiogenesis [61]. Cancer cells can evade host immune surveillance through various mechanisms to achieve immune escape [62]. CAFs play a key role in this process [63,64]. They can secrete immunosuppressive factors, such as TGF-β and prostaglandin E2 (PGE2) [65,66], which impair immune cell function and facilitate the recruitment of

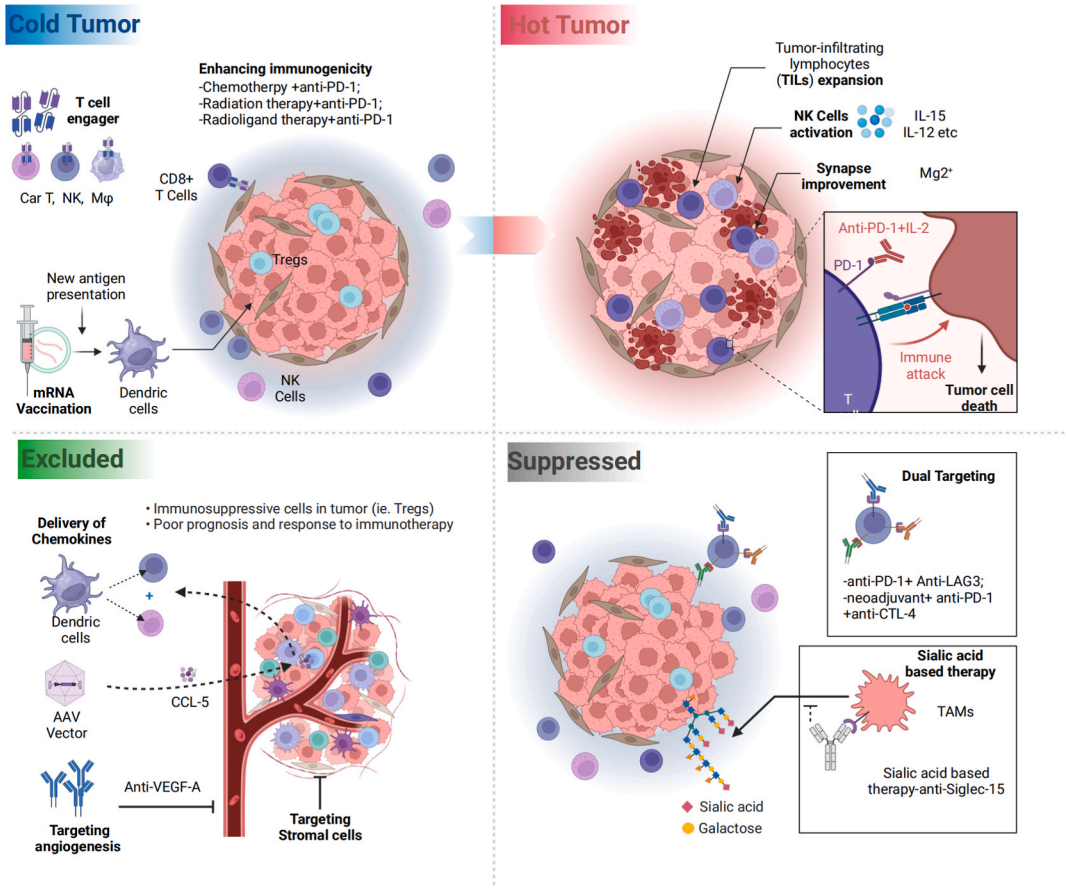

Fig. 1. Combined immunotherapy tailored to the complexity of the TME. Tumors can be broadly categorized based on the characteristics of their microenvironment into hot, cold, immunosuppressive, and excluded tumors. Hot tumors exhibit prominent features such as extensive infiltration by T cells, elevated levels of PD-L1, increased TMB, and enhanced gamma-interferon signaling. Therapeutic approaches include *ex vivo* expanded and adoptively transferred tumor-infiltrating lymphocytes (TIL-ACT) and chemotherapy. Cold tumors, characterized by scant T cell presence, low TMB, and diminished MHC and PD-L1 expression, may benefit from interventions like CAR-T therapy, radiation, and chemotherapy. Immunosuppressive tumors present with moderate T cell infiltration but are marked by a TME that hinders additional immune cell recruitment and activation. Tumor cells achieve immune escape by releasing IL-10 and TGF-β, recruiting Tregs and TAMs, with immune checkpoints such as TIGIT and LAG3 playing pivotal roles. Excluded tumors are characterized by the aggregation of T cells and other effector cells at the invasive margin, unable to effectively infiltrate into the tumor core. Tumor cells form a stromal barrier, which facilitates angiogenesis and embeds into an immunosuppressive microenvironment characterized by hypoxia and metabolic deprivation. Therapeutic strategies, including the targeting of VEGFA with specific antibodies, aim to dismantle these barriers and modulate the tumor microenvironment to restore immune surveillance and enhance anti-tumor responses.

immunosuppressive cells, thereby diminishing the effectiveness of tumor immunotherapy [67].

