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Comprehensive Treatment Strategies for "Cardiac-Cerebral Comorbidities" in Cardiovascular Surgery

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Abstract:

The comorbidity of cardiovascular diseases and neurological disorders (referred to as "cardiac-cerebral comorbidities") is receiving increasing attention in the field of cardiovascular surgery. The "heart-brain synergy" strategy, as a comprehensive treatment concept, emphasizes the interaction and balance between the heart and brain, offering a novel perspective for the simultaneous treatment of "cardiac-cerebral comorbidities." This article focuses on common conditions in cardiovascular surgery and their perioperative neurological complications, elucidating the "heart-brain synergy" strategy to provide clinical practitioners with more scientific and effective treatment guidance.

Keywords:

Cardiovascular diseases
Neurological disorders
Comorbidity phenomenon
Cardiovascular surgery
Review

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1. Introduction

With the development of panvascular medicine, the treatment of comorbid cardiovascular and neurological diseases (hereafter referred to as "cardio-cerebral comorbidity") by cardiovascular surgery has drawn increasing attention. There is a significant comorbid relationship between cardiovascular diseases such as coronary artery disease, aortic dissection, hypertension, and atrial fibrillation, and cerebrovascular diseases such as ischemic and hemorrhagic strokes [1]. The comorbidity rate has been rising annually [2], particularly among the elderly population [3], adding complexity to cardiovascular surgical procedures and postoperative outcomes, while increasing the risk of disability and mortality. Against this backdrop, the "cardio-cerebral co-treatment" strategy has emerged as a crucial approach.

The "cardio-cerebral co-treatment" strategy is based on the interaction and balance between the heart and brain [4], emphasizing a comprehensive treatment concept. It advocates for the concurrent treatment of cardiovascular and neurological diseases and, in the field of cardiovascular surgery, focuses on preventing perioperative neurological complications, improving surgical success rates, and enhancing patient outcomes.

Although the application of the "cardio-cerebral co-treatment" strategy in cardiovascular surgery is still in its early stages, its potential and significance are increasingly recognized by clinicians and researchers [1].

This article discusses the "cardio-cerebral co-treatment" strategy for "cardio-cerebral comorbidity" in cardiovascular surgery, along with the principles for managing perioperative neurological complications, aiming to provide clinicians with more scientific and effective treatment guidance.

2. Coronary artery disease and carotid artery stenosis comorbidities

The comorbidity of coronary artery disease (CAD) and carotid artery stenosis is relatively common, with approximately 11.8% of CAD patients aged 60 and above also having carotid artery stenosis [5]. These two conditions are closely related in terms of pathophysiological mechanisms, clinical manifestations, and potential complications, presenting significant challenges in clinical treatment. Coronary artery bypass grafting (CABG) can improve myocardial blood supply and alleviate ischemic symptoms in CAD patients, while carotid endarterectomy (CEA) is an effective treatment for carotid artery stenosis, reducing the incidence of ischemic cerebrovascular events.

For CAD patients with severe carotid artery stenosis (70%–99% stenosis), undergoing standalone CEA may result in stress responses such as blood pressure fluctuations and heart rate changes, potentially worsening coronary artery stenosis and increasing the risk of perioperative myocardial infarction (7%–8%) [6]. Conversely, during standalone CABG, hemodynamic changes can affect cerebral blood flow, and the presence of carotid artery stenosis significantly increases the risk of perioperative cerebral hypoperfusion and stroke (7.4%–9.1%) [7-10].

Adopting a "cardio-cerebral co-treatment" strategy by performing simultaneous CABG and CEA offers distinct advantages: first, it significantly reduces the risk of perioperative neurological complications, particularly cerebrovascular events, thereby protecting both cardiovascular and cerebrovascular systems [11]; second, it shortens anesthesia and hospitalization durations, lowers medical costs, and improves hospital bed utilization rates [12]; finally, it optimizes cardiovascular and cerebrovascular hemodynamics, improving long-term outcomes and enhancing quality of life.

However, simultaneous surgery may increase the risk of postoperative cognitive dysfunction. Therefore, it is crucial to conduct a thorough preoperative evaluation of cerebrovascular conditions, especially carotid and intracranial artery stenosis [8], and to develop individualized treatment plans to minimize the risk of perioperative neurological complications and improve surgical success rates [9]. This will be an important direction for future research.

