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Review article:

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF) IN INFLAMMATORY LUNG DISEASES: PATHOGENIC CONTRIBUTOR AND THERAPEUTIC TARGET

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ABSTRACT

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an integral pathogenic factor in inflammatory lung pathologies including asthma, COPD, and lung cancer. As a pro-inflammatory cytokine, GM-CSF triggers the division and stimulation of granulocytes and macrophages, exacerbating the inflammatory response and promoting lung tissue damage. GM-CSF is an essential factor in promoting the production of the corresponding cytokines, levelling the effect of local activity by stimulating the infiltration of immune cells and maintaining chronic inflammation. Therefore, its neutralization in many ways leads to the cessation of the progression and exacerbation of inflammation in the lungs of patients with corresponding pathologies. Inhibitory therapy associated with GM-CSF reduces the number of immune cells and activates them at the inflammatory focus. The use of neutralizing antibodies to treat an acute inflammatory process is promising because they relatively quickly neutralize the effect of pathogenic GM-CSF. However, the immunocyte response can also be inhibited at the level of formation. Therapy with GM-CSF inhibitors can significantly reduce acute inflammation but can lead to adverse changes in the innate immunity of the patient. This review highlights GM-CSF's dual function of GM-CSF as a pathogenic contributor and possible treatment targets.

Keywords: Granulocyte-macrophage colony-stimulating factor, asthma, COPD, lung cancer, inflammation

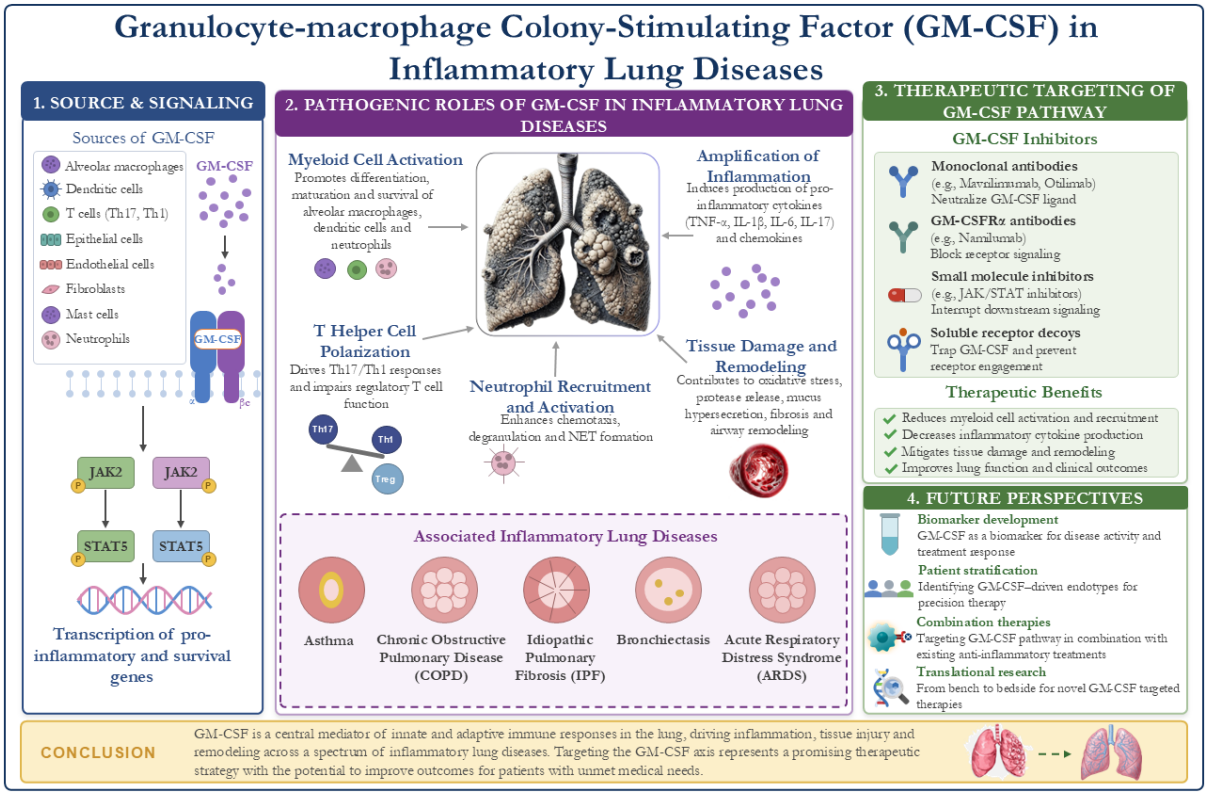

Figure 1: Graphical abstract

INTRODUCTION

Inflammatory lung diseases (ILDs) comprise a broad category of respiratory ailments characterized by chronic inflammation and significant morbidity, including altered pulmonary function and environmental burden (Bhat et al., 2024a). Asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis are notable due to their frequency, influence on quality of life (QoL), and associated healthcare expenditure (Roth, 2014). Asthma is a prevalent chronic respiratory illness characterized by airway inflammation that leads to signs of chest tightness, coughing, shortness of breath, and wheezing (Bhat et al., 2024f). Symptoms are provoked by various environmental factors, including allergens, tobacco smoke, cold air, and exercise (Thapa et al., 2023a). Inflammation causes the airways to be extra sensitive, narrowing them

and causing the mucous cells to produce more mucus (Holgate and Thomas, 2017). Asthma may affect people of any age, although it is more frequent in young people. The worldwide asthma burden is high, with 341 million people affected as of 2016, causing approximately 417,918 deaths annually (Song et al., 2022). Despite the availability of many treatments, asthma's chronic nature and the necessity for treatment, such as trigger avoidance, inhaler medicines, and steroid usage during exacerbations, take a heavy toll on the patient's QoL (Thapa et al., 2023b). COPD is a group of lung conditions, including emphysema and chronic bronchitis, characterized by long-term poor airflow and inflammation, which causes an irreversible reduction in the ability to breathe out (Falk et al., 2008). The common signs and symptoms of COPD include breathing difficulties, cough, mucus production, and wheezing (Bozinovski et al., 2002, Vlahos et al., 2010). The most common risk factor is long-term exposure to irritating gases or particulate matter, most commonly from tobacco smoking (Dean, 2017). The disease also increases the chances of getting heart disease, lung cancer, and other related illness (Brenner et al., 2017). COPD affects over 251 million people globally and is the third-leading cause of fatality, claiming over 3 million lives each year (Morgan et al., 2018). Although it can be slowed, it cannot be reversed, and treatment only attempts to reduce the symptoms and maintain the patient's QoL. Pulmonary fibrosis is a collection of lung illnesses affecting the development of scar tissue in the lungs, leading to severe and irreversible tissue damage over time (Yu and Tang, 2022). Scarring reduces flexibility and stiffens the tissue, preventing oxygen from passing into the bloodstream (Broide and Firestein, 1991, Bry et al., 1997). The common symptoms of pulmonary fibrosis include dry cough that does not go away, fatigue, weight loss, aching limbs, muscle pain, and progressive shortness of breath (Shenshen et al., 2023). Several types of pulmonary fibrosis exist, and the cause may be idiopathic or linked to environmental influences, medications, and other illnesses (Buergin et al., 2023). Even with medications that might slow disease progression, this disease usually has a grim future (Gandhi et al., 2023). It often affects life expectancy, with many patients requiring oxygen therapy or lung transplantation. The crux of the matter is that the impact of ILDs, including asthma, COPD, and pulmonary fibrosis, affects both the overall health of the individual patient and the broader healthcare system and society (Timofte et al., 2020). These disorders frequently result in decreased physical activity, long-term illness and disability, frequent hospital admissions, and high medical costs. Furthermore, they may complicate and worsen the management of other chronic health conditions, resulting in a vicious cycle of poor health (Booth et al., 2012).

Significance of GM-CSF in inflammatory lung diseases

The importance of GM-CSF in ILDs lies in several factors. GM-CSF is a crucial cytokine that regulates granulocyte and macrophage populations in the immune system and is a critical mediator of immune responses and inflammation (Ushach and Zlotnik, 2016). Understanding GM-CSF function and its part in asthma, COPD, and pulmonary fibrosis may help advance new approaches to positively affect patients suffering from these diseases (Thapa et al., 2024b). Myeloid cells, including granulocytes and macrophages, rely on GM-CSF for their survival, proliferation, and function (Choi et al., 2008). They are also essential for the initiation and persistence of inflammation (Chen et al., 2023b). All these lung diseases involve complicated immune-mediated pathways in which these cells play a pivotal role. Asthma and COPD typically feature GM-CSF overexpression, which is likely to influence their pathogenesis (Barnes, 2008). GM-CSF not only recruits immune cells into the lungs but also improves their activity and maintains a proinflammatory profile (Corkill et al., 2021, Cowburn et al., 2011). This cytokine is also known to participate in the proliferation and differentiation of different cells involved in airway remodelling, a typical sign of all chronic ILDs (Lee et al., 2020b). Studying GM-CSF could reveal how abnormalities in its signalling contribute to disease progression

(Thapa et al., 2023c). It represents a promising pharmacological target, as inhibiting GM-CSF or its receptor may stop excessive immune cells from converting the recruited and activated patterns in the inflammation spots (Nicol et al., 2018). The current scope of anti-GM-CSF monoclonal antibodies (mAbs) and receptor inhibitors has demonstrated excellent efficiency in clinical trials. Peripheral blood or biopsy GM-CSF levels can be utilized to assess inflammatory activity (Lang et al., 2020). Increased serum or lung concentrations may correlate with aggravated inflammation or predict exacerbation; therefore, it would be useful for patient management and follow-up. The goal of this review article is to integrate modern information on GM-CSF functions in the pathogenesis of ILD, focusing on asthma, COPD, and pulmonary fibrosis, and to survey its pharmacological potential.

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

Structure of GM-CSF

GM-CSF is a cytokine that is a critical regulator of the immune system, triggering the generation and function of granulocytes and macrophages (Rao et al., 2023, Sen et al., 2024b). GM-CSF contributes to various inflammatory and autoimmune diseases and is clinically used in the management of neutropenia (Bagley et al., 1995). GM-CSF is a monomeric glycoprotein that typically consists of a single polypeptide chain (Crotti et al., 2017). The mature human GM-CSF peptide is estimated to be 127 amino acids long and weighs approximately 14-35 kDa, varying depending on different levels of glycosylation (Benmerzoug et al., 2018). The primary structure is the essential sequence of amino acids linked together by peptide bonds. This primary sequence is responsible for its biological activity and specificity (Dhagat et al., 2018). This sequence can be slightly manipulated in various species, affecting the potential and characteristics of the transferred sequence. The secondary structure is generally composed of α-helices and loops (Dougan et al., 2019). It normally consists of four alpha circular peptides called α-helices, labelled A, B, C, and D, and organized in an up-up-down-down topology (Hansen et al., 2008).

In humans, GM-CSF is mainly a monomer; however, dimerization or even higher oligomeric length constructions can occur (Robertson, 2007). Human sequences are typically glycosylated at different asparagine residues within the polypeptide chain (Louis et al., 2020). This affects the stability, activity, and interaction of the molecule with the reinforcing terminal receptor. The tertiary arrangement is mainly a whole polypeptide chain, but potential non-reduced and reduced isoforms with disulfide bridges exist (Miyajima, 1992). This configuration is produced because GM-CSF is synthesized on the ribosome and packets its helices in a more compact globular arrangement (Monfardini et al., 2002). Quaternary arrangement-specific configurations are created by monomers, dimers, and possibly tetramers, with minimal activity (Murphy and Young, 2006).