1.2. Combined immunotherapy tailored to TME complexity

Tumors can be broadly classified into hot, cold, immunosuppressive, and excluded phenotypes based on TME characteristics. Hot tumors exhibit pronounced T cell infiltration and PD-L1 expression, rendering them particularly responsive to PD-1/PD-L1 blockade therapies [68]. In contrast, cold tumors demonstrate diminished tumor mutational burden (TMB), limited T cell infiltration, and reduced expression levels of major histocompatibility complex (MHC) and PD-L1 [69]. Consequently, alternative therapeutic strategies such as chimeric antigen receptor T-cell (CAR-T) therapy, radiotherapy, and chemotherapy have become imperative to achieve desired treatment outcomes. Immunosuppressive tumors, characterized by a moderate number of infiltrating T cells, engage in immune evasion through the secretion of immunosuppressive molecules, including interleukin (IL)-10, TGF-β, and the recruitment of Tregs and tumor-associated macrophages (TAMs). Further, they involve the presence of immune checkpoints such as T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) and lymphocyte-activation gene 3 (LAG3) [70]. Excluded tumors feature an accumulation of T cells and other effector cells at their invasive margins, forming a natural barrier that prevents effective infiltration into the tumor mass [71,72]. Therapeutic strategies, such as anti-angiogenesis, aim to remodel the peri-tumoral microenvironment, thereby enhancing the penetration and efficacy of therapeutic interventions [73]. Details are shown in Fig. 1.

2. GC production by tumor cells and its role in immunosuppression

2.1. Immunosuppressive microenvironment formed by tumor cells

Conventionally, TME is recognized for harboring cells exhibiting immunosuppressive properties, and the resistance observed towards immune checkpoint inhibitors (ICIs) in cancer has been closely linked to this particular attribute [74–76]. Tregs, MDSCs, and M2 phenotype TAMs foster the suppression of immune responses through a cytokine network, thereby inducing immunosuppression [77]. Tregs exert their suppressive effects on T cell responses through diverse mechanisms, and their association with adverse clinical outcomes is commonly observed in individuals with LC [78]. In a recent study evaluating patients with NSCLC and those with other solid tumors, a marked increase in the proportion of PD-1^+ Tregs among patients refractory to PD-1/PD-L1 blockade therapies was observed [79]. This investigation underscores the significance of evaluating the balance of PD-1 expression between $CD8^+$ T cells and Tregs in the TME as a potentially more accurate predictor of the clinical response to ICI therapy than conventional markers such as PD-L1 expression or TMB. Although anti-PD-1/PD-L1 ICIs exhibit efficacy in reinvigorating dysfunctional PD-1^+ $CD8^+$ T cells, they also have the propensity to intensify immunosuppressive activity mediated by PD-1^+ Tregs. A prior investigation involving 73 NSCLC patients who underwent treatment with anti-PD-1/PD-L1 ICIs highlighted the significance of PD-$L1^+$ Tregs in the TME as a supplementary predictive biomarker for ICI responsiveness. Therefore, targeting Tregs presents a promising avenue for augmenting the therapeutic effectiveness of ICIs in LC [80].

MDSCs orchestrate a multifaceted immunosuppressive condition in the TME through several mechanisms: (i) the production of nitric oxide (NO) and reactive oxygen species (ROS); (ii) depletion of crucial nutrients, including L-arginine and L-tryptophan, essential for T cells; iii) disruption of T cell homing and transport; (iv) induction of checkpoint upregulation; and (v) secretion of immunoregulatory molecules such as adenosine, VEGF-α, and inhibitory cytokines (IL-10) [81]. MDSCs, similar to Tregs, express the ectonucleotidases CD39 and CD73, converting ATP to adenosine, which is considered a key mediator of immunosuppression in the TME [82]. MDSCs expressing CD39 and CD73 have been detected in tumor tissues of NSCLC patients, with their expression positively associated with disease progression [83]. However, chemotherapy interventions significantly reduce the abundance of these cells. The involvement of MDSCs in the progression of LC and resistance to ICI therapy has been extensively investigated using preclinical mouse models [84–86]. These investigations have underscored the significant role of MDSCs in promoting LC metastasis, highlighting the potential of MDSC inhibition as a strategy to circumvent resistance to ICIs.

The investigation into the impact of TAMs in an NSCLC patient cohort highlighted the presence of $CD163^+$ $CD33^+$ PD-$L1^+$ TAMs of M2 phenotype in highly progressive disease states, characterized by their epithelioid (alveolar macrophage-like) morphology and propensity to cluster within neoplastic lesions [87]. In 33 stage II–IV NSCLC patients receiving ICI therapy, low levels of $CD8^+$ PD-$L1^+$ T cells and $CD68^+$ $CD163^+$ TAMs of the M2 phenotype predicted a positive response [88]. Based on DNA-based quantitative immunofluorescence and confocal microscopy, the predominant PD-$L1^+$ cell population was identified as $CD68^+$ macrophages. In a cohort of 81 patients receiving anti-PD-1 therapy (YTMA404 cohort), an elevated presence of PD-$L1^+$ $CD68^+$ macrophages in the TME was linked to enhanced overall survival (OS) [89].