3. Managing aortic dissection with the heart-brain synergy strategy

Aortic dissection is a critical cardiovascular emergency that disrupts the structural integrity of the aorta and often involves the carotid arteries, leading to the formation of a false lumen. This can impair cerebral hemodynamics, causing ischemic brain events such as stroke, transient ischemic attacks (TIA), and cognitive dysfunction [13], resulting in permanent neurological deficits or even death [14,15]. Aortic dissection typically requires urgent open-chest surgical intervention to repair or replace the damaged aorta, a procedure associated with high risks, including neurological complications that severely impact patient outcomes and may lead to long-term cognitive and motor impairments.

The "cardio-cerebral co-treatment" strategy encompasses meticulous surgical techniques, comprehensive bedside monitoring (e.g., vital signs, neurophysiological monitoring, bedside ultrasound), and intraoperative cardiac and cerebral protective measures. This approach simultaneously addresses the aortic dissection and its potential neurological complications.

In 2022, the cardiovascular surgery team at Xiangya Second Hospital of Central South University proposed an innovative treatment strategy known as the "Brain-Heart Priority." During cardiopulmonary bypass in aortic dissection surgery, this strategy redefined the surgical workflow, cardiac perfusion, and cerebral protection methods. Unlike the conventional deep hypothermia (20–25°C) surgical environment, this approach utilizes mild

hypothermia (≥ 30°C) to reduce cooling and rewarming times effectively.

The surgical sequence is altered by first repairing and reconstructing the proximal ascending aorta and/or aortic root, followed by anastomosis of the left common carotid artery. Intraoperatively, cardiac and left common carotid artery perfusion is restored and maintained, significantly shortening the ischemic duration for both the heart and brain. Cardiopulmonary bypass management is optimized by adjusting cerebral perfusion flow to 1.00–1.23 L/(m²·min), aligning more closely with physiological needs without increasing the risk of stroke [16].

This strategy has yielded satisfactory outcomes, providing protection for both the cardiovascular and cerebrovascular systems, reducing the risk of perioperative stroke and other neurological complications, and improving the quality of life and long-term prognosis for patients. Additionally, it shortens intensive care unit stays and overall hospitalization durations, alleviating the economic burden on healthcare systems [16].

4. Patent foramen ovale and neurological comorbidities

Patent foramen ovale (PFO) is a congenital heart defect that allows thrombi or air emboli to pass from the right atrium to the left atrium through the unclosed foramen ovale, potentially causing ischemic stroke [17,18] or other neurological disorders such as transient ischemic attack and migraines [19,20]. For patients with PFO comorbid with neurological diseases, performing either PFO closure alone or intracranial arterial stenting alone has certain limitations.

While PFO closure can effectively prevent cardioembolic emboli from entering the cerebral vasculature via the unclosed foramen ovale, performing this procedure alone may miss the critical window for treating cerebral vascular stenosis. Conversely, intracranial arterial stenting alone cannot prevent cardioembolic emboli originating from the unclosed PFO, increasing the risk of stroke. Furthermore, long-term anticoagulation therapy required after intracranial arterial stenting increases the risk of intracranial hemorrhage in patients with comorbid PFO.

Simultaneously performing PFO closure combined with intracranial arterial stenting offers a more comprehensive treatment approach. This combined strategy not only addresses the limitations mentioned above but also reduces the risks associated with multiple surgeries for the patient.

5. Cardiac myxoma and neurological complications

Atrial myxoma is a rare cardiac tumor that, during its development, may shed emboli consisting of tumor fragments or surface-adhered thrombi. These emboli can travel through the bloodstream to the cerebral vasculature, causing cerebral ischemia [21]. A 2022 case report described a patient with biatrial myxoma who experienced pulmonary embolism and ischemic stroke during the perioperative period [22].

For patients with atrial myxoma comorbid with ischemic stroke, surgical treatment is more complex, with a heightened risk of postoperative cognitive dysfunction. The key to successful surgical treatment lies in comprehensive preoperative evaluation and a multidisciplinary team (MDT) approach. This strategy helps to clarify tumor characteristics (size, location, nature, and presence of thrombi), embolic risk (whether the tumor surface has easily dislodged thrombi), and tumor activity.