Function of GM-CSF

GM-CSF is a critical cytokine with diverse functions, mainly related to immune/inflammatory response regulation (Thapa et al., 2024a). GM-CSF plays a role in hematopoiesis by stimulating precursor cell differentiation and proliferation into GM-containing lineage cells, comprising granulocytes and macrophages (Becher et al., 2016). This plays a role in normal immune system function and during and after bone marrow suppression, such as in the treatment of cancer with agents that suppress bone marrow production (Cuevas et al., 2022, De Alessandris et al., 2019). GM-CSF also enhances the activity of mature leukocytes (Chen et al., 2023b). It increases neutrophil activity, including phagocytic extent and ROS formation. It also increases the activities of mature macrophages in forming reactive oxygen species, phagocytic extent, and cell-killing capacity (Gschwend et al., 2021). In addition, GM-CSF triggers the release of

other pro-inflammatory mediators (IL-6 and 1), leading to increased phagocytic activity and other macrophage activities, such as immune antigen-presenting cell activity, which in turn results in the stimulation of adaptive immunity (Hamilton and Anderson, 2004). GM-CSF is also responsible for initiating and maintaining inflammatory responses. When macrophages and neutrophils, the two granulocytes, are stimulated by GM-CSF, they produce other pro-inflammatory cytokines and chemokines, stimulating an inflammatory response (Kumar et al., 2022). GM-CSF is also critical for lung tissue because it helps maintain the function of alveolar macrophages, which are essential for clearing surfactant and other debris in the alveoli, thereby homogeneously maintaining the lung (Lellahi et al., 2022). In addition, GM-CSF enhances the immune system's ability to clear fungal infections; when macrophages and dendritic cells (DCs) are stimulated by GM-CSF, the result is a functionally more active cell with increased phagocytic homogeneity, reduced cell killing time homogeneity, and improved pathogen antigen presentation homogeneity (Mehta et al., 2015). However, GM-CSF has disadvantages in that when overproduced or abnormally expressed in the body, it alters normal body function, leading to inflammatory and autoimmune diseases (Zhan et al., 2019). Overexpression of GM-CSF is a leading cause of Alzheimer's disease, whereas under expression of GM-CSF causes pulmonary alveolar proteinosis in certain fungal and viral infections. This was followed by the development of GM-CSF inhibitor therapies, which reduce protein expression (Zhan et al., 2012).

Cellular sources and targets

GM-CSF is a restricted cytokine that predominantly regulates the function and development of immune cells (Singla et al., 2023). GM-CSF and its production and target cells are limited within diverse tissues and cell types; however, the cytokine's presence and activity are crucial for immune responses and hematopoiesis (Barzin et al., 2023). This cytokine is released by various cells, mainly following immune stimulation. T lymphocytes and natural killer cells are the dominant GM-CSF producers, especially when activated by antigens, cytokines, or additional stimulatory signals (Deng et al., 2018). B cells and monocytes/macrophages also produce GM-CSF following activating stimuli; unlike T and NK cells, they are quickly activated, resulting in cytokine secretion (Delaney et al., 2021, Du et al., 2022). Monocytes-macrophages releases GM-CSF in response to inflammatory factor from pathogens or injury (Gomez-Cabrera et al., 2012). Endothelial cells (ECs) can also release GM-CSF in response to inflammatory signals, where they function not only to modulate the immune responses of emerging cells but also to alter the immune conditions of vascular tissues (Harrell et al., 2019). Fibroblasts within connective tissues can also secrete GM-CSF, especially in response to inflammatory stimuli (Higashi et al., 2017). Epithelial cell types, predominantly within the gastrointestinal and respiratory tracts, rapidly produce GM-CSF upon microbial invasion or other irritative stimuli (Kisseleva and Brenner, 2021).

GM-CSF's main targets are cells of the myeloid lineage, thus affecting their growth and functional activation (Saini et al., 2024, Sen et al., 2024a). GM-CSF is an important factor promoting the differentiation and proliferation of granulocytes and macrophages from hematopoietic progenitor cells in the bone marrow (Mushahary et al., 2018). GM-CSF binds to the surface molecule GM-CSF receptor, which is found on cells such as these. GM-CSF promotes the development and maturation of DCs, which are required for antigen presentation and initiation of adaptive immune responses (Quaglino et al., 2020). It influences their differentiation from progenitor cells and enhances their ability to process and present antigens (Taubmann et al., 2024). In addition to being sources for GM-CSF, although relatively weak compared to their activity as cells, ECs also respond to GM-CSF in a cell-autonomous or paracrine role that influences vascular repair processes and the inflammatory response (Walker and McKenzie, 2018). By affecting all of these cell types, GM-CSF regulates a variety of immune functions

that range from individual cells within the bone marrow to immune regulation (Rosas et al., 2007). Therefore, it is active in immune surveillance of health as well as inflammatory and autoimmune diseases, where GM-CSF directly influences disease progression and therapeutic outcomes (Xiang et al., 2023).

Physiological roles in the immune system and lung homeostasis

GM-CSF, which was also identified in this reaction, is significant for the body's immune system and homeostasis. It links typical immunity traits to lung function (Amor et al., 2020). It is pivotal in enhancing the growth, living, and adjustment of certain blood cells, including neutrophils and macrophages, which are crucial in protecting the system from infections (Cheng et al., 2017). GM-CSF ensures an ideal immune reaction by increasing the development of myeloid germ cells in the bone marrow into neutrophils, eosinophils, basophils, and macrophages (Elpa et al., 2021). It also enhances the germ-killing abilities of the cells through functions such as intake, digestion, and oxidization in the destructive prompting of oxygen elements (Faith et al., 2008, Foster et al., 2008). The dangers do not end with innate immunity. GM-CSF also enhances adaptive immunity (Hou et al., 2021). It is vital for the survival and adjustment of DCs, which accumulate antigens and respond to T-cell promotion (Liu et al., 2023b). Proper DC adjustments aid in initiating and modulating the adaptive immune reaction more quickly, so that the body can prevent immediate infections or foster a stable memory by producing memory T-cells (Sattler, 2017).

In the lungs, GM-CSF offers a critical role in preserving pulmonary homeostasis and supporting robust immune responses (Rawat et al., 2023). Growth factors are required for the normal function of alveolar macrophages, which are responsible for clearing pathogens and any alveolar space material, including apoptotic cells and debris (Siddiqui et al., 2023). More significantly, GM-CSF controls the production and secretion of surfactant proteins by alveolar macrophages (Franken et al., 2022). Surfactants are key to decreasing alveolar surface tension and preventing lung collapse (Szappanos et al., 2018). Pulmonary alveolar proteinosis occurs in GM-CSF knockout mice, showing that GM-CSF deficiency or dysfunction leads to lung collapse. GM-CSF also boosts the lung's ability to defend itself against immune infections (Tojo et al., 2014). This factor is upregulated during respiratory infections to enhance the capacity of lung macrophages and other lung immune cells to launch robust immune responses, thus protecting the lungs from infection and inflammation (Wiese et al., 2023). The immune fucntion of GM-CSF in the lung is interconnected with the growth factor's ability to control surfactant production, indicating that alveolar macrophage function is dependent on GM-CSF (Trapnell and Whitsett, 2002). Therefore, GM-CSF can be modified to boost the capacity of macrophages to defend the lungs against pathogens. This clinical implication underscores the treatment potential of GM-CSF in immune and pulmonary diseases (McCormick et al., 2021).

GM-CSF is protective in that it helps maintain alveolar macrophage maturation and surfactant clearance; however, GM-CSF deficiency or its functional neutralization can lead to pulmonary alveolar proteinosis, whereas overproduction or chronic GM-CSF signaling can result in myeloid cell activation and tissue injury in ILD (Trapnell and Whitsett, 2002).

Genetic and epigenetic regulation of GM-CSF in inflammatory lung disease

The level of GM-CSF expression can vary between individuals, and genetic variability can explain these differences, thus modulating the magnitude of GM-CSF expression. The asthma-associated coding variant CSF2 rs25882 (Ile117Thr) is differentially expressed, with the asthma risk allele being associated with a 27.4 % increase in CSF2 mRNA, offering a functional link between genotype and increased GM-CSF output (Burkhardt et al., 2012). Candidate-gene analyses of variation in CSF2 have also been linked to lung function phenotypes in smokers with

COPD; however, the results are population-specific and have yet to be validated for clinical application (He et al., 2008). Thus, genetic effects seem to modulate susceptibility or disease severity but not the presence of a single GM-CSF-driven endotype.

There is a second layer of regulation on top of that: epigenetic and post-transcriptional. Basal histone acetylation and BRG1-containing SWI/SNF chromatin remodeling are required for transcriptional competence at the GM-CSF promoter, and promoter CpG methylation can turn off transcription following chromatin remodeling, suggesting that DNA methylation and nucleosome remodeling are used at different steps in immune cells (Brettingham-Moore et al., 2008). miR-223-3p targets and downregulates pro-inflammatory GM-CSF and CXCL8 secretion and is a negative-feedback regulator of cigarette smoke-induced inflammation, but is less effective in COPD-derived epithelial cells (Roffel et al., 2021). Genetic variation, chromatin state, DNA methylation, and miRNA-based regulation may together regulate the strength and duration of GM-CSF signaling, which in turn affects the survival of myeloid cells, priming of DCs, eosinophilic and neutrophilic inflammation, and airway remodeling (Figure 2). They represent good biomarker candidates but still need to be validated in future in pre-specified asthma, COPD, fibrosis, and lung cancer endotypes.

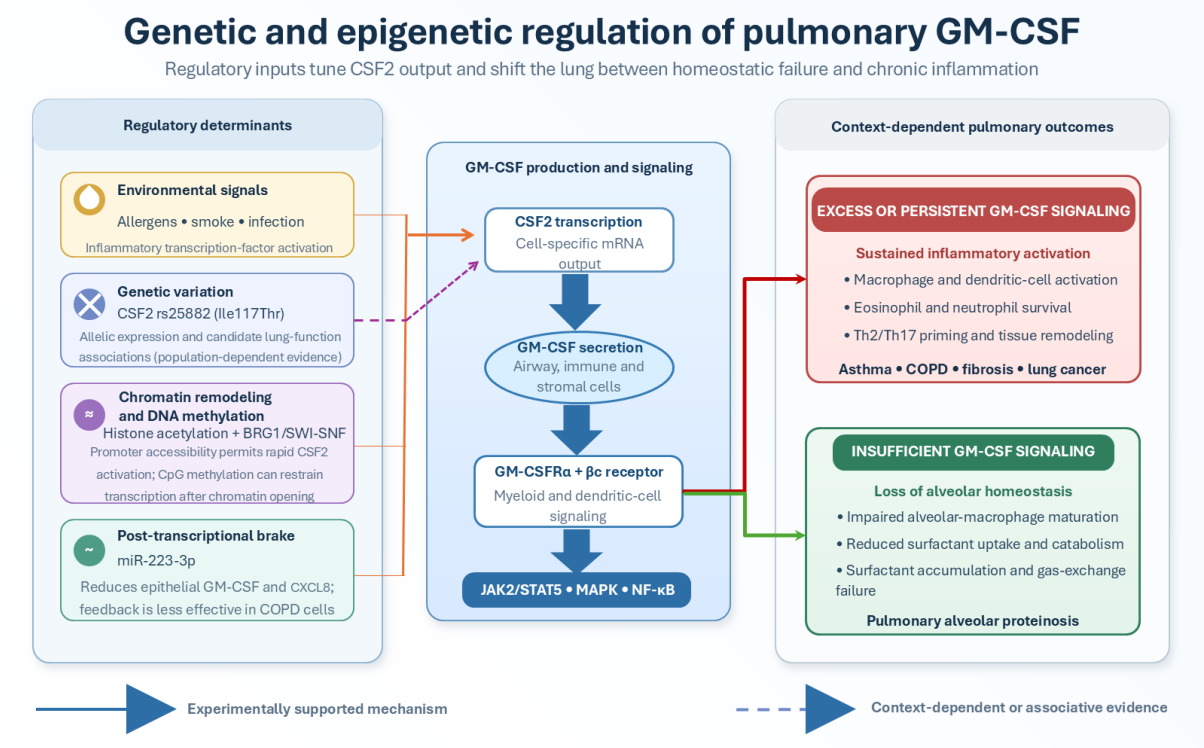

Figure 2: This diagram shows the production of GM-CSF by alveolar macrophages in response to TSLP via STAT5 activation. E3 ubiquitin ligase AMFR ubiquitinates CIS for K48-linked proteasomal degradation, leading to the removal of CIS-mediated inhibition of STAT5 phosphorylation and increased downstream GM-CSF production, where earlier it was referred to as 'AMFG', which is incorrect.