Kargl et al. identified a negative association between the abundance of neutrophils in the TME and the presence of $CD8^+$ and $CD4^+$ T cells, including Th1 and Th17 subsets, but found no correlation with Treg. This finding suggests a potential immunosuppressive function of neutrophils in NSCLC [90,91]. In preclinical investigations using IL-17:K-Ras mutant transgenic mice, the depletion of neutrophils was elucidated to eliminate resistance to PD-1 therapy, thereby restoring T cell activation [92]. The involvement of neutrophils in conferring resistance to ICI therapy in patients with NSCLC remains to be clarified.

Exploration of the tumor immunosuppressive microenvironment is pivotal for elucidating tumor immune evasion mechanisms and identifying novel targets for immunotherapeutic interventions. Treatments aimed at modulating the tumor immunosuppressive microenvironment, including ICIs and CAR-T therapy, have shown remarkable clinical success [93]. Nonetheless, the inherent complexity of the tumor immunosuppressive landscape continues to pose significant challenges for the development of targeted therapies, particularly in terms of enhancing treatment efficacy and minimizing adverse effects [94].

2.2. GC production by tumor cells and its immunomodulatory effects

GCs, hormones synthesized by the adrenal glands, are released into the bloodstream to maintain homeostasis and regulate the body's response to various stressors [95,96]. These hormones exert their effects through interaction with the GC receptor (GR), which is ubiquitously expressed across various cell types, thereby influencing a broad spectrum of pathophysiological pathways with pronounced impacts on metabolism and immunity [97]. The suppressive effect of GCs on T cell functionality is well established [98,99]. For instance, the deletion of the GR in T cells infected with *Toxoplasma gondii* leads to extensive cytokine secretion, resulting in the death of the mice [100]. GCs not only suppress the antigen presentation and cytokine secretion functions of DCs but also curtail the differentiation of helper T cells and compromise T cell function [101]. Recent studies have also demonstrated that GCs suppress immunity by affecting the function of Tregs [102].

Adrenal cells can process cholesterol into GCs through a novel synthetic pathway involving various mitochondrial and microsomal enzymes [103]. P450c11β (encoded by *Cyp11b1*) is the final enzyme in this conversion process, capable of transforming steroid precursors into active GCs (cortisol in humans, corticosterone in mice) [104]. GCs are metabolized in the kidneys and colon into inactive forms—cortisone in humans and dehydrocorticosterone (DHC) in mice—by 11βHSD2 (encoded by *Hsd11b2*) [105]. These inactive metabolites are transported *via* the bloodstream and can be converted back into active GCs under the influence of 11βHSD1 (encoded by *Hsd11b1*) through a recycling pathway [106]. 11βHSD1 is predominantly expressed in the liver but is also present in adipose tissues, the brain, and lymphoid organs [107]. In addition to the adrenal glands, other organs can synthesize GCs, especially in sites prone to immune activation, such as the thymus, intestines, and skin [108]. Compared with systemic administration of GCs, its local synthesis and secretion not only suppress immunity but also avoid the side effects associated with systemic administration [109]. Local synthesis often occurs in cells that are highly proliferative and mutation-prone. Therefore, it is plausible that tumor cells themselves may synthesize GCs, thereby suppressing the anti-tumor immunity of immune cells [110].

3. Mechanistic pathways of GC action in tumor cells

The intricate molecular mechanisms underlying the actions of GCs constitute a critical foundation for refining their clinical applications [111]. These mechanisms can be categorized into genomic and non-genomic pathways, where the classic genomic mechanism involves mediation by cytoplasmic GC receptor α (cGCRα) [112]. The non-genomic mechanisms encompass three types [113]: (i) cGCR-mediated non-genomic mechanisms; (ii) specific non-genomic mechanisms, such as physicochemical interactions with the plasma membrane at elevated GC concentrations; and (iii) membrane GCR-mediated mechanisms.