6. Conclusion

Intraoperatively, precise surgical techniques and stable hemodynamic management are critical, along with real-time neuroelectrophysiological monitoring to prevent emboli from entering the cerebral vasculature. Perioperative pharmacological treatment, particularly the appropriate use of anticoagulants and antiplatelet agents, is essential to reduce thrombus formation, while coagulation function should be closely monitored (international normalized ratio [INR] 2.00–2.50) to balance bleeding risk.

Implementing this “heart-brain synergy” strategy can effectively reduce the risk of perioperative neurological complications, enhance surgical safety and success rates, and improve patient outcomes.

In summary, the implementation of the "heart-brain synergy" strategy in cardiovascular surgery indicates significant potential for pan-vascular medicine in improving surgical success rates, reducing perioperative complications, and alleviating the economic burden on healthcare systems. The future development of the "heart-brain synergy" strategy should focus on precise identification of indications, requiring comprehensive evaluation of "cardiac-cerebral comorbidities" and multidisciplinary collaboration involving experts from cardiovascular and neurosurgery fields.

Simultaneous surgeries should prioritize not only surgical success rates but also long-term outcomes and quality of life. Additionally, prospective multicenter clinical studies should be conducted to provide high-level evidence-based support for refining the "heart-brain synergy" strategy.

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Disclosure statement

The author declares no conflict of interest.

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Research Progress of Cyclophilin A in Pulmonary Infectious Diseases

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Abstract:

Cyclophilin A (CyPA) is an immunophilin with peptidyl-prolyl cis-trans isomerase (PPIase) activity, widely expressed in various tissues and organs, including the lungs. Under inflammatory responses or external cytokine stimulation, CyPA is secreted extracellularly and binds to receptors such as CD147, activating signaling pathways like ERK/NF-κB. This promotes inflammatory cell chemotaxis and cytokine release, playing a role in the pathophysiological processes of various inflammatory diseases. The expression level of CyPA is positively correlated with the severity of inflammation in pulmonary diseases such as chronic airway inflammation, acute respiratory distress syndrome (ARDS), and COVID-19 pneumonia. Targeting CyPA has been shown to reduce inflammation and improve prognosis. This article reviews the research progress of CyPA in common pulmonary infectious diseases, providing insights into its mechanism of action in such conditions.

Keywords:

Cyclophilin A
Chronic airway inflammation
Acute respiratory distress syndrome
Viral pneumonia

Online publication:

1. Introduction

In 1984, Handschumacher *et al.* [1] first reported an 18 kD protein derived from bovine thymocytes, which was identified as the intracellular receptor for the immunosuppressant cyclosporin A and formally named Cyclophilin A (CyPA). Subsequently, Fischer *et al.* [2] discovered that CyPA and peptidylprolyl isomerase A (PPIA) are the same molecule, possessing peptidyl-prolyl cis-trans isomerase activity. CyPA is expressed in various cell types, such as vascular smooth muscle cells, endothelial cells, epithelial cells, and macrophages, and plays a role in multiple system diseases, including those of the cardiovascular, digestive, urinary, nervous, and rheumatic immune systems [3-6].

Beyond its intracellular functions, such as protein

folding and transport, CyPA has garnered attention in recent years as a novel inflammatory biomarker [7]. In a mouse model of systemic inflammation induced by a high-fat diet, elevated levels of CyPA and CD147 were detected in multiple organs and tissues [8]. Additionally, numerous studies have confirmed CyPA expression in inflammatory diseases such as vascular inflammation, rheumatoid arthritis, sepsis, and periodontitis [7,9,10]. However, its role in pulmonary infectious diseases remains underexplored.

The lungs, as a common site of infection, are a leading cause of mortality worldwide [11]. Pulmonary infections often result in severe respiratory failure and cardiovascular complications, characterized by high incidence, hospitalization rates, intensive care unit admissions, and mortality. For instance, hospitalized patients with community-acquired pneumonia (CAP) have in-hospital and one-year mortality rates of 6.5% and 30.6%, respectively, while for CAP patients admitted to the ICU, these rates increase to 17% and 47%, respectively [12]. Pulmonary infections significantly impact individual quality of life and impose a substantial economic burden on nations.