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IN ASTHMA

Role of GM-CSF in asthma pathogenesis

The proinflammatory role of GM-CSF is highly relevant to asthma pathogenesis. GM-CSF concentrations are increased in asthma, promoting airway hyper-responsiveness and inflammation (Patel et al., 2024). It further recruits and activates eosinophils and neutrophils, thereby

worsening airway inflammation and damage (Abdullah, 2021). Additionally, GM-CSF promotes the proliferation and differentiation of DCs necessary for Th activation. These cells further stimulate a Th2-focused bundle, perpetuating ongoing inflammation (Bhattacharya et al., 2015). These immune pathways are largely influenced by this cytokine, illustrating its value in disease pathogenesis and justifying its use as a treatment target (Jiang et al., 2022). Saha et al. somewhat validated this perspective by examining the expression of this cytokine in individuals with asthma and COPD. The results indicated that GM-CSF levels were higher in individuals with severe asthma and all COPD phases than in controls, with GM-CSF levels correlating with sputum eosinophilia in individuals with asthma. These findings suggest a mediating role in disease pathogenesis, particularly in severe asthma (Saha et al., 2009). The DC-T-cell inflammatory circuit is vital for initiating and securing the immune response. This circuit is particularly crucial during inflammation. DCs are antigen-presenting cells (Kelly et al., 2022). They navigate the body and scavenge tissues to sense and consume pathogens. They collect and eat pathogens and transport processed antigen fragments to lymphatic lymphocytes (Hirayama et al., 2017). Antigen uptake induces DCs development, guiding them to migrate to the lymph base (Fujiwara et al., 2021). Several modifications of the levels of surface molecules and production of pro-inflammatory mediators guide the cell on the path to follow (Castenmiller et al., 2021). Nobs et al. examined the function of GM-CSF, which is uncommon in chronic asthma pathophysiology, via a DCs-T cell inflammatory pathway. The study indicates that GM-CSF, which is vital for controlling diverse cell functions in the lung, is necessary for neutrophil mobilization throughout chronic illness. These outcomes show GM-CSF as a potential novel target for the care of chronic inflamed lung illnesses (Nobs et al., 2021).

IL-5 is a cytokine contribute in the growth and differentiation of eosinophils, which are white blood cells crucial in the immune response to allergic and parasitic reactions. Various cell types produce this cytokine (Tao et al., 2022). Its sources are T helper 2 cells, mast cells, and eosinophils. IL-5 increases the activation, survival, and recruitment of eosinophils to inflammatory endpoints (Gevaert et al., 2022). Gibson et al., studied the expression of the IL-5 and GM-CSF gene in bronchoalveolar cells in chronic cough sufferers in comparison to patients with asthma. According to the results, it appears that increased expression of these cytokines is corelated with airway inflammation and chronic cough, similar to allergic asthma. The resulting data indicate the possibility of rejecting the null hypothesis; IL-5 and GM-CSF expression was observed in patients with corticosteroid-responsive chronic cough and was absent in non-responsive cases (Gibson et al., 1998). BAL lymphocytes are lymphocytes aspirated from the lung's bronchoalveolar space during a BAL procedure (Gajewska et al., 2003). Bronchoalveolar lavage is performed by advancing a bronchoscope through the mouth or nose into the lungs and then washing the bronchial and alveolar surfaces of a lung segment with saline (Davidson et al., 2020). The resultant fluid contains cells and other materials from the lower respiratory tract. As mentioned in the introduction, BAL lymphocyte analysis is a diagnostic tool for a wide range of pulmonary diseases, including infections, interstitial lung diseases, and malignancies (Harbeck, 1998). Broide et al. studied to identify the cellular sources of GM-CSF in asthmatics post-endobronchial allergen challenge using in situ hybridization and immunoassays. Their data suggest that exposure to the allergen increases the production of GM-CSF, primarily from BAL lymphocytes and secondarily from alveolar macrophages. The correlation with eosinophilic infiltration in the airway confirms that GM-CSF is a mediator of the inflammatory response in asthma (Broide and Firestein, 1991).

The autocrine motility factor receptor (AMFR), also known as gp78, is a multifunctional protein that serves as a receptor for autocrine motility factor (AMF) (Gauldie et al., 1993, Goncalves and Eze, 2023). AMF is a cytokine responsible for cell motility, affecting processes (Nabi et al., 1992). AMFR is a type II transmembrane protein of the ER membrane that acts as

an E3 ubiquitin ligase. Ubiquitin ligase function is vital to the ER-associated degradation pathway, as it controls protein quality (Joshi et al., 2017). This process is used to degrade misfolded and improperly assembled proteins. AMFR is expressed at relatively high levels in various cancer types and is often associated with higher invasiveness and poor prognosis (Gonzalez-Juarrero et al., 2005). Additionally, there is growing proof that it can be used as a potential target for treatment (Chen et al., 2017). Zhang et al. have recently showed that GM-CSF release by alveolar macrophages is promoted by AMFR, which is ultimately responsible for inducing allergic asthma development. This is consistent with the results showing allergic responses and inflammation. Thus, targeting AMFR has not been attempted previously and may offer a new pathway to improve health conditions (Zhang et al., 2022a). IL-3 is a pleiotropic cytokine composed mainly of activated T cells, although to a lesser degree, mast cells and eosinophils. It offers a vital part in hematopoiesis and helps stem cell growth and differentiation into various blood cells (Fujita et al., 2022). IL-3 promotes granulocyte-macrophage differentiation and megakaryocyte-erythrocyte development (Hamaguchi et al., 2024); thus, IL-3 signals via a receptor composed of an IL-3Rα subunit, expressing hematopoietic progenitors (Hercus et al., 2009). IL-3R binding strengthens several signalling pathways that support cell survival, enhance cell cycling, and promote differentiation (Hamilton, 2008, Hansbro et al., 2011). Systemic mucosal immune system functions are important in asthma, particularly those of basophils and eosinophils (Athari, 2019). Wallaert et al. researched the characteristics of IL-3, IL-5, and GM-CSF immunoreactivity by the intestinal mucosa in bronchial asthma patients. They found a more substantial rise in the number of IELs and blasts/eosinophils and reported mononuclear cell accumulation in the lamina propria in both asthmatics and atopic controls. These cytokines were detected in the eosinophils of the nose, and many mast cells were recognized individually. Thus, the author clearly indicates the systemic mucosal immune system manifestation of asthmatic mucus beyond the respiratory system (Wallaert et al., 1995). IL-2 has marked clinical relevance, IL-2 has been clinically translated for the cure of certain cancers, in which IL-2 has been administered to boost the immune system's ability to target and kill cancerous cells (Wrangle et al., 2018). IL-2 involvement in Treg function and maintenance has led to IL-2 trials for autoimmune diseases and post-transplant immunosuppression, which often administer IL-2 at low doses to allow the selective expansion of Tregs over effector T cells (Harris et al., 2023). In 1988, Nakamura et al. demonstrated increased GM-CSF production by peripheral blood mononuclear cells from individuals with asthma, especially when stimulated with IL-2. They found that GM-CSF production is elevated in asthma and is downregulated by glucocorticoids in both clinical and in vivo asthma, supporting its critical role in disease pathogenesis (Nakamura et al., 1993) (Figure 3).

Mechanisms through which GM-CSF modulates eosinophil and T-cell function in asthma

GM-CSF is an essential cytokine in the pathophysiology of asthma and is specifically responsible for modulating eosinophils and T-cells (Hercus et al., 2009, Holgate et al., 2009). It is produced by airway epithelial cells, ECs, and T cells of the lungs and is produced in increased amounts after exposure to allergenic stimuli (Kazakov et al., 2024). Eosinophils are dependent on GM-CSF as a survival factor, and its presence in the environment of asthmatic airways should have otherwise led to their death (Holgate, 2000). Therefore, this cytokine suppresses apoptosis in T cells while promoting increased activation (Macchia et al., 2023). The infiltration of eosinophils into asthmatic airways is followed by their increased activation (Holgate et al., 2019). This process involves the induction of adhesion properties within the tissues, apportioning of MBP- and EPX-containing granules, and release of leukotrienes (Shi et al., 1997). In T cells, GM-CSF contributed to the differentiation and resultant maintenance of Th2 cells in

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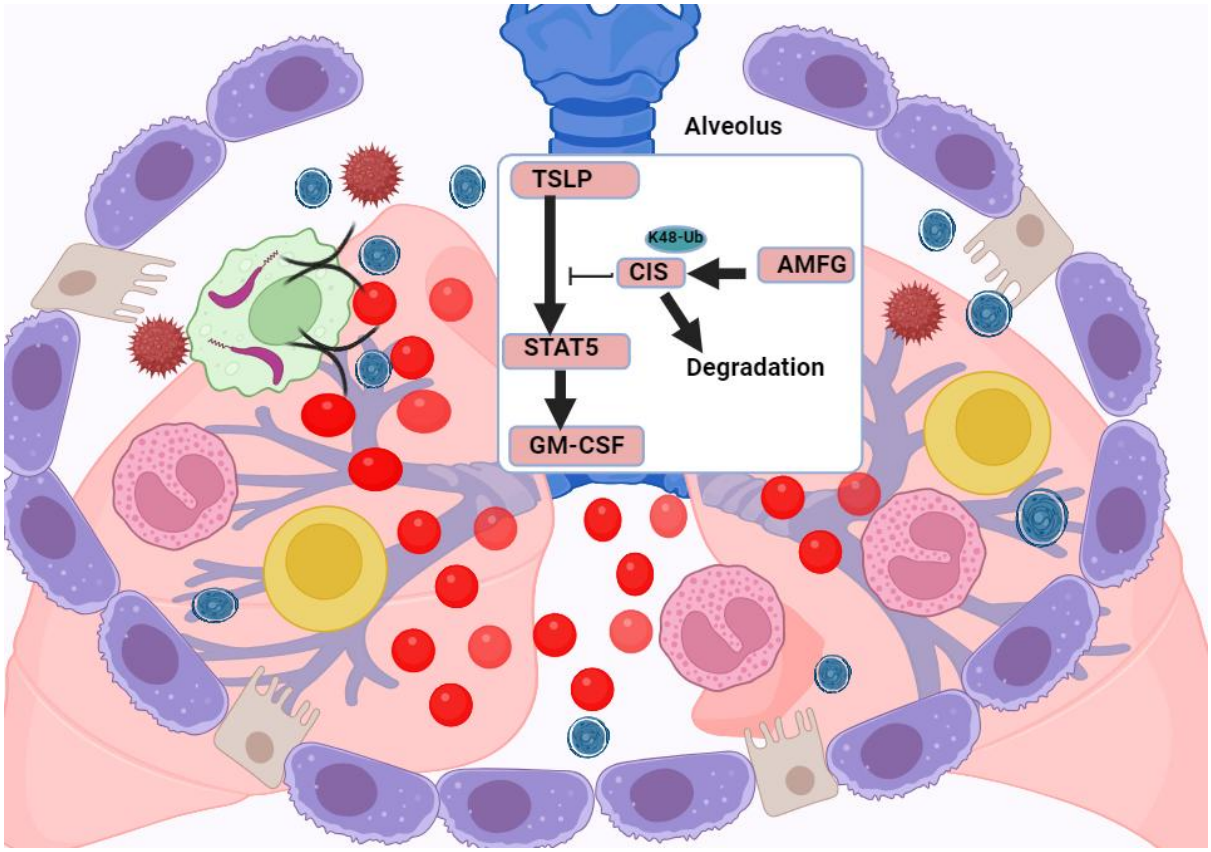

Figure 3: This diagram displays the molecular signalling within the alveolus, highlighting the pathway from TSLP (thymic stromal lymphopoietin) stimulation to GM-CSF (Granulocyte-macrophage colony-stimulating factor) production, mediated by STAT5 activation. It also shows the regulation of this pathway by CIS (Cytokine-inducible SH2-containing protein) and AMFG, which promote degradation via K48-linked ubiquitination, thus controlling the intensity of the immune response in the alveolar environment.

asthma. Functionally, it corresponds to the role of secreting and enhancing the survival and logistical migration of IL-5, IL-9, and IL-4 secreting cells (Shiomi and Usui, 2015). It is responsible for airway amplification. This is based on the fact that it permits T cells to interact and engage other leukocytes within the asthmatic airways (Lloyd and Hessel, 2010). Kamei et al. formulated a study that linked Dermatophagoides farinae-induced and intrinsic T-cell expression. The expression of IL-5 and GM-CSF by T-cells and eosinophil activity corresponds to the contribution to the pathogenesis of asthma (Kamei et al., 1993). CD4+ T cells, also called helper T cells, are a type of WBCs that are centrally involved in immunity (Hui et al., 2018, Mombaerts et al., 1992). CD4+ T cells bear the CD4 receptor on the surface of their plasma membranes, which helps them recognize antigens from the MHC class II complex (Hamieh et al., 2023). Lai et al. examined gene expression of IL-3 and GM-CSF in circulating CD4+ T cells in acute severe asthma. They also discovered that IL-3 expression was substantially increased and decreased after steroid therapy. BEC activity and its enhanced expression of particular pro-inflammatory mediators due to these evaluated cytokines and stimulants indicate a role for them in acute florid episodes such as asthma (Lai et al., 1996).