3.1. Canonical cGCR-mediated genomic mechanism

The cGCR is a complex multiprotein structure in the majority of cells in the body [114]. This receptor complex comprises various heat shock proteins (Hsps), such as Hsp40, Hsp70, Hsp90, and Hsp56 [115]. Additionally, the cGCR interacts with immunophilins, co-chaperones such as p23 and Src, and kinases involved in the mitogen-activated protein kinase (MAPK) pathway [116]. GCs, belonging to a group of glucocorticosteroids (GCSs) characterized by their lipophilic nature, enable easy diffusion across cell membranes [117]. Upon binding to the cGCR, GCs initiate the activation of the GC-cGCR, which in turn coordinates gene transcription [118]. Concurrently, chaperone proteins associated with the cGCR undergo translocation into the cytoplasm. Following a 20-min binding, the activated GC-cGCR complex is transported to the nucleus, where its binding to distinct DNA sites modulates processes of transcription and translation in the nucleus [119]. Certain genes are upregulated to enhance the production of anti-inflammatory proteins, whereas the expression of genes responsible for generating pro-inflammatory mediators is suppressed, leading to immunosuppressive effects [120]. However, GCSs typically take several hours or days to diffuse to the cell membrane, bind to cGCRs, transport the resulting GC-cGCR complex to the nucleus, interact with target gene promoter regions, and initiate transcription and translation processes leading to protein synthesis [121]. Hence, the rapid manifestation of anti-inflammatory and anti-allergic effects elicited by GCSs cannot be solely attributed to the conventional genomic mechanism.

3.2. Non-genomic mechanisms of GCSs

The rapid anti-inflammatory and immunosuppressive reactions elicited by GCSs can be attributed to three principal non-genomic pathways [122,123]: (i) Non-specific interactions between GCSs and the cell membrane. Elevated concentrations of GCSs can directly permeate the cell membrane, modifying the physicochemical properties and activities of membrane-bound proteins. This alteration results in diminished calcium and sodium transport across the membranes of immune cells, facilitating rapid immunosuppression. (ii) Non-genomic actions orchestrated by the cGCR. The unbound cGCR engages in a complex interplay involving ligands like Src, Hsps, and signaling molecules. Upon GC binding, these constituents are released, eliciting immediate immunosuppressive effects. (iii) Non-genomic effects mediated by membrane-bound GCR (mGCR). mGCR is present on the surface of immune cells, and upon binding with GCs, it leads to the rapid onset of non-genomic immunomodulatory effects.

3.3. Impact of GCSs on the immune system responses

The activation of T cell functions by ICIs can lead to a series of inflammatory adverse events, the precise pathophysiological mechanisms of which are not fully understood [124]. Current understanding suggests that immune-related adverse events (irAEs) may

arise through various pathways involving autoreactive T cells, autoantibodies, and cytokines [125]. ICIs are thought to cause abnormal activation of T lymphocytes, with irAEs primarily resulting from the immune attack by these activated T lymphocytes, as substantiated through pathological biopsies in myocarditis, pneumonitis, skin toxicity, and other types of irAEs [126]. Consequently, GCSs are considered a first-line treatment option [127,128]. GCSs possess anti-inflammatory and immunosuppressive properties, capable of mitigating the damage caused by immune attacks and alleviating symptoms associated with irAEs [129].

GCs, pivotal in mediating anti-inflammatory and immunosuppressive responses, are classified into endogenous and exogenous categories, each playing a vital role in physiological and therapeutic contexts [130]. Endogenously produced GCs provide basal anti-inflammatory effects, with an escalated secretion in response to inflammatory challenges [131]. Hence, animals and humans with adrenal insufficiency demonstrate amplified responses to minor injuries post-adrenalectomy [132,133]. This observation has prompted speculation regarding the potential role of insufficient GC secretion in response to trauma or infection in the pathogenesis of select chronic inflammatory disorders [134,135]. Exogenously administered GCs demonstrate remarkable efficacy as anti-inflammatory agents to impede the functions of both the innate and adaptive immune systems [136]. Both endogenously produced and externally administered GCs exhibit effectiveness in addressing inflammatory responses [137]. They can attenuate nearly all manifestations of inflammation, regardless of whether they are triggered by invading pathogens, chemical or physical agents, or aberrant immune reactions such as hypersensitivity or autoimmune conditions [138]. GCs are more effective in restricting the initiation and progression of immune responses when used prophylactically to inhibit transplant rejection than in preventing already initiated clonal proliferation responses [139,140]. They can also alter gene expression, given the capacity of GCs to modulate the expression of numerous genes, influencing approximately 1 % of the total genome. With the pattern and extent of GC-mediated gene expression varying between tissues and even at different stages of the disease, their impact is significant and wide-ranging [141–143].