Accurately assessing the severity and prognosis of pulmonary infections is therefore critical, and targeted therapies may help address issues such as antibiotic overuse and rising resistance. This review discusses the roles and mechanisms of CyPA in pulmonary infectious diseases, aiming to provide a reference for its potential application in these conditions.

2. Structure and pro-inflammatory mechanisms of CyPA

Cyclophilin A, a member of the immunophilin protein family, is composed of 165 amino acids and contains 8 β-strands and 2 α-helices. It exhibits PPIA activity and is widely expressed in both prokaryotic and eukaryotic organisms [13]. CyPA is involved in various processes such as protein folding, cell proliferation and apoptosis, and cholesterol metabolism [5].

In addition to its catalytic role via PPIA activity, CyPA is secreted extracellularly under inflammatory conditions or external cytokine stimulation, functioning as extracellular CyPA (eCyPA) to mediate inflammatory responses. It exhibits strong chemotactic effects on lymphocytes, monocytes, and neutrophils [14], primarily through specific binding to CD147 [15,16]. However, the specific interaction groups between CyPA and CD147 remain controversial [5].

Apart from CD147, studies have shown that CyPA enhances the signaling specificity of myeloid cell trigger receptor-2 (TREM2), upregulating the production of pro-inflammatory cytokines, suggesting that TREM2 may be a novel receptor for CyPA [17]. CyPA also plays multiple roles in inflammation by participating in bacterial pathogenesis, such as regulating the formation of host actin cytoskeleton or membrane translocation of bacterial toxins [18].

Moreover, CyPA regulates the transcriptional activity of NF-κB p65, thereby increasing the production of pro-inflammatory cytokines [19]. For example, in atypical pathogens, the adhesion molecule MgPa secreted by Mycoplasma genitalium induces the secretion of eCyPA and its binding to CD147 on urinary epithelial cells, activating the extracellular signal-regulated kinase (ERK) phosphorylation/NF-κB pathway and mediating the adhesion and invasion of Mycoplasma genitalium into human urethral epithelial cells [20,21]. Similar mechanisms have been reported in Mycoplasma pneumoniae infections [22].

Additionally, CyPA regulates the degradation of the IL-6 membrane receptor gp130, positively modulating the IL-6 trans-signaling pathway and increasing downstream IL-6 and CyPA expression [23]. It promotes inflammation activation by increasing IL-1β production and facilitates inflammation resolution by enhancing pro-IL-1β degradation and IL-1-induced epithelial-mesenchymal transition [24].

In summary, CyPA plays a crucial role in inflammatory responses and is implicated in the pathogenesis of common pulmonary infections.

3. CyPA expression and mechanisms in different pulmonary infectious diseases

3.1. Progress in research on CyPA in chronic airway inflammatory diseases

3.1.1. Asthma

Asthma is one of the most common chronic airway inflammatory diseases, affecting approximately 272 million people worldwide as of 2017 [11]. It is

characterized by acute airway spasms, excessive mucus secretion, and pulmonary inflammation caused by various genetic and environmental factors [25]. Stemmy *et al.* [26] detected persistently elevated expression of eCyPA in the bronchoalveolar lavage fluid of a mouse model of chronic allergic asthma. In a rat model of asthma, treatment with recombinant CyPA protein (rCyPA) significantly reduced airway resistance, with no significant difference compared to traditional asthma medications such as terbutaline and hydrocortisone. *In vitro* experiments showed that rCyPA inhibited the secretion of both Th1 and Th2 cytokines [27].

The role of CyPA in asthma pathogenesis is complex. On one hand, CyPA inhibitors are thought to reduce the expression of inflammatory cells in asthma patients by targeting leukocyte recruitment [26]. On the other hand, since asthma is a Th2 immune response, research indicates that CyPA facilitates asthma development by catalyzing interleukin-2-inducible T-cell kinase (Itk) dimerization, reducing Itk protein kinase activity, and inhibiting T-cell activation [28].

Additionally, oxidative stress is a key mechanism in asthma pathogenesis, and antioxidant therapy has been shown to improve airway remodeling and hyperreactivity [29]. CyPA protects cardiomyocytes from oxidative damage via the AKT/Nox2 pathway [30]. Based on this, researchers suggest that oxidative stress may also be a mechanism by which CyPA contributes to asthma and propose CyPA as a potential therapeutic target for the disease [27].