Cytokine-inducible SH2-containing protein (CIS) is a suppressor of the cytokine signalling family member SOCS1 (Ilmarinen and Kankaanranta, 2014, Itoh et al., 1998). The CIS gene Cgene CISH is encoded and is part of the negative regulation mechanism of cytokine signalling

in immune homeostasis and excessive inflammatory responses (Yoshimura et al., 2018). CIS is an SH2 domain-containing protein that binds to phosphorylated tyrosine residues on various cytokine receptors (Itoh et al., 1990). Once bound, the primary mechanism of most CIS actions is to interfere with the subsequent transcription pathways of these cytokines (Morris et al., 2018). This may be due to the direct binding of CIS to the receptor or binding to a signalling intermediate, preventing further signal transduction (Sunshine and Iruela-Arispe, 2017). Zhang et al. examined the function of the autocrine motility factor receptor in allergic asthma. They specifically examined the impact of receptors on alveolar macrophages. Their results suggested that AMFR is increased in asthma and promotes inflammation by interacting with the cuer1 total/CIS binding protein, increasing GM-CSF production, and exacerbating T helper 2 and eosinophil inflammation in asthma. Consequently, the authors regard the AMFR receptor as a beneficial treatment target for asthma (Zhang et al., 2022b). Atopic asthma is a form of asthma often associated with hypersensitivity reactions to environmental allergens (Ali, 2011). According to Woolley et al., asthma is a chronic inflammatory airway disease. It is a chronic disorder in which exposure to a certain allergen triggers an immune response and causes asthma symptoms. This type of asthma is usually a part of the atopic syndrome, which also includes diseases, including allergic rhinitis or hay fever and atopic dermatitis or eczema. Woolley et al. studied the function of eosinophils and GM-CSF in atopic allergen-dependent mild asthma. They compared the number of activated eosinophils and GM-CSF levels in asthmatic and non-asthmatic patients. The results revealed spiked numbers of both activated eosinophils and GM-CSF levels in individuals with asthma, which were also closely correlated with airway responsiveness. These outcomes shows that GM-CSF-regulated eosinophils are closely involved in airway dysfunction in mild asthma (Woolley et al., 1994).

Eosinophils are white blood cells that are not considered extremely proliferative once they mature and exit the bone marrow (Jansen et al., 2024, John et al., 1998). Nevertheless, studying eosinophil proliferation during development and factors influencing their survival in tissues elucidates information regarding conditions in which eosinophilia occurs (Rosenberg et al., 2013). Patients with asthma, eosinophilic esophagitis, and hyper eosinophilic syndromes experience proliferation and enhanced survival (Kato et al., 1992). These diseases affect tissues when eosinophils are produced at high levels, and targeting the signalling pathways and factors plays an essential role in therapeutic intervention (Akuthota and Weller, 2012). Palacionyte et al. examined the proliferative capacity of two cytokines, IL-5 and GM-CSF, in producing the proliferating behavior of different eosinophil subtypes in asthma patients. The study indicated that the two cytokines facilitated the proliferation of eosinophils, with a significant effect on the morphology of airway smooth muscle cells. The study addresses the roles of these cytokines in modulating eosinophil behavior among patients with asthma; hence, they play a critical role in disease pathophysiology and therapeutic agents (Palacionyte et al., 2022). Using a different approach but with a similar objective, Sullivan and Broide investigated eosinophil compartmentalization of GM-CSF expression in human asthma. They showed that ex vivo, exposure to allergens causes eosinophils present in bronchoalveolar lavage but not those in the peripheral blood of allergic asthmatics to express GM-CSF mRNA and protein. Consistent with the localization of eosinophils GM-CSF expression in the lung, this factor may signal inflammation and specifically eosinophilic inflammation of the airway in the post-allergen challenge setting (Sullivan and Broide, 1996).

The molecular mechanism of the CSF1-CSF1R signalling pathway is critical for the survival, proliferation, and differentiation of mononuclear phagocyte systems, including monocytes, macrophages, and their precursor cells (Stanley and Chitu, 2014). This connection is released on interaction between colony-stimulating factor 1, also known as macrophage colony-stimulating factor, M-CSF, and the receptor cytoplasmic macrophage colony stimulator CSF1

receptor (Kato and Schleimer, 1994, Kaur et al., 2015). The CSF1-CSF1R signalling pathway is essential for the function and regulation of lung macrophages, which exert a dual effect on the innate and adaptive immune responses in the lungs (Mun et al., 2020). Given that this pathway is necessary for antiapoptotic functions and anti-inflammatory and antifibrotic processes, it is a critical signalling pathway in the pathogenesis of ILDs, making it a promising target for pathogenetic therapy (Wilson and Wynn, 2009). Pathogenetic therapy to inhibit the CSF1-CSF1R signalling pathway in the treatment of asthma was also considered by Moon et al. According to the data presented, this pathway can be a new approach to asthma therapy, as targeting this signalling pathway can prevent allergen sensitization or reduce allergic inflammation in a chronic asthma model (Moon et al., 2020).

Therapeutic targeting of GM-CSF in inflammatory asthma

Targeted therapy against GM-CSF offers significant therapeutic potential for inflammatory asthma (Kempuraj et al., 2020). GM-CSF is a crucial mediator in the persistence phase of inflammation, as it increases the recruitment and activation of phagocytes, eosinophils, neutrophils, and T cells to the site of inflammation (Mathias et al., 2015). Along with this, GM-CSF promotes DC maturation, which is associated with the persistent Th2 phenotype and the generation of a pro-inflammatory environment (Kim et al., 2016, Knol et al., 1996). The presence of high GM-CSF levels in the airways of individuals with asthma correlates with disease severity, validating its candidacy as a therapeutic target (Shiomi et al., 2016). Different therapeutic GM-CSF targeting strategies are being developed, including the use of neutralizing antibodies and receptor antagonists. Neutralizing antibodies have the advantage of precisely neutralizing the target while exhibiting limited off-target effects (Hamilton, 2020). Inhibition occurs when neutralizing antibodies bind to GM-CSF binding ends, hampering its interaction with the GM-CSF receptor and downstream signalling cascades (Lang et al., 2020). The limiting effect on immune cell recruitment and activation translates to reduced inflammatory airway hyperresponsiveness (Vico et al., 2022). Anti-GM-CSF antibodies have shown promise in clinical trials for reducing disease severity and enhancing lung function in individuals with asthma (Lee et al., 2020a, Lei et al., 1998). Cyclosporin A achieves its immunosuppressive effects by targeting calcineurin, a vital enzyme in the upregulation of T-cells, which are an important unit of the adaptive immune system (Ataya et al., 2021). Calcineurin activates the transcription factor NFAT nuclear factor of activated T-cells; its target genes include those coding for G-interferon and ILs, notably IL-2. IL-2 is vital for the differentiation, activation, and proliferation of T cells (Kipanyula et al., 2016). Sano et al. ascertained the suitability of FK506 and cyclosporin A as generators of immunomodulatory agents for asthma by inhibiting GM-CSF production in mononuclear cells. Although both agents inhibited GM-CSF production, FK506 was more efficient in lowering its production than cyclosporin A (Sano et al., 1995). Representative anti-GM-CSF antibodies that neutralize the ligand are otilimab and lenzilumab, whereas mavrilimumab binds to the GM-CSF receptor alpha chain instead of GM-CSF (Crotti et al., 2017).

Dexamethasone is an efficient synthetic corticosteroid with strong anti-inflammatory and immunosuppressive properties (Liu et al., 2018). It is one of the most prominent drugs used in various medical fields to treat multiple diseases because it can lower inflammation and modify the immune response (Coutinho and Chapman, 2011). Dexamethasone functions by imitating the actions of cortisol, a natural hormone produced by the adrenal cortex, and is responsible for regulating metabolism and immune response (Louis et al., 2015). To display its effects, the drug must enter the cells and bind to the glucocorticoid receptor, and its specific functions can be performed via transactivation (Ramamoorthy and Cidlowski, 2016). Inhibition of natural processes that increase mRNA concentration is called transrepression, and the difference between these two terms lies solely on the binding target, which can be an activator or an inhibitor

(Busillo and Cidlowski, 2013). Li et al. researched the broad effects of dexamethasone on cytokine receptors mRNA expression within the eosinophils of a guinea pig asthma model. Dexamethasone exploits apoptosis of eosinophils in BALF and disrupts the expression of IL-5Rα, IL-3Rα, and GM-CSFRα, which leads to a decrease in eosinophil infiltration of lung tissue and helps to explain the anti-inflammatory mechanism of corticosteroids in asthma (Li et al., 2001). Similarly, Lazzeri et al. studied the influence of drugs leading to a rise in prostaglandin E2 and cyclic AMP on GM-CSF release in human airway smooth muscle cells. The findings showed that COX-2 inhibitors enhanced GM-CSF generation, whereas PGE2 and cAMP-elevating drugs suppressed this mediator, suggesting that these pathways might be advantageous in the pharmacotherapy of asthma (Lazzeri et al., 2001).

Antisense oligonucleotides are short, synthetic strands of nucleic acids designed to bind specifically to mRNA molecules inside a cell (Gupta et al., 2023a, Gupta et al., 2023b). By doing so, ASOs can stop the expression of specific genes at the RNA level, as their binding leads to decreased production of the desired protein (Mortberg et al., 2023). ASOs utilize the natural mechanism of RNA interference; thus, their unique design will work for virtually any gene. Therefore, these agents can be successfully used for both research and therapeutic purposes (Gagliardi and Ashizawa, 2021). The mechanism by which ASOs function can differ based on their design and purpose. Some ASOs lead to mRNA degradation by activating RNase H activity, thereby reducing the production of the desired protein (Liang et al., 2019). Allakhverdi et al. tested antisense oligonucleotides against the common beta chain of IL-3, IL-5, and GM-CSF receptors in a rat model of allergic asthma. This chain is involved in signal transduction through these three receptors into T-lymphocytes, and thus offers a role in allergic inflammation. Although the agents did not reduce inflammation, their administration reduced eosinophilia and airway hyperresponsiveness following antigen challenge, indicating another potential pathway for asthma treatment (Allakhverdi et al., 2002). CD69 is markedly upregulated on T, B, NK, and DCs within hours of initiation. Its expression is transient; as the cell returns to rest, CD69 levels return to pre-stimulation baselines 66 (Borrego et al., 1999). Because it is rapidly induced following initiation, CD69 is a useful indicator for monitoring cell activation in clinical and in vitro studies. Because the tissue provides CD69+ cells constitute recently triggered populations that may help reveal patterns or functions initiated locally, monitoring CD69 levels via flow cytometry should be used to establish tissue subpopulations and their plastic functions following changes or activation in a variety of physiological and pathological states (Li et al., 2024). This study will also benefit from enhanced CD69+ detection and fingerprinting, which will help develop better function-specific COVID-19 therapies more quickly. Because it is overexpressed, CM from these cells may be employed to enhance studies into development methods and become CM-derived stem cells (Arsenault et al., 2023). Targeting CD69 or its pathways is a viable strategy for increasing immunity to pathogens and cancers and reducing autoimmune disorders and damage (Gorabi et al., 2020). In a mouse model of asthma, Wang et al. assessed the effectiveness of anti-CD69 mAb in decreasing airway inflammation. PM-CWS treatment reduced eosinophil infiltration and mucus production. Anti-CD69 mAb treatment reduced eosinophil glaze and goblet cell pens, showing that CD69 may be a viable target for the development of adjunctive asthma cure (Wang et al., 2015). Zhao et al. studied whether S100A8 could inhibit mast cell function and restrain eosinophil migration in an acute asthma murine model. According to the authors (Zhao et al., 2011), S100A8 exerts beneficial effects against allergic inflammation induced by its inhibitory activity on mast cell degranulation and by reducing eosinophil migration, most likely owing to its protective properties as an antioxidant (Shen et al., 2011) (Table 1).

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Table 1: The table summarises key information from various research studies on GM-CSF and related cytokines in asthma. It lists the study focus, main findings, impacted cells or pathways, contextual relevance and type of study. This table compares how different studies address asthma pathogenesis, cellular impact, and potential therapeutic targets, providing a clear overview of current research trends and findings.