GCSs target several primary and secondary inflammatory cells, dampening the activation, proliferation, differentiation, and viability of diverse inflammatory cell subsets, including T lymphocytes and macrophages [144]. Furthermore, GCSs facilitate apoptosis through the modulation of cytokine production, particularly triggering apoptosis in immature and activated T lymphocytes [145]. They do not induce a notable acute alteration in the count of circulating B lymphocytes, and no studies have offered evidence

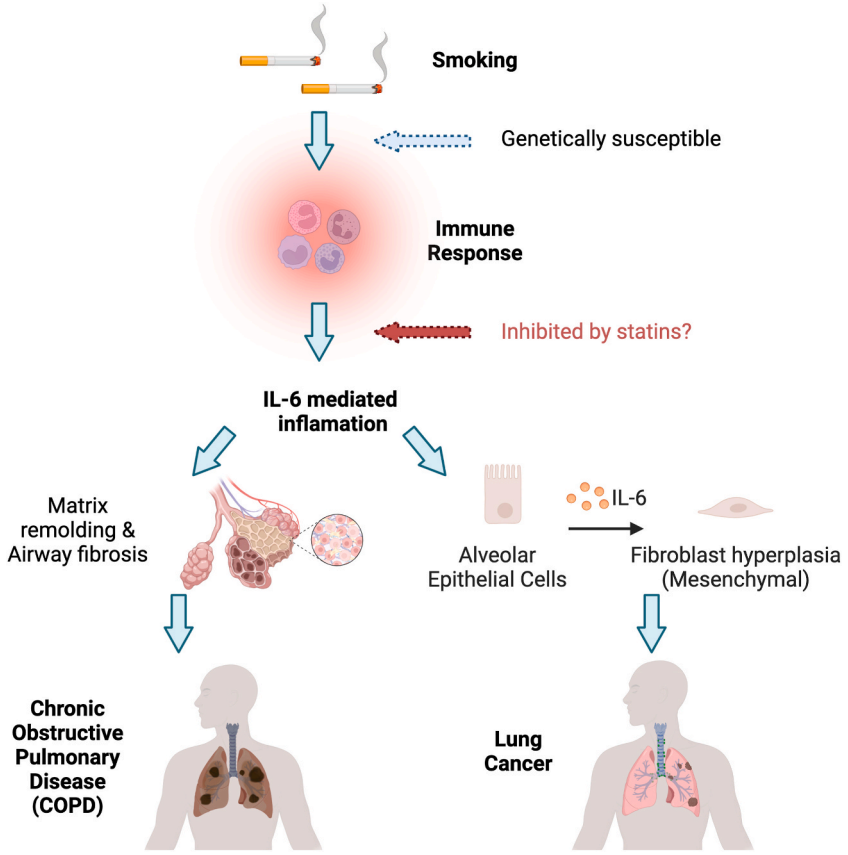

Fig. 2. Pathophysiological links between smoking, genetic susceptibility, immune response, and the development of COPD and LC. The link between COPD and LC is intricately connected, with both conditions occurring in aging lungs. Moreover, oxidative stress can serve as a common trigger for both. Each cigarette contains approximately 10^{15} free radicals, including reactive nitrogen and oxygen species (RNOS), which can cause tumor proliferation through DNA damage and lead to COPD through inflammation. Additionally, COPD and LC share several pathological factors, such as telomere shortening, genetic susceptibility, and epigenetics.

indicating any impact of GCSs on IgM levels [146,147]. GCSs exhibit a slight capacity to induce neutrophil activation. Furthermore, GCSs can curb the generation of adhesion molecules to diminish endothelial cell adhesion and lower vascular permeability, thus reducing inflammatory exudation [148]. Supraphysiological concentrations of GCSs demonstrate the capacity to restrain fibroblast proliferation and attenuate the production of IL-1 and tumor necrosis factor (TNF)-α, demonstrating their effective anti-inflammatory action [149]. The effects on inflammatory cells include: (i) reducing the number of neutrophils in the blood, lowering the activation of neutrophils, macrophages, and mast cells, which is secondary to the inhibition of cell adhesion molecule and cytokine gene transcription [150]; (ii) lowering the overall activation rate of helper T (Th) cells, reducing T cell clonal proliferation, and initiating the transition from Th1-type immune response to Th2-type immune response [151]; (iii) reducing the functionality of fibroblasts, decreasing the production of collagen and glycosaminoglycans, and in some cases, reducing healing and repair capabilities [152].

The effects of GCSs on mediators of inflammation and immune responses include: (i) reducing the production of prostaglandin compounds by decreasing the expression of cyclooxygenase II and inhibiting the release of arachidonic acid substrates [153]; (ii) decreasing the production of numerous cytokines, including TNF-α, cell adhesion molecules, IL-1, IL-3, IL-2, IL-4, IL-6, IL-5, IL-8, and granulocyte-macrophage colony-stimulating factor, largely secondary to the inhibition of gene transcription [154]; (iii) lowering the concentration of complement components in plasma [155]; (iv) reducing the production of NO by inducing the production of nitric oxide synthase 2 (NOS2) isoforms [156]; (v) decreasing the release of histamine and other mediators from basophils and mast cells [157]; (vi) reducing the production of immunoglobulin G (IgG) [158]; (vii) increasing the synthesis of anti-inflammatory factors such as IL-10, IL-1 soluble receptor, and clusterin [159]; (viii) endogenous GCs entering the bloodstream increase in quantity during inflammation and stress events [160], playing a crucial regulatory role in preventing excessive activation of inflammation and other potent defense responses, which, if left uncontrolled, may lead to a state of dysregulation in the organism [161].