3.1.2. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is another common chronic airway inflammatory disease characterized by irreversible airflow limitation, chronic airway inflammation, and emphysema [31]. In a study of 83 COPD patients with pulmonary infections, CyPA expression in peripheral blood was significantly elevated compared to controls and positively correlated with disease severity, making CyPA a valuable predictor of disease progression in COPD [32].

Another study found significantly increased serum CyPA levels during both the acute exacerbation and recovery phases of COPD. The researchers proposed that CyPA enhances its pro-inflammatory effects by inducing the expression of IL-6 and MMP-9. Serum CyPA levels were negatively correlated with lung function parameters such as FEV1% and FEV1/FVC during the recovery phase of COPD [33].

These findings suggest that serum CyPA could serve as a potential inflammatory biomarker for COPD, with its levels reflecting disease severity. However, current research on CyPA in COPD is limited to clinical studies, and its molecular mechanisms remain unclear, requiring further investigation.

3.2. Progress in research on CyPA in acute lung injury/acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) or acute lung injury is one of the common critical respiratory conditions. It occurs when severe infections, trauma, burns, or other factors cause damage to pulmonary capillary endothelial cells and alveolar epithelial cells, resulting in diffuse pulmonary interstitial and alveolar edema, leading to persistent hypoxemia and respiratory distress. ARDS is considered a primary manifestation of systemic inflammatory response syndrome in the lungs [34].

In a retrospective study, Koh *et al.* [35] analyzed animal and human bronchoalveolar lavage fluid (BALF) samples and proposed that eCyPA is a biomarker for ventilator-induced lung injury (VILI). Compared to healthy volunteers, eCyPA levels in the BALF of ARDS patients were 5–6 times higher. The study also found a positive correlation between eCyPA levels in BALF from VILI mice and markers of lung injury and alveolar epithelial permeability. Blocking CyPA improved survival rates and lung injury, including lung function and oxygenation, in overventilated mice [35]. This suggests the potential value of eCyPA in reflecting alveolar epithelial injury.

In a sepsis mouse model, neutralizing mouse CyPA with an anti-*Clonorchis sinensis* CyPA antibody increased the 72-hour survival rate of septic mice. The protective effect was dose-dependent, with treated mice showing reduced histopathological damage and inflammatory cell infiltration in the lungs and other tissues [36]. This finding supports earlier studies showing that targeting CyPA alleviates lung injury in septic mice [37].

In the pathogenesis of ARDS, experiments have demonstrated that alveolar epithelial cells secrete eCyPA under mechanical stress, such as stretching. eCyPA interacts with CD147 to activate alveolar macrophages,

inducing cytokine secretion and matrix metalloproteinase release within the lungs, ultimately increasing the permeability of the alveolar epithelial barrier [35].

CD147 plays a significant role in the pathophysiology of acute lung injury, but understanding of the downstream mechanisms activated by CD147 remains limited. Koh *et al.* [35] also reported that eCyPA levels in serum samples from acute lung injury patients did not differ significantly from controls. Furthermore, early BALF samples are typically unavailable in patients who can breathe independently.

Although CyPA is a promising therapeutic target for mitigating lung injury and improving survival in ARDS patients, clinical application remains challenging. Gaining a better understanding of CyPA's mechanisms of action and developing simpler methods for sample collection will aid in addressing these issues [38].

3.3. Progress in research on CyPA in viral pneumonia

3.3.1. COVID-19

The coronavirus disease 2019 (COVID-19) is highly infectious and has rapidly spread worldwide since its outbreak in Wuhan in late 2019. Both the number of infections and the geographic spread of the epidemic have far surpassed previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks [39], posing a significant threat to global public health. A meta-analysis of host genes associated with beta-coronavirus infections identified the gene encoding CyPA (PPIA) as the most significant among over 5,000 related genes [40]. ELISA analyses revealed that CyPA levels in the plasma of severe/critical COVID-19 patients were significantly higher than in mild cases and healthy controls. Additionally, in lung tissues of COVID-19 patients, CyPA was strongly positively correlated with CD68, CCL2, and IL-6 [41]. This suggests that CyPA is linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and may serve as a critical pro-inflammatory factor.