Study Focus	Main Findings	Impacted Cells/ Pathways	Context	Study Type	Reference
GM-CSF in asthma and COPD	Higher GM-CSF levels in severe asthma and COPD	Eosinophils, Neutrophils	Pathogenesis, Severe Asthma	Observational Study	Saha et al., 2009
GM-CSF in chronic asthma	GM-CSF necessary for neutrophil mobilization	Dendritic Cells, T Cells	Chronic Asthma, Inflammation	Observational Study	Nobs et al., 2021
IL-5 and GM-CSF in chronic cough and asthma	Increased cytokine expression linked to inflammation	Bronchoalveolar Cells	Chronic Cough, Asthma	Comparative Study	Gibson et al., 1998
GM-CSF sources post-allergen challenge in asthma	GM-CSF production from BAL lymphocytes and macrophages	BAL Lymphocytes, Alveolar Macrophages	Asthma, Allergen Challenge	Observational Study	Broide and Firestein, 1991
AMFR's role in allergic asthma	AMFR promotes GM-CSF production and inflammation	Alveolar Macrophages	Allergic Asthma, Inflammation	Observational Study	Zhang et al., 2022a
Cytokines in intestinal mucosa in asthma	Increase in IELs and eosinophils, cytokine presence	Intestinal Mucosa, Eosinophils	Systemic Mucosal Immune Response	Observational Study	Wallaert et al., 1995
GM-CSF production by PBMCs in asthma	Increased GM-CSF production, affected by glucocorticoids	Peripheral Blood Mononuclear Cells	Asthma, Immunomodulation	Clinical Study	Nakamura et al., 1993
T-cell expression in asthma	Link between T-cell expression of cytokines and asthma	T-Cells, Eosinophils	Asthma, T-Cell Mediated Response	Observational Study	Kamei et al., 1993
Gene expression in CD4+ T cells in severe asthma	Increased IL-3 expression, steroid response	CD4+ T Cells	Severe Asthma, Steroid Therapy	Clinical Study	Lai et al., 1996
AMFR in allergic asthma	Increased AMFR associated with exacerbation of asthma	Alveolar Macrophages	Allergic Asthma, Therapeutic Target	Observational Study	Zhang et al., 2022b
GM-CSF in atopic asthma	High eosinophils and GM-CSF correlated with airway issues	Eosinophils	Mild Atopic Asthma	Observational Study	Woolley et al., 1994
Eosinophil behavior in asthma	Cytokines promote eosinophil proliferation	Eosinophils	Asthma, Eosinophil Behavior	Observational Study	Palacionyte et al., 2022
GM-CSF expression in asthma	Localized GM-CSF expression post allergen challenge	Eosinophils in BAL	Asthma, Post-Allergen Response	Observational Study	Sullivan and Broide, 1996
CSF1-CSF1R in asthma therapy	Targeting CSF1-CSF1R can reduce allergic inflammation	Mononuclear Phagocyte System	Asthma, New Therapeutic Approach	Experimental Study	Förster et al., 2022

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Study Focus	Main Findings	Impacted Cells/ Pathways	Context	Study Type	Reference
FK506 and Cyclosporin A in asthma	FK506 more efficient than Cyclosporin A in inhibiting GM-CSF	Mononuclear Cells	Asthma, Immunomodulatory Agents	Clinical Trial	Thomas et al., 2021
Dexamethasone effects in asthma	Reduced eosinophil infiltration and cytokine receptor expression	Eosinophils	Asthma, Corticosteroid Mechanism	Experimental Study	Li et al., 2001
GM-CSF release in asthma	COX-2 inhibitors enhance GM-CSF generation	Human Airway Smooth Muscle Cells	Asthma, Drug Response	Observational Study	Lazzeri et al., 2001
ASOs against cytokine receptors in asthma	Reduced eosinophilia and airway hyperresponsiveness	T-lymphocytes	Asthma, Antisense Oligonucleotide	Experimental Study	Allakhverdi et al., 2002
Anti-CD69 mAb in asthma	Reduced eosinophil infiltration and mucus production	T cells, B cells	Asthma, Immune Modulation	Experimental Study	Wang et al., 2015
S100A8 in acute asthma	Inhibited mast cell function and reduced eosinophil migration	Mast Cells, Eosinophils	Acute Asthma, Anti-inflammatory	Experimental Study	Zhao et al., 2011

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GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Involvement of GM-CSF in chronic obstructive pulmonary disease progression

GM-CSF is a critical factor participated in the pathogenesis of COPD (Mitra et al., 2018). In COPD, GM-CSF is upregulated and contributes to the chronic inflammatory environment observed in this disease. GM-CSF is essential for the survival, maturation, and activation of macrophages and neutrophils, which are essential in the TCA associated with COPD (Akata and van Eeden, 2020). These cells produce proteases and ROS that directly degrade elastin and other structural components of the lungs, leading to COPD (Markin et al., 2022), fibrosis of the small airways, and alveolar destruction that manifests as emphysema and chronic bronchitis. In addition, GM-CSF enhances the antigen processing and presenting properties of macrophages, leading to their continuous activation and enhanced T cell activation (De Rose et al., 2018). The activation of this cycle not only perpetuates but also impacts COPD progression by maintaining the lung recruitment and activation of additional host immune cells (Masso-Silva et al., 2022, Matute-Bello and Martin, 2003). Two well-known intracellular signalling cascades that modulate differentiation, growth, proliferation, and survival are AKT and ERK (Mercer and D'Armiento, 2006). Various growth factors, cytokines, and other external signals activate these pathways. AKT, also known as protein kinase B, is activated via phosphoinositide 3-kinase in response to numerous growth factors and cytokines (He et al., 2021). In the context of lung disorders, AKT stimulation increases the survival and proliferation of airway smooth muscle cells, fibroblasts, and myocytes, contributing to airway remodelling in asthma and fibrosis in COPD (Mehta et al., 2020). This activation enhances the synthesis of inflammatory cytokines and mucus secretion from epithelial cells, furthering inflammation and airway blockage (Bozinovski et al., 2006). Activated ERK is a part of the mitogen-activated protein kinase family and the chain reaction induced by growth factors; it is crucial for cell differentiation and growth (Najafi-Fard et al., 2023). In inflammatory reactions, ERK signalling is coupled with bronchial smooth muscle cell hyperactivity, proliferation, and the production of inflammatory mediators (Roberts, 2012). Bozinovski et al. suggested that GM-CSF imbalance via the AKT/ERK pathway plays an essential function in lung machinery and could be a factor of inflammatory infection. They studied the effect of GM-CSF on lung immunity with lipopolysaccharide and reported that GM-CSF neutralizing alveolitis with LPS impaired inflammation, decreased protease breakdown, and disrupted AP-1/NF-κB activation (Bozinovski et al., 2002).

TNF-α functions a critical part in the systemic inflammation process and can induce fever, apoptotic cell death, cancer, inflammation, and cachexia (Nakata et al., 2003). While elevated TNF-α expression are usually observed in inflammatory and autoimmune disorders, several effective treatments for this cytokine are available (van Loo and Bertrand, 2023). TNF-α-targeting therapy is one of the methods used to treat the abovementioned conditions, indicating the importance of TNF-α in the pathophysiology of chronic inflammation (Nathan et al., 2018, Nobs et al., 2021). In addition, measuring the type and intensity of immune responses in patients may provide diagnostically relevant information for healthcare professionals (Popa et al., 2007). Thus, monitoring TNF-α concentration in the serum can assist in diagnosis and support disease progression and treatment decisions by determining the extent of the inflammatory response and type of immune reaction (Pahari et al., 2023). However, the same applies to the other cytokines analyzed in the present study. Hence, cytokine levels can also vary widely due to the specific focus area, unique characteristics of the immune response, the status of an individual's immunity, and other factors, such as medication, comorbidity, and infection (Nayem et al., 2023). Mitra et al. analysed cytokine level in South Indian COPD patients. The authors reported higher serum cytokine levels of GM-CSF, IFN-γ, IL-4, and TNF-α. South Indian patients with COPD who smoked had a higher serum concentration of these cytokines than

smokers without COPD. This pilot study demonstrated possible COPD susceptibility biomarkers in the Indian population. However, further validation is required (Mitra et al., 2018). In the same manner, Vlahos et al. revealed that neutralization of GM-CSF in mice attenuated cigarette smoke-induced lung inflammation, suppressed the increased recruitment of macrophages and neutrophils, and reduced the levels of TNF-α, MIP-2, and MMP-12 expression. Altogether, these data suggest that smoke-induced inflammation is dependent on GM-CSF and can be pharmacologically targeted (Vlahos et al., 2010). Inhalation of fungal spores can trigger strong inflammatory responses in the lungs, particularly in individuals with weakened immune barriers and antifungal host defense (Bhat et al., 2024b). When inhaled, fungal spores germinate and colonize lung tissue, causing immune activation, including alveolar macrophages and other immune cell recruitment, such as neutrophils and T cells, which secrete pro-inflammatory mediators (Chotirmall et al., 2013). These responses can cause physiological responses from mild allergic reactions to serious disorders, such as hypersensitivity pneumonitis or even invasive fungal infections, exemplified by aspergillosis, depending on the ability of the fungal species to disseminate and the host's immune suppression (Hohl, 2017). Wrench et al. noted that phagocytosis of fungal spores in individuals with COPD was impaired due to deficient phagocytosis in GM-CSF and M-CSF-derived macrophages, indicating increased pathologic colonization. This deficiency promotes an increased susceptibility to fungal infections in individuals with COPD (Wrench et al., 2018).

Therapeutic targeting of GM-CSF in inflammatory chronic obstructive pulmonary disease

Therapeutic targeting of GM-CSF in COPD entails modulation of the function of this molecule to sustain chronic inflammation, which is characteristic of COPD. GM-CSF is an indispensable element in the life cycle, differentiation, and activation of myeloid cells, which are central mediators of inflammation in COPD (Vlahos et al., 2006). These cells cause tissue damage via the production of proteases, reactive oxygen species, and pro-inflammatory mediators, thus exacerbating airway obstruction and pulmonary diseases (Bhat et al., 2023b). Targeting GM-CSF or its receptor GM-CSFR in clinical trials has the potential to limit the occurrence of exacerbations and improve lung function by diminishing the pulmonary inflammatory environment (Fung et al., 2022). Inhibition of GM-CSF lowers the degree of activation and life of these inflammatory cells, potentially stopping the spread of airway inflammation and remodelling post-work in COPD screening (Paine et al., 2000, Palacionyte et al., 2022). Tools such as mAbs against GM-CSF or its receptor are being investigated to assess their safety and effectiveness for COPD patients with COPD (Tsantikos et al., 2018). The drug targets individuals with a specific infectious profile in which there is an elevation of GM-CSF in the blood, presenting a tailored approach to managing this complicated study. Given this focus, the drug would open up a new way for the disease to be treated in smoke-like lung conditions in patients unresponsive to current treatments (Stonedahl et al., 2023). Matrix metalloproteinases are an assembly of proteolytic catalysts that reduce the levels of the extracellular matrix. They play a substantive role in both normal functions, such as cellular regeneration, and pathological situations, such as lung disease (Cui et al., 2017). Their activities are continuously followed regularly under normal circumstances, although conditions may change during the onset of diseases, as they may result in excess matrix degradation and inflammation (Lu et al., 2011). Vlahos et al. assessed the neutralization of GM-CSF to prevent inflammation caused by cigarette smoke. Treatment of mice with anti-GM-CSF substantially reduced BALF macrophages and neutrophils. It remarkably decreased the levels of TNF-α, MIP-2, and MMP-12. However, it did not affect MMP-9 levels or phagocytic function of AMs. Neutralization could be an effective therapy for smoking-related diseases, including COPD (Vlahos et al., 2010).

Resveratrol is a naturally occurring compound found in red wine, grapes, berries, and peanuts. Surprisingly, a polyphenolic compound found in grapes, berries, and peanuts has promising anti-inflammatory characteristics (Ndiaye et al., 2011). It inhibits critical signalling cascades (NF-κB and MAPK), lowering the production of TNF-α, IL-1β, and IL-6. Furthermore, resveratrol downregulates COX-2 expression and modulates immune cell function to avoid excessive immune responses (Behl et al., 2021). Resveratrol supplementation generally appears to have potential in chemically induced and chronic inflammatory disorders, such as cardiovascular diseases, arthritis, and neurodegenerative disorders (Patel et al., 2023). Resveratrol also exerts tissue-protective antioxidant effects (Khattar et al., 2022). According to Knobloch et al., resveratrol significantly impaired the release of IL-6, IL-8, GM-CSF, MCP-1, and MMP-9 from LPS exposure of alveolar macrophages in COPD compared with dexamethasone. This study supports the idea that resveratrol is an ideal candidate for future clinical trials of corticosteroid-resistant airway inflammation in individuals with COPD (Knobloch et al., 2011). Knobloch et al. also studied the impact of the same drugs on the release of cytokines from human airway smooth muscle cells. Inhibition of cytokine release after the activity of both resveratrol and dexamethasone was observed. Despite its superiority to resveratrol, the COPD drug resveratrol provides an opportunity to identify new treatment targets and reduce the concentration of IL-8 and GM-CSF, without inhibiting VEGF. Thus, corticosteroids may be less suitable for COPD therapy because of the broad spectrum of activity of their benzopyrene derivatives (Knobloch et al., 2010). Phosphodiesterase-4 has been predominantly developed for COPD therapy. PDE4 is an enzyme involved in inflammatory processes, and its inhibitors reduce inflammation by inhibiting this enzyme (Petrina et al., 2021, Presneill et al., 2002). The intention is to diminish lung inflammation and subsequent bronchoconstriction and to diminish symptoms caused by COPD (Brown, 2007). Profita et al. explored the action of PDE4 inhibitor Cilomilast on inflammatory mediators. Cilomilast administration deeply decreased TNF-alpha, and GM-CSF liberation is shown by bronchial and sputum cells, while in IL-8, there was a minor variation. Similarly, neutrophil chemotaxis was considerably reduced. These outcomes suggest that cilomilast reduces COPD and cigarette smoke-associated neutrophilic inflammation (Profita et al., 2003) (Table 2).