4. Association between chronic obstructive pulmonary disease (COPD) and LC

4.1. Interrelated pathogenesis of COPD and LC

Globally, COPD and LC are prominent contributors to high morbidity and mortality in chronic respiratory diseases [162]. In 2016, COPD ranked as the fifth most prevalent cause of mortality in China, with projections anticipating its elevation to the third leading cause of death by 2030 [163]. LC remains the primary cause of cancer-related deaths, imposing significant social and economic burdens [164,165]. A correlation exists between COPD and LC, sharing common risk factors such as smoking, environmental exposure, and occupational hazards, along with similar pathogenesis mechanisms, including chronic inflammation, oxidative stress, and lung aging [166,167]. The precise mechanisms by which COPD transitions to LC remain unclear, but evidence suggests that chronic inflammation, epigenetic modifications, genetic susceptibility, and environmental factors play a role in this transformation [168]. Smokers with COPD have up to a fivefold higher risk of developing LC than those with other lung diseases [169]. COPD is a significant risk factor for LC, regardless of smoking status. Lung inflammation and pulmonary matrix remodeling may serve as crucial precursors to the development of LC [170–172]. Details are shown in Fig. 2.

In addition to shared etiological factors, LC and COPD demonstrate concordance in genetic vulnerability beyond the scope of tobacco-induced pathologies [173]. The exploration of genome-wide association studies (GWAS) focusing on lung function and LC has revealed numerous common loci, suggesting a shared genetic basis between susceptibility to COPD and LC in smokers [174]. Epithelial-mesenchymal transition (EMT) is a common pathological characteristic of both COPD and LC, alongside inflammatory processes [175]. Notably, the rs7326277TT genotype in VEGFR1 potentiates these pathways and tumor progression, presenting as a susceptibility locus for both diseases [176].

Compared with smokers with normal pulmonary function, individuals with mild to moderate COPD face a threefold increase in the risk of developing LC within a decade [177]. This risk increases tenfold in those with severe COPD [178]. The inflammatory environment associated with COPD is implicated in this elevated cancer risk [179]. Chronic inflammation in COPD can lead to persistent mitosis, increasing the likelihood of endogenous DNA damage mutating into cancerous changes [180]. Chronic inflammation caused by airway obstruction may play a critical role in lung carcinogenesis and could be a significant component of the field cancerization effect. In COPD, chronic inflammation within the airways, particularly in the small airways, is characterized by an accumulation of macrophages, $CD4^+$ and $CD8^+$ T cells, DCs, and neutrophils. Chronic inflammation in the lower airways is hypothesized to induce carcinogenesis, with inflammatory mediators in these microenvironments strengthening bronchioalveolar stem cells and inducing pro-tumorigenic mutations, proliferation, resistance to apoptosis, angiogenesis, invasion, metastasis, and the secretion of immunosuppressive factors [181].

4.2. Impact of COPD on LC prognosis

In addition to their close association with the pathogenesis, COPD influences the prognosis of LC. In a study involving 105,304 LC patients, the presence of COPD was independently associated with poorer survival. In another retrospective study involving 902 stage IA–IB NSCLC patients, those with COPD had a 5-year OS of 54.4 %, significantly lower than the 69.0 % in patients without COPD. The 5-year progression-free survival (PFS) in patients with COPD was 50.1 % compared with 60.6 % in those without COPD [182]. Furthermore, the severity of COPD affects the incidence of LC. In a longitudinal follow-up study of 5402 COPD patients over 22 years, the presence of moderate to severe COPD increased the risk of developing LC by 2.8 times [183].

4.3. Impact of COPD on LC treatment outcomes

COPD affects the management of LC. Generally, assessing lung function preoperatively using forced expiratory volume in 1 s (FEV1) and diffusing capacity for carbon monoxide (DLCO) is necessary. Recent guidelines recommend cardiopulmonary exercise testing to calculate surgical risk if predicted postoperative (PPO) FEV1 and/or PPO DLCO are less than 30 % of the predicted value. This categorizes patients with severe COPD (preoperative FEV1 $<$ 50 % predicted) as high-risk, often contraindicating surgery in many cases [184].

In a real-world study in China, clinical outcomes were compared between LC patients who did and did not receive regular COPD treatment. Results showed no significant difference in the objective response rate (ORR) and disease control rate (DCR) between the two groups. However, patients receiving regular COPD treatment had significantly longer PFS and OS, suggesting that standard management of COPD in NSCLC patients can extend OS and PFS [185].

Regarding prevention, inhaled GCs (ICSs) may be an effective measure. A 2021 meta-analysis reviewed studies published between 1974 and 2020 on the association between ICS use and LC risk, ultimately including ten studies with 234,920 patients. The analysis showed that ICS use could reduce the risk of LC in COPD patients. It could also decrease the risk of LC in asthma patients as well as in patients with both COPD and asthma [186].