A multicenter, randomized, double-blind, controlled international clinical trial showed that the CD147 inhibitor Meplazumab produced beneficial outcomes in severe COVID-19 patients, including reduced mortality, viral load, and cytokine levels [42]. Animal experiments confirmed that *CD147* gene knockout significantly inhibited SARS-CoV-2 infection, and Meplazumab effectively suppressed all viral variants except Kappa [43]. These findings underline the role of CD147 in SARS-CoV-2 infection and suggest its potential as a therapeutic target.

Researchers have proposed the "spike protein-CD147-CyPA signaling axis" as a mechanism for the cytokine storm in COVID-19. Spike protein binding to CD147 activates the JAK-STAT pathway, inducing CyPA expression. CyPA then binds to CD147, triggering the MAPK pathway, which regulates cytokine and chemokine expression, thereby promoting the cytokine storm [41]. However, some scholars argue that CD147 directly or indirectly influences SARS-CoV-2 entry into host cells via angiotensin-converting enzyme 2 (ACE2), rather than through the CD147-CyPA complex [44]. Despite these debates, targeting the CyPA/CD147 axis is regarded as a promising therapeutic approach for COVID-19.

3.3.2. Other viral pneumonia

Beyond COVID-19, CyPA plays a role in the pathogenesis of other viral pneumonia. For example, CyPA expression was significantly upregulated in bone marrow-derived macrophages infected with influenza A virus (IAV) [45]. Bai *et al.* [46] demonstrated in an IAV-induced mouse model that CyPA promotes integrin α5 expression and actin cytoskeleton rearrangement via the FAK/Akt pathway, enhancing Streptococcus group A infection and increasing pulmonary inflammatory infiltration. Further studies revealed that cyclosporin binding to CyPA reduced IAV-induced inflammation by shifting macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype through the IFN-γ/STAT1 and IL-4/STAT6 pathways [47].

Other studies have shown that CyPA interacts with the IAV matrix protein M1, regulating ubiquitin-proteasome-mediated M1 degradation to inhibit viral replication [48]. In mice infected with influenza B virus (IBV), enzymes promoting CyPA degradation (proteolysis-targeting chimeras, PROTACs) reduced inflammation and lung damage. Combined treatment with oseltamivir and PROTACs was most effective in suppressing inflammatory cytokines [49]. These findings suggest that targeting CyPA with PROTACs may be a

potential therapeutic strategy for IBV-induced pneumonia.

3.3.3. Balancing pro-inflammatory and antiviral roles

In addition to its pro-inflammatory effects, CyPA also has antiviral properties. For example, human CyPA can block the binding of the SARS-CoV-2 receptor-binding domain (RBD) to the ACE2 receptor, thereby preventing SARS-CoV-2 entry into host cells [50]. Dittmar *et al.* [51] demonstrated that cyclosporin analogs exhibit strong anti-SARS-CoV-2 activity in alveolar epithelial cells in a CyPA-dependent manner. In a respiratory syncytial virus (RSV) mouse model, CyPA knockdown resulted in more severe lung inflammation and increased inflammatory cell infiltration compared to controls [52], suggesting that CyPA inhibits RSV replication.

Therefore, achieving a balance between the pro-inflammatory and antiviral roles of CyPA is crucial for the development of CyPA-targeted therapies for viral pneumonia.

4. Summary

Cyclophilin A is a multifunctional protein that plays a critical role in various pathological conditions. It is secreted from cells through paracrine or autocrine mechanisms, mediating the release of inflammatory cytokines. The expression level of CyPA reflects the severity and prognosis of inflammation. Targeting CyPA for therapy can reduce pulmonary inflammation and improve disease outcomes.

Thus, CyPA can serve as a biomarker for the diagnosis and prognosis of various inflammatory lung diseases and holds promise as a key therapeutic target for alternative treatments in pulmonary infectious diseases. However, current research on CyPA-targeted therapies primarily focuses on its antiviral properties, with clinical applications in anti-inflammatory treatment remaining limited. Additionally, studies on CyPA in bacterial, Mycobacterium tuberculosis, and atypical pathogen infections and treatments are relatively scarce, requiring further investigation.

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