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Table 2: The table summarizes research studies on the role of GM-CSF in COPD. It details findings from various studies highlighting the effects of GM-CSF on lung immunity, cytokine levels, and inflammation modulation in COPD.

Study Focus	Main Findings	Impacted Cells/Pathways	Context	Study Type	Reference
GM-CSF and Lung Immunity	GM-CSF neutralizing decreased protease breakdown and inflammation	Macrophages, Neutrophils	COPD, AKT/ERK Pathway	Experimental Study	Bozinovski et al., 2002
Cytokine Levels in COPD	Higher serum cytokine levels in smokers with COPD compared to smokers without COPD	Serum cytokines	COPD Susceptibility, Indian Population	Pilot Study	Mitra et al., 2018
Neutralization of GM-CSF	Attenuated lung inflammation, decreased macrophage and neutrophil recruitment	Macrophages, Neutrophils	Cigarette Smoke-Induced COPD	Experimental Study	Vlahos et al., 2010
Phagocytosis in COPD	Impaired phagocytosis in GM-CSF and M-CSF-derived macrophages	Macrophages	COPD Susceptibility to Fungal Infection	Observational Study	Wrench et al., 2018
Resveratrol in COPD	Resveratrol impaired cytokine release compared to dexamethasone	Alveolar Macrophages	COPD Airway Inflammation, Corticosteroid-Resistant	Experimental Study	Knobloch et al., 2011
PDE4 Inhibitor in COPD	Reduced TNF-alpha and GM-CSF release; minor variation in IL-8	Bronchial and Sputum Cells	COPD, Cigarette Smoke-Related Inflammation	Clinical Study	Profita et al., 2003

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GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IN LUNG CANCER

Involvement of GM-CSF in inflammatory lung cancer progression

GM-CSF participated in the regulation of immune and inflammatory responses, which is significantly relevant to lung pathophysiology, especially as a contributing factor in lung cancer progression (Bhat et al., 2024c). GM-CSF primarily stimulates the differentiation, proliferation, and survival of granulocyte and macrophage precursors (Shi et al., 2006). The pro-tumorigenic role of GM-CSF and inflammation, referred to as inflammatory lung cancer in this study, is versatile (Qudus et al., 2023, Radmark, 2022). In particular, GM-CSF production generates an immunosuppressive microenvironment for tumor growth and spread (Duits and de Visser, 2021). As the multiplication of myeloid-derived suppressor cells and macrophages is a conducive factor for tumor cell promotion, GM-CSF enables their suppressive effect on anti-tumor immunity (Ritz et al., 2002, Sampson, 2000). Another promoting factor is the survival signalling within the tumor; GM-CSF boosts the survival and fostering of suppressor-type cells inside the tumor microenvironment (Zhao et al., 2023). Additionally, GM-CSF produced by various other tissues triggers the release of other pro-inflammatory mediators (Schulert et al., 2019). The environment generated fuels blood vessel development, which is crucial for tumor development and the spread of cancerous cells (Ngaha et al., 2023). Altogether, GM-CSF is a candidate for a new drug target in lung cancer treatment. The reduction in the mobilization effect of growth factors and the inhibition of their pathways is being elaborated to reduce the tumorigenic power of the factor (Park and Chung, 2024). Oshika et al. revealed an experiment checking up on the effect of GM-CSF on non-small cell lung cancer (NSCLC) xenografts. Induction of GM-CSF significantly enforced the growth of tumors compared to the controls, suggesting that GM-CSF may have a stimulating effect on the development of NSCLC. Therefore, this factor should be avoided in certain therapeutic applications because of its participatory action. This demands a discriminatory attitude in the evaluation of GM-CSF activity (Oshika et al., 1998). Recent molecular studies further indicate that lung cancer progression is influenced by pathways beyond GM-CSF signalling. Xiao et al. investigated membrane progesterone receptor α (mPRα)/progestin and adipoQ receptor family member 7 (PAQR7) across human cancers and specifically validated its role in lung squamous cell carcinoma (Xiao et al., 2025). Their findings noted aberrant overexpression of mPRα in LUSC cells, while mPRα knockdown impaired malignant cellular characteristics. Moreover, higher mPRα protein expression was corelated with poorer overall survival in patients with LUSC, suggesting that mPRα/PAQR7 may represent a potential biomarker and therapeutic target in this lung cancer subtype.

Cyclooxygenase-2 (COX-2) is an enzyme primarily involved in inflammatory processes by synthesizing prostaglandins from arachidonic acid, which mediates pain, inflammation, and fever. While the constitutive expression of the homologue enzyme, COX-1, is present in almost all tissues, COX-2 is induced by inflammatory signals, growth factors, and tumor promoters (Ricciotti and FitzGerald, 2011). COX-2 overexpression is observed in numerous pathological conditions, including cancer, where it promotes tumor growth, angiogenesis, and resistance to apoptosis. High COX-2 expression correlates with a worse prognosis in several cancers (Szweda et al., 2019). COX-2 inhibitors were explored for their anti-inflammatory properties and their possible therapeutic role as anti-cancer agents, reducing cancer-induced inflammation, and tumor growth by G-CSF and GM-CSF effects on lung cancer progression were observed by Uemura et al. Both growth factors upregulated COX-2 expression, facilitating increased proliferation and migration of lung cancer cells. Since one of the ways in which G-CSF and GM-CSF could enhance cancer progression is through COX-2-mediated pathways, demonstrating therapeutic potential suggests that such treatments could reduce the pro-inflammatory environment, allowing tumor growth and metastasis (Uemura et al., 2007). Autologous tumor

vaccines are a type of immunotherapy that introduces the patient's cancerous cells to the immune system to facilitate direct confrontation with the tumor (Bhat et al., 2024d). This patient-specific method enables the creation of an optimal vaccine that allows the immune system to produce a more targeted and robust response to cancer (Liu et al., 2023a). GM-CSF gene-modified autologous tumor vaccines were tested by Nemunaitis et al. in patients with NSCLC. Despite some patients experiencing clinical effects, such as prolonged life and recurrent disease, the general efficacy of the vaccine was limited. Based on this study, it can be concluded that the existing vaccine formulations or co-treatment approaches need to be better optimized to achieve more immunological success and effectiveness. At the same time; however, the study shows promise for the future identification of genetically modified autologous vaccines as promising potential components of cancer treatment systems (Nemunaitis et al., 2004). Later, Maung et al. examined the possible use of GM-CSF gene-transduced tumor vaccine treatment for patients with NSCLC. The authors emphasized that in early clinical trials, GVAX showed a high immunogenic response to vaccines, suggesting that GM-CSF-modulated vaccines can activate the immune system against tumor cells. Moreover, they found that additional research is warranted to improve the technique and evaluate its treatment effect in a more diverse group of patients (Maung et al., 2001).

Urokinase plasminogen activator (uPA) is a serine protease that plays a central role in fibrinolysis. tPA promotes the conversion of inactive plasminogen to active plasmin, which in turn causes the degradation of fibrin and destroys clots (Altaf et al., 2021). uPA's fibrinolytic action of uPA is essential for blood clot resolution and tissue remodelling, which are important processes in normal physiology, such as wound healing. However, several pathological circumstances may influence its expression (Mukhopadhyay et al., 2019). It is overexpressed in several kinds of cancer and supports tumor growth, invasion, and metastasis by remodeling the ECM and activating development-inducing factors that help spread tumor cells (Bhat et al., 2022). In addition, it offers a significant role in cardiovascular diseases by promoting thrombus formation (Huang et al., 2021). Pei et al. evaluated the impact of granulocyte, granulocyte-macrophage and macrophage colony-stimulating factors on the invasion potential of lung cancer cells. They discovered that treatment with these CSFs increased the production of matrix metalloproteinase and urokinase plasminogen activator. Increased invasiveness was associated with increased proteolytic activity. Increased CSF manufacturing is a biochemical mechanism by which lung cancer cells invade adjacent body tissues and spread to distant locations (Pei et al., 1999). ILs are a subset of cytokines that are crucial for the immune system. They serve as messengers that help regulate inflammation (Bhat et al., 2024e). Proinflammatory interleukins are involved in the induction and continuation of inflammation (Iyer and Cheng, 2012). Pro-inflammatory interleukins activate the endothelium and attract neutrophils to the site of inflammation. Anti-inflammatory interleukins are responsible for suppressing inflammation and protecting tissues from serious damage (Al-Qahtani et al., 2024). The duality of the effects of interleukins is critical for their effective application in the immune response. Extreme imbalance can lead to chronic inflammation or the development of autoimmune disorders. Therefore, interleukins are the cornerstone of several pharmacological approaches in modern clinical practice (Hirano, 2010). Pedrazzoli et al. described the effects of GM-CSF and IL-3 on small-cell lung cancer. The authors assessed the impact of these interleukins on clonal growth and DNA synthesis. The levels of mRNA encoding oncogenes were also quantified in cell lines from two SCLC patients. The authors concluded that GM-CSF and IL-3 growth factors have growth-promoting activity on H69 and N417 SCLC cells; they reduce the time of DNA synthesis of the cells and increase the cloning efficiency (Pedrazzoli et al., 1994). This is consistent with the assumption that some non-hematopoietic malignant cells respond to hematopoietic growth factors. Thus, before being introduced into clinical practice for solid tumor chemotherapy, the application of GM-CSF and

IL-3 must be thoroughly assessed, as they can stimulate tumor proliferation (Bhat et al., 2023a). Similarly, Takahashi et al. investigated the ability of GM and IL-2 to increase lymphokine-activated killer (LAK) antitumor activity in lung cancer patients through macrophages. Their results showed that the direct effect of GM on PCMs, PLYs, or PBLs did not lead to antitumor activity in lung cancer. The addition of LAK activities and GM with IL-2 significantly increased LAK activity in PLY and PBLs, especially in GM-CSFR-alpha-positive PCMs. This implies that GM-CSF activation enhances the immune system activities in lung cancer by activating GM-CSFR-alpha-positive macrophages, which intensify the antitumor activities of lymphocytes (Takahashi et al., 2000).

Therapeutic targeting of GM-CSF in inflammatory lung cancer

Recently, GM-CSF has been increasingly implicated in promoting inflammation-associated lung cancer. GM-CSF helps establish a tumorigenic microenvironment by recruiting and stimulating myeloid cells, which facilitate tumor expansion and metastasis by promoting inflammatory signalling (Bayne et al., 2012). Although this cytokine sustains tumor cell survival and division, it also supports angiogenesis, which is essential for tumor nutrition and expansion. Therapeutic immunization against GM-CSF shows considerable promise for attenuating ISC progression (Hong, 2016). Inhibition of GM-CSF or its receptor can interfere with the protumorigenic properties of myeloid cells, likely reducing tumor progression. Several trials have employed antibodies that neutralize this cytokine or its receptor, and some have reported satisfactory results, including depleting inflammatory signalling within the tumor and enhancing the efficacy of additional anticancer treatments (Smirnova et al., 2021). Inflammatory lung cancer therapy centers on targeting GM-CSF, which is a promising approach with the potential to improve current cancer treatment options, such as chemotherapy and immunotherapy. This effort provides hope for reducing the chances of cancerous cells depending on inflammatory factors for their proliferation and survival (Muhammad et al., 2023). Cisplatin is a commonly used chemotherapy drug for treating various cancers, including lung cancer. This compound mainly functions by linking to cancer cell DNA and sabotaging DNA repair mechanisms, resulting in cancer cell death (Brown et al., 2019). However, cisplatin resistance is a common obstacle in cancer therapy, particularly in lung cancer. This resistance efficiently inhibits the effects of chemotherapy on the overall treatment method (Rocha et al., 2018). Pass et al. provided evidence that the inhibition of CSF-1 receptor increased cisplatin sensitivity, enhancing the efficacy of the treatment. This finding guides the development of even more efficient treatment regimens that combine cisplatin and CSF-1R inhibition to enhance cisplatin sensitivity in lung cancer patients (Pass et al., 2016).