4.4. Screening and early diagnosis of LC in COPD patients

Despite the intricate connections between COPD and LC in terms of pathogenesis, prognosis, prevention, and treatment, the diagnosis and management of COPD among LC patients in China face significant challenges [187]. A retrospective analysis of 703 LC patients who underwent comprehensive pulmonary function testing revealed that approximately 92.5 % of pre-surgical patients met the diagnostic criteria for COPD, with a similar percentage of 92.7 % among those undergoing surgery. In contrast, only three cases (0.43 %) were diagnosed with COPD and received standardized treatment prior to hospitalization, and merely five cases (0.7 %) were diagnosed upon discharge. This finding indicates a lack of sufficient attention to COPD in LC patients within clinical practice.

Globally, tools have been developed to screen for high-risk LC patients among those with COPD. Regression analysis identified independent correlations with LC diagnosis, including age $>$60 years, BMI $<$25 kg/m^2, smoking pack-years $>$60, and DLCO $<$60 %. The COPD-LUCSS-DLCO tool can assess LC risk in COPD patients, categorizing them into low risk (0–3 points) and high risk. High-risk patients have a 2.4 times higher risk of dying from LC than low-risk patients [188].

Therefore, recognizing the LC risk within the COPD patient cohort underscores the imperative for vigilant screening and preventive measures. Beyond the shared etiological contributors, the management of COPD, including the strategic use of high-dose inhaled corticosteroids, confers a pivotal role in mitigating LC risk. This advocates for an integrated approach to patient care that addresses both the pulmonary and oncological dimensions of COPD and LC.

4.5. Association between ICSs and LC risk in patients with COPD

Research has established a link of systemic inflammation to the frequent exacerbations and higher mortality rates in patients with COPD [189]. ICSs are non-specific anti-inflammatory medications widely used in the clinical management of COPD to alleviate severe symptoms, reduce acute exacerbations, improve pulmonary function, and enhance patient quality of life. Studies suggest that chronic inflammation associated with COPD may lead to changes in the bronchial epithelium, potentially initiating LC [190]. Consequently, the association between ICS use and LC risk has been observed, indicating that ICS may serve a chemopreventive role against LC. However, current clinical guidelines have yet to provide recommendations on this matter, and some studies have found no association between ICS use and reduced LC risk [191].

Preliminary explorations into the chemopreventive role of ICSs against LC have been conducted in animal models and clinical trials, though the mechanisms remain unclear [192]. Mahmood et al. found that the precursor to malignant tumors, type III EMT, is active in the airways of COPD patients, but this change can be mitigated through ICS treatment [193]. Thus, ICSs may inhibit the chronic inflammatory process in the airways of COPD patients by suppressing the activation of airway epithelial cells and EMT, thereby preventing the onset of LC. However, these findings require further confirmatory studies for validation [194].

5. Impact of GC use on the efficacy of ICIs in advanced NSCLC

GCs, a class of hormones with anti-inflammatory, anti-allergic, and anti-shock properties, are utilized in the anti-tumor treatment of certain cancers and are widely used to prevent and alleviate the adverse reactions of chemotherapy drugs [195]. High-dose GC use affects the effectiveness of immunotherapy [196]. This condition is attributed to the mechanism that high-dose GCs suppress the activation, proliferation, and function of immune cells (such as T cells, NK cells, and DCs), thereby reducing the capacity of the immune system to attack tumor cells [197]. Additionally, high-dose GCs increase the levels of PD-L1 expression on tumor cells (a molecule that can bind to PD-1 and inhibit T cell responses), thereby increasing tumor cell resistance to ICIs (such as PD-1/PD-L1 inhibitors) [198, 199]. Several clinical trials have confirmed the detrimental impact of high-dose GC use on the efficacy of immunotherapy. An analysis of data from 640 LC patients who received immunotherapy between 2011 and 2017 found that the median OS of 90 patients using $\geq$10 mg of prednisone (a commonly used oral or intravenous synthetic potent steroid) was significantly shorter than that of those using $<$10 mg of prednisone or not using prednisone at all [200]. Another retrospective analysis of 196 NSCLC patients treated with ICIs found that patients using high-dose GCs ($>$10 mg of prednisone equivalent) to alleviate cancer-related symptoms experienced significantly

lower OS and PFS than those who did not use GCs or used low-dose GCs (≤10 mg of prednisone equivalent) [201]. These findings indicate that high-dose GC use may reduce the effectiveness of immunotherapy in LC patients.

Patients undergoing immunotherapy may experience side effects, and GCs, a type of steroid, can be used to treat these side effects [202]. GCs are commonly used to modulate immune responses in asthma, Crohn's disease, and even COVID-19 [203]. In a recent study, researchers from the Cold Spring Harbor Laboratory (CSHL) in the United States may have come closer to elucidating how GCs could indirectly contribute to the failure of some immunotherapies [204]. Their study suggests that GCs may stimulate the production of a protein called cystatin C (CyC), and higher levels of CyC are associated with poorer outcomes in this type of therapy.