Sintilimab, an immune checkpoint inhibitor, is a relatively new drug used in cancer immunotherapy. It is an anti–PD-1 mAb. PD-1 is a protein located on the membrane surface of T cells, which are part of the immune system (Zhang et al., 2020). Sintilimab inhibits the indirect interaction of the protein with ligands: PD-L1 and PD-L2, which are present in malignant cells. When the connection is broken through the blockade, the immune response enhances the activity of the body against cancerous cells (Zhang et al., 2020). To date, sintilimab has been tested and used for the treatment of several oncological diseases. Among these, there are diseases such as NSCLC, Hodgkin lymphoma, and HCC (Zhang et al., 2022c). This drug is registered in certain regions, such as China, but is actively tested worldwide in various clinical studies on oncology to assess the effectiveness and safety of sintilimab when combined with other treatments (Lu et al., 2022). Ni et al. studied the safety of including sintilimab, stereotactic body radiotherapy, and GM-CSF in the treatment scheme of individuals with advanced NSCLC. According to the results, the safety was acceptable, and the number of side effects was small. This allows us to consider the combination of these drugs as an alternative option for second-line

therapy for NSCLC and to study the possibility of its use in clinical practice. Various approaches to the impact of several factors on the development of malignant neoplasms may help prevent resistance to aggressive treatment and improve the prognosis of malignant neoplasms (Ni et al., 2021). Tjan-Heijnen et al. investigated on strategies to increase the dose of chemotherapy in small cell lung cancer and the contribution of granulocyte colony-stimulating factor and GM-CSF. They concluded that although growth factors reduce the dose of chemotherapy by only 150 % compared to the usual regimens, several phase III studies should be conducted, and an increase in the intensity of treatment could make a significant contribution to increasing patient survival (Tjan-Heijnen et al., 1997) (Table 3).

CURRENT THERAPEUTIC APPROACHES TARGETING GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

Given its pivotal role in immune modulation, GM-CSF has emerged as an essential treatment target for treating various lung inflammatory diseases. GM-CSF is known for its importance in immune cell activation and recruitment, such as macrophages and neutrophils, during infections in the lungs (Lang et al., 2020). There are two main approaches to therapeutically target GM-CSF, as outlined above: inhibition and supplementation, which can be used to effectively manage some pathologies. GM-CSF inhibition, in particular, seems to be effective in congestive obstructive pulmonary disease (Ifergan et al., 2017). The pathophysiology of COPD is associated with chronic inflammation, where the recruitment and activation of macrophages and neutrophils exacerbate the disease process. These immune cells are sustained and activated by GM-CSF, creating a vicious cycle of inflammation, worsening, and airflow limitation over time (Jasper et al., 2019). GM-CSF neutralization reduces neutrophils and macrophages in the lung, reducing inflammation and promoting healing. In cigarette smoke-induced lung inflammation, GM-CSF inhibition significantly reduced lung neutrophils and macrophages, suggesting that it can effectively reduce COPD symptoms (Puljic et al., 2007, Vlahos et al., 2006). Furthermore, GM-CSF inhibition is an area of intense research to combat COVID-19-related hyperinflammation, which could facilitate the avoidance of ARDS. GM-CSF levels were higher in individuals with ARDS, and excessive lung fluid cytokine levels were indicative of an inflammatory loop involving macrophages, resulting in excessive macrophage activation and pro-inflammatory cytokine production. This can be blocked by inhibiting GM-CSF, as shown in Figure 4 (Mehta et al., 2020). Emerging targeted delivery approaches also provide alternative strategies for controlling excessive pulmonary inflammation. Yuan et al. developed an inhalable PD-L1-engineered hybrid cellular vesicle system containing resveratrol that targets injured lung tissue and suppresses excessive neutrophil activation through PD-1/PD-L1 signalling. In experimental lung ischemia-reperfusion injury and methicillin-resistant *Staphylococcus aureus*-induced pneumonia, nebulized treatment reduced inflammatory cytokine release and lung tissue injury, improved alveolar barrier integrity and pulmonary function, and restored mitochondrial homeostasis through PINK1-mediated mitophagy (Yuan et al., 2026). These findings show the potential of inhaled biohybrid vesicles as a complementary strategy for simultaneously modulating inflammatory, oxidative and mitochondrial abnormalities in severe lung injury and pneumonia. In severe pulmonary infections caused by multidrug-resistant pathogens, pathogen-directed antimicrobial therapy remains essential alongside strategies aimed at controlling excessive inflammation. In a multicentre propensity score-matched real-world study of carbapenem-resistant *Klebsiella pneumoniae* infections, ceftazidime/avibactam-based regimens were associated with higher clinical efficacy, microbiological clearance, and a lower prevalence of acute kidney injury than polymyxin B-based regimens (Zhuang et al., 2025). These findings emphasize the importance of integrating effective antimicrobial therapy with approaches directed at dysregulated host inflammatory responses in severe lung infections.

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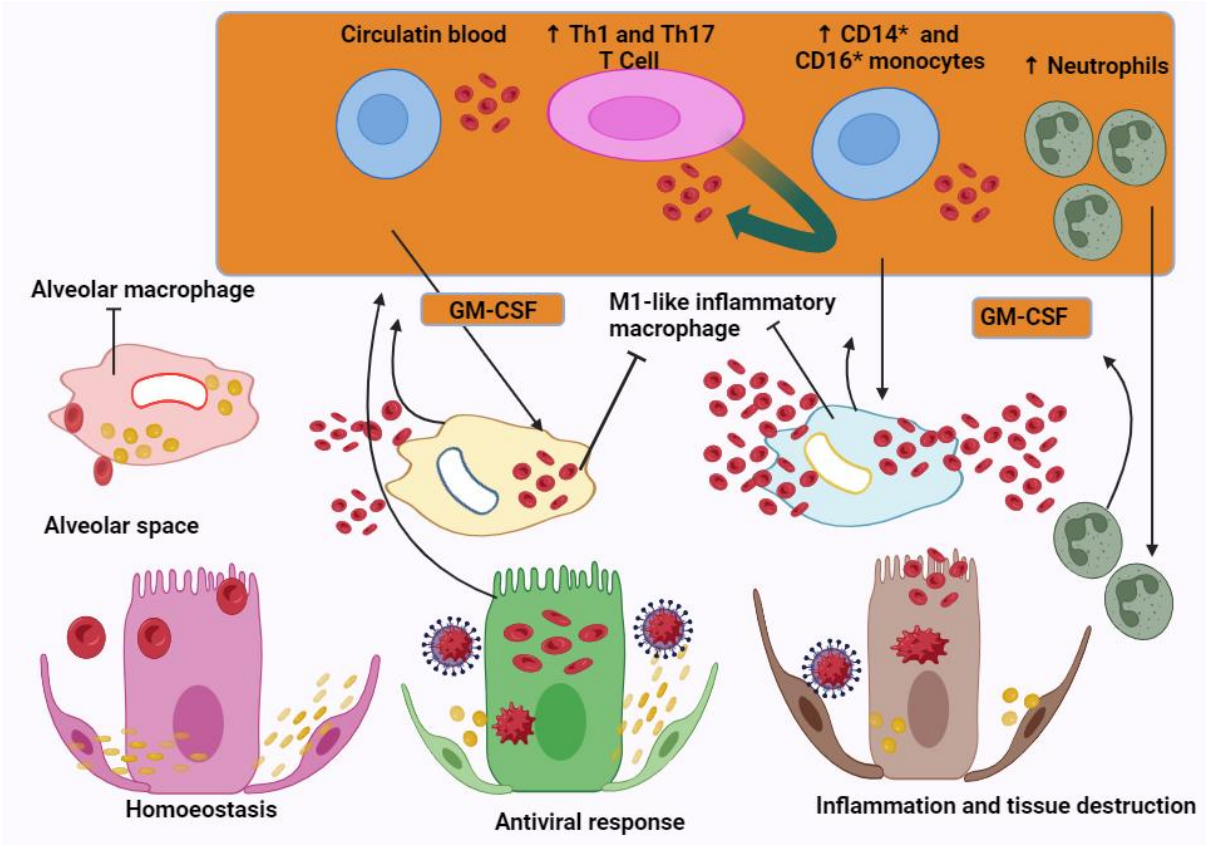

Figure 4: This diagram illustrates the immune response in the alveolar space of the lungs, particularly how various cells and signals interact during homeostasis, antiviral responses, and inflammatory processes. Key components include alveolar macrophages, Th1 and Th17 T cells, CD14+ and CD16+ monocytes, and neutrophils. The cytokine GM-CSF plays a central role in activating M1-like inflammatory macrophages, which are crucial for both antiviral defences and the propagation of inflammation that can lead to tissue destruction.

GM-CSF inhibition has been useful in the treatment of autoimmune diseases such as RA; it is beneficial in that, following GM-CSF inhibition, joint inflammation and pain are reduced. Neutralization of GM-CSF eliminates the inflammatory response, making this inflammatory mediator a possible target for autoimmune diseases (Shiomi et al., 2016). In RA, GM-CSF blockage counteracts inflammation and retards the progression of arthritis. It would also eliminate pain by preventing immune cell access to inflamed joints (Lin et al., 2020). However, GM-CSF supplementation is beneficial in cases of idiopathic acquired alveolar proteinosis. This rare pulmonary condition is characterized by disruption of surfactant homeostasis. This causes a buildup and impairs gas exchange due to excess surfactant generation. GM-CSF administration would help in the clearance of surfactant, re-establishing normal pulmonary function (Seymour et al., 2001). On the other hand, the administration of GM-CSF in patients with tuberculosis is feasible, as GM-CSF gene transfer is known to enhance antimycobacterial immunity. It recruits host macrophages to the lungs, which are important cells for handling mycobacterial infections. The approach is to modulate the host immune response by activating lung macrophages, which subsequently reduces mycobacterial loads (Singpiel et al., 2016). In addition to host-directed immunomodulation, optimization of antimicrobial exposure is important in the management of opportunistic pulmonary infections. In a retrospective cohort of

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Table 3: The table summarizes research on GM-CSF in lung cancer, detailing its role in promoting tumorigenic environments and influencing tumor progression through various biological mechanisms.

Study Focus	Main Findings	Impacted Cells/Pathways	Context	Key Mechanisms	Reference
GM-CSF and NSCLC Xenografts	Induction of GM-CSF enhanced tumor growth.	Tumor microenvironment	NSCLC, Tumor Growth	Tumor Promotion, Cell Proliferation	Oshika et al., 1998
COX-2 and Lung Cancer	GM-CSF and G-CSF increased COX-2 expression, promoting tumor growth.	Lung cancer cells	COX-2-mediated cancer progression	COX-2 Upregulation, Cancer Cell Migration	Soufi et al., 2009
GM-CSF Gene-Modified Vaccines	Limited efficacy in clinical outcomes but potential for future optimization.	Immune cells, Tumor cells	NSCLC, Immunotherapy	Immunomodulation, Vaccine Optimization	Nemunaitis et al., 2004
GM-CSF Gene Transduced Vaccines	High immunogenic response, needs more research.	Immune system	NSCLC, Vaccine Effectiveness	Immune System Activation, Immunogenic Response	Maung et al., 2001
GM-CSF and uPA in Lung Cancer	GM-CSF increased uPA and matrix metalloproteinase production.	Lung cancer cells	Cancer cell invasion and metastasis	Protease Activation, Tumor Cell Invasion	Pei et al., 1999
GM-CSF and IL-3 on SCLC	Stimulated tumor proliferation and shortened DNA synthesis time.	SCLC cells	SCLC, Hematopoietic Growth Factors	Cell Growth Promotion, DNA Synthesis Acceleration	Berdel et al., 1992
GM-CSF and LAK Activity in Lung Cancer	Enhanced LAK cell antitumor activity in lung cancer.	Macrophages, lymphocytes	Lung cancer, Immune activation	Lymphocyte Activation, Enhanced Antitumor Activity	Takahashi et al., 2000
Combination Therapy with GM-CSF and Sintilimab	Safety and effectiveness in advanced NSCLC.	Immune system	NSCLC, Combination therapy	Immunotherapy, PD-1 Pathway Blockade	Ni et al., 2021
Chemotherapy Dosing with GM-CSF	Growth factors enabled increased chemotherapy dose intensity.	Cancer treatment	SCLC, Treatment intensity	Chemotherapy Enhancement, Dose Adjustment	Cerny et al., 2002

non-HIV patients with *Pneumocystis jirovecii* pneumonia receiving predominantly low-dose trimethoprim-sulfamethoxazole, higher sulfamethoxazole peak blood concentrations (>100 μg/mL) were associated with higher clinical improvement rates and lower 28-day mortality (Deng et al., 2026). The findings support therapeutic drug monitoring as a potential approach to individualized antimicrobial dosing in non-HIV PJP, particularly when conventional weight-based dosing does not reliably achieve therapeutic exposure. While these contrasting approaches to GM-CSF therapy reflect the pleiotropic roles of cytokines, they also underscore the importance of tailoring treatment strategies based on specific disease pathologies (Vebr et al., 2023). Whether it is an inhibition or supplementation, it is not a simple matter of more or less; it comes to the right ways to calibrate the treatment to strike the balance to enhance the immune defense while reducing pathological inflammation (Cicchese et al., 2018).

CHALLENGES AND FUTURE DIRECTIONS IN GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR INHIBITION

One of the major challenges of GM-CSF inhibition is that it shows promising results with a few critical challenges. As GM-CSF inhibition causes a range of toxicities and adverse immune responses, including CRS and neurotoxicity, it might be generally more concerning. Although CAR-T cell-based therapy is effective in CAR-T cell function, CRS and neurotoxicity are still crucial issues (Morris et al., 2022). Thus, organ infiltration and destruction are hindered. GM-CSF block has been successful in lowering these significant side effects while enhancing antitumor action. Some clinical trials have shown that GM-CSF blockade affects immune reactions (Sterner et al., 2019). Other studies have also noted that patients may develop neutralizing antibodies against GM-CSF products, potentially impairing therapeutic efficacy (Wadhwa et al., 2003). Patient selection strategies largely determine the success of GM-CSF inhibition. The selection of suitable biomarkers allows for the identification of appropriate therapeutic approaches and personalized therapy. For example, PBMC analysis was effective in revealing differences in T cell and myeloid cell populations between patients treated with checkpoint inhibitors and GM-CSF. Responders show significant differences in classical monocytes and DCs in the circulation compared to non-responders, which unlocks possible biomarkers for clinical outcomes (Keenan et al., 2019). Additionally, elevated expression of GM-CSF receptors on myeloid progenitors can serve as a potential marker for therapeutic response in chronic myelomonocytic leukaemia (CMML), offering avenues for personalized strategies (Padron et al., 2013)

Combining GM-CSF inhibition with other treatments, such as checkpoint inhibitors and immunotherapy, can yield synergistic effects. Combining pembrolizumab with GM-CSF results in durable responses and influences the T cell repertoire in advanced biliary cancer (Keenan et al., 2019). In CAR-T therapy, neutralizing GM-CSF minimizes CRS and neuroinflammation while enhancing antitumor activity (Sterner et al., 2019). In colorectal cancer models, combining a CSF-1R inhibitor, oncolytic viruses, and an anti-PD-1 antibody increases the proportion of CD8+ T cells in the tumor and bolsters antitumor immunity (Shi et al., 2019). Current research is in progress to improve GM-CSF inhibition methods and advance novel combination therapies. Single-cell immune profiling broadens the understanding of the impact of GM-CSF inhibition on cellular functionality. Such opportunities enable the detection of personal patient markers to make treatment methods more specific. Regarding CAR-T therapy, investigations have been conducted on how cells deficient in GM-CSF affect tumor cell activity (Sterner et al., 2019). Additionally, GM-CSF antagonists continue to be refined through affinity maturation and optimization to enhance the potency and specificity of therapeutic antibodies (Steidl et al., 2008) (Figure 5).

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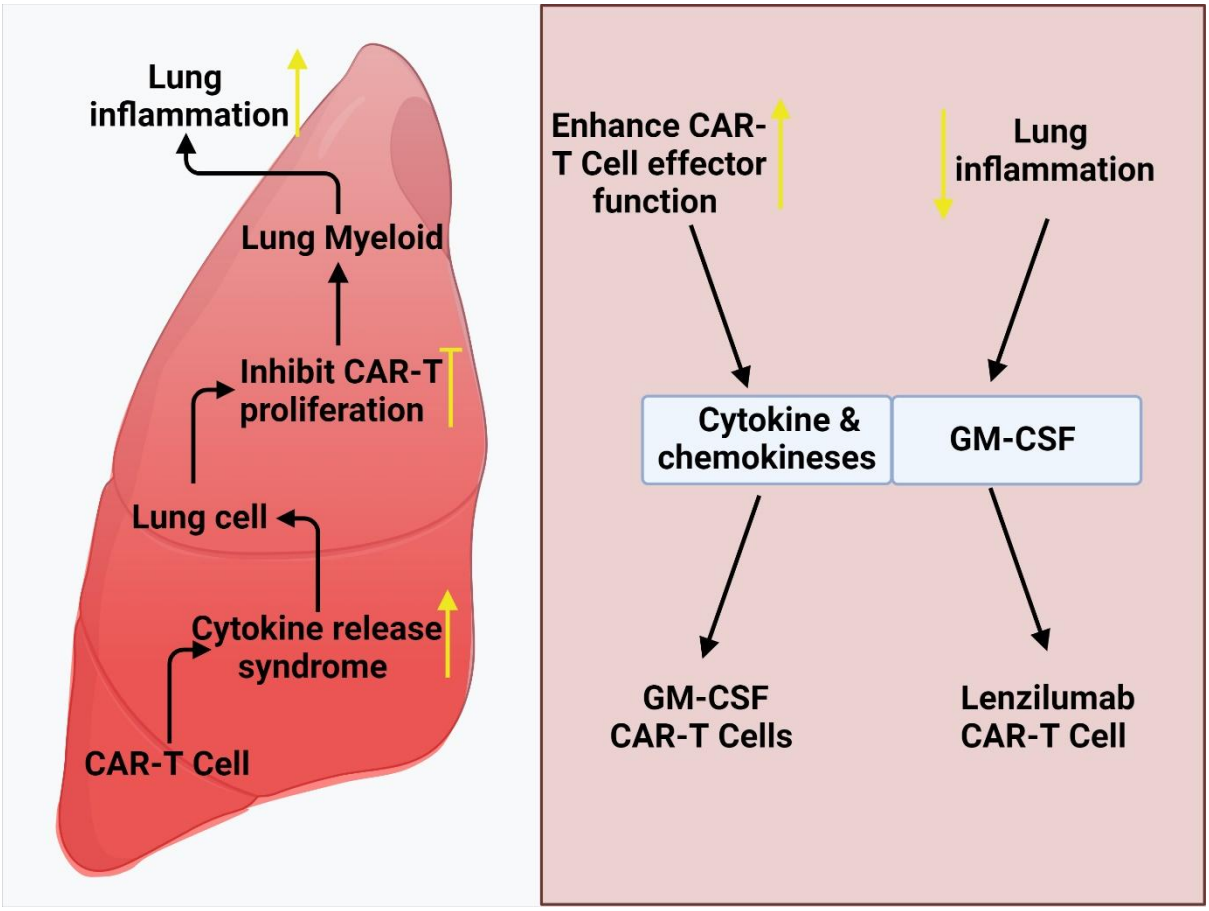

Figure 5: This diagram explores the interaction between CAR-T cells, lung cells, and inflammatory processes in the lung. It outlines how CAR-T cells can lead to cytokine release syndrome, subsequently inhibiting their own proliferation. Conversely, interventions like cytokines, chemokines, GM-CSF, and lenzilumab can enhance CAR-T cell effector function.

Key clinical and research implications

- GM-CSF directed therapy should be tailored to the disease context: GM-CSF blockade may prove useful for specific hyperinflammatory disease phenotypes, but signals are needed for alveolar macrophage function and surfactant clearance.
- Patient selection should incorporate GM-CSF, GM-CSFR expression, myeloid activation markers, and, once validated, genetic or epigenetic markers.
- In long-term trials, the following should be actively monitored: infection, pulmonary surfactant handling, risk of pulmonary alveolar proteinosis, and disruption of immune homeostasis.
- Mechanism-informed studies should compare ligand- and receptor-directed antagonists and evaluate rational combinations with immunotherapy with stratified clinical and pharmacodynamic endpoints.

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CONCLUSION AND FUTURE PERSPECTIVES

GM-CSF offers a crucial part in immune regulation and inflammation and is primarily implicated in ILDs. High levels of GM-CSF are reported to be corelated with the severity of ILDs, driving the assumption of its role in pathogenesis (Aegerter et al., 2022). Thus, GM-CSF induces asthma by affecting DC function and enhancing eosinophil migration into the respiratory airways, resulting in airway hyperresponsiveness and inflammation. In COPD, GM-CSF contributes to the perpetuation of the inflammatory response through a longer duration of macrophages and neutrophils (Frey et al., 2020). Moreover, GM-CSF is involved in lung cancer progression by promoting tumor necrosis and activating the inflammatory pathways. Various therapeutic approaches include GM-CSF inhibitors, particularly neutralizing antibodies, suggesting promise with reduced inflammation in these diseases (Essogmo et al., 2023). In chronic asthma and COPD, inhibition and neutralizing antibodies against GM-CSF could help reduce inflammation and improve clinical outcomes. Administering these compounds for cancer treatment could prevent exacerbations and serve as supportive treatments for patients resistant to anti-cancer drugs (Caramori et al., 2014). When combined with existing immunotherapeutic drugs, specifically neutralizing antibodies and GM-CSF inhibitors, the anti-cancer effects of these drugs could be enhanced. Moreover, carefully inhibiting GM-CSF may help manage anti-tumor activity in the cancer stage by controlling the stimulation of inflammatory pathways that trigger tumor development (Yuan et al., 2023). Blood and tumor tissues of the lung extracted from patients suspected of having the disease should be monitored regularly to determine increased or reduced GM-CSF levels. This may guide physicians in choosing a therapeutic approach by considering the patient's GM-CSF profile (Arndt et al., 2010).

Further investigation is required to improve GM-CSF inhibition strategies. To maximize therapeutic effectiveness and minimize off-target effects, therapeutic antibodies must be optimized to increase their specificity and affinity for GM-CSF. Another interesting avenue for investigating the direct effects of GM-CSF depletion on immune function and disease progression is the generation of GM-CSF-deficient cells (Fu et al., 2022). With the help of these cells, researchers may be able to simulate the effects of GM-CSF inhibition in a controlled setting, yielding insightful information that may help guide the clinical development of tailored treatments for patients with AML. The long-term effects of GM-CSF inhibition on immunological homeostasis must also be understood, as protracted suppression may make it more difficult for the immune system to fight infections and other immune threats (Chen et al., 2023a). Therefore, the combination of GM-CSF inhibitors with other treatment approaches should be investigated. This could include combining checkpoint inhibitors with GM-CSF inhibition as immunotherapies to boost antitumor responses in cancer therapy (Ouyang et al., 2024). It is important to do further study to determine the best way to combine these medications in order to optimize therapeutic advantages and minimize side effects. The creation of reliable biomarkers for the activation of the GM-CSF pathway is essential for patient classification and therapeutic observation (Arafah et al., 2023). Clinicians will be able to anticipate which patients would benefit the most from GM-CSF-targeted medicines by identifying these biomarkers. Furthermore, tracking these biomarkers over time may provide information on the progression of the illness and help modify treatment strategies (Thal et al., 2006). Clinical trial validation of these biomarkers will guarantee their precision and practicality in clinical practice, lowering the possibility of side effects and enhancing therapy effectiveness (Antoniou et al., 2019).

Author contributions

Muhammad Afzal: Data Curation, Investigation, Writing – Original Draft. Sami I. Alzarea: Investigation, Methodology, Writing – Original Draft. Imran Kazmi: Investigation, Methodology, Writing – Original Draft. Abida Khan: Investigation, Software, Validation. Surya Nath Pandey: Data Curation, Software, Visualization. Arcot Rekha: Formal Analysis, Visualization, Writing – Review & Editing. Jyoti Kalra: Investigation, Resources, Visualization. Rakhi Mishra: Conceptualization, Resources, Validation, Visualization. Deepika Raina: Formal Analysis, Software, Validation. **Gaurav Gupta**: Conceptualization, Supervision, Writing – Review & Editing. Kapil Kalra: Investigation, Resources, Visualization. **Md Sadique Hussain**: Conceptualization, Supervision, Writing – Review & Editing, Project Administration.

All authors have approved the final version of the manuscript.

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Consent to participate

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Clinical trial number

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Declaration of generative AI and AI-assisted technologies in the writing process

The authors utilized ChatGPT model 5 for editing parts of the manuscript, checking grammar, and improving the use of academic English. After using this tool, the authors thoroughly reviewed and edited the content and take full responsibility for the publication.

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