The immunosuppressive nature of GCs, particularly pivotal for managing ICI-induced irAEs, necessitates their cautious application in the treatment of advanced NSCLC [205]. Patients with advanced NSCLC may require GCs to control related clinical symptoms such as dyspnea, pulmonary infections, and palliative care [206]. A retrospective analysis by Fucà et al., encompassing 151 NSCLC patients treated with ICI, found that GCs increased the risk of PFS by 80 % [207]. Petrelli et al.demonstrated that patients taking steroids had increased risks of OS and PFS compared with those not taking steroids [208]. Moreover, they revealed that steroids used for brain metastases and supportive care were adverse factors for OS but not when used for treating irAEs [209]. This finding may be attributed to the subgroup of patients receiving palliative care with corticosteroids inherently having a poorer overall prognosis. The adverse effects of corticosteroids are significant only when treating tumor-related palliative indications and are not associated with poor prognosis when used for non-tumor-related conditions, such as autoimmune diseases, exacerbations of COPD, and preventing allergic reactions. In the KEYNOTE-407 study, adding pembrolizumab to a platinum-based chemotherapy regimen improved OS in squamous NSCLC patients, regardless of whether paclitaxel requiring steroid premedication for allergy prevention or albumin-bound paclitaxel not requiring premedication was used. In the treatment of NSCLC patients with ICI, the use of steroid hormones to control symptoms caused by the tumor itself requires caution [210].

6. Research on reshaping the TME

Reshaping the TIME is a critical strategy for enhancing the efficacy of immunotherapy. The transformation of the TME through existing strategies, as well as the discovery of new ones, is essential for developing immunotherapies that can adapt to the complexities of the TME [211]. Enhancing the efficacy of cancer immunotherapy is a central focus of current and future research endeavors, with the anticipation of novel pharmacological discoveries. GCs are pivotal hormones in regulating immune responses, playing a key role in the development, differentiation, activation, and inflammatory responses of immune cells [212]. However, their misapplication poses a risk of fostering immunosuppression and tumor development, rendering the study of the influence of GCs on the immune microenvironment highly relevant.

On the one hand, GCs can influence immune responses by regulating the functions of DCs and T cells [213]. Studies have shown that GCs enhance the maturation and antigen-presenting ability of DCs while inhibiting the activation and proliferation of T cells [214–216]. This regulatory action helps maintain immune homeostasis but may also lead to immunosuppression and tumor progression. Therefore, a comprehensive understanding of the regulatory mechanisms of GCs on immune cells can offer new strategies for cancer immunotherapy. On the other hand, GCs regulate tumor progression by influencing the TME [217]. Elevated levels of GCs in the TME may promote the proliferation, invasion, and metastasis of tumor cells. Research indicates that GCs can promote the growth and survival of tumor cells by activating signaling pathways such as PI3K/Akt and MAPK/ERK. Therefore, reducing GC levels or inhibiting their associated signaling pathways may help suppress tumor progression and enhance the effects of immunotherapy [218].

The TNF superfamily comprises molecules pivotal to the orchestration and efficacy of both innate and adaptive immune responses, making many members of this family targets for drug development in tumor immunotherapy and anti-inflammatory medication [219]. The GC-induced TNF receptor family-related protein (GITR) is an immune checkpoint molecule involved in the regulation of T cell responses [220]. The phenomenon that the single structural domain of GITR mediates its binding with ligands suggests that this unique mode of action may represent an ancient binding pattern in the evolution of the TNF/TNFR superfamily [221,222]. In contrast, other TNFR superfamily members have evolved to bind with ligands through two distinct structural domains for specificity and high affinity [223]. Activating monoclonal antibodies targeting GITR have shown good drug tolerance and significant tumor-suppressive activity in clinical studies, providing a crucial theoretical basis for understanding T cell immune regulation mechanisms and drug development based on immune checkpoint molecules [224,225].

Collectively, the study of the role of GCs in modulating the immune microenvironment holds promise for innovating cancer immunotherapy strategies and methodologies. Future research should delve deeper into the regulatory mechanisms of GCs on immune and tumor cells and investigate how intervening in the actions of GCs can enhance the effectiveness of immunotherapy. Concurrently, considering individual differences and drug side effects, there is a need for cautious use of related drugs in clinical practice, along with strengthened monitoring of drug efficacy and management of adverse reactions.

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CRediT authorship contribution statement

Wenhui Xu: Writing – original draft. **Jinghong Ye:** Writing – original draft. **Zhendong Cao:** Conceptualization. **Yupei Zhao:** Validation. **Yimin Zhu:** Writing – review & editing. **Lei Li:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Lei Li reports financial support was provided by Jiangsu Province Traditional Chinese Medicine Science and Technology Development Project. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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