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Title:

Amphiregulin and Its Emerging Roles in Pulmonary Pathophysiology

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Abstract

Amphiregulin (AREG), a member of the epidermal growth factor (EGF) family, is widely expressed in multiple tissues and regulates various physiological and pathological processes through activation of the epidermal growth factor receptor (EGFR). Accumulating evidence suggests that AREG exerts significant influence on a range of pulmonary conditions, including lung injury, inflammatory disorders, chronic airway diseases, bronchopulmonary dysplasia, and lung cancer. By modulating epithelial repair, immune cell function, fibroblast proliferation, and airway remodeling, AREG contributes to both protective and pathogenic outcomes in diverse lung pathologies. This review summarizes the structural and functional attributes of AREG, and synthesizes current knowledge on its involvement in pulmonary diseases. Understanding the molecular and cellular mechanisms underlying AREG's actions in the lung may inform the development of novel therapeutic strategies to manage and treat respiratory conditions.

1. Introduction

Amphiregulin (AREG) was first identified as a bifunctional growth factor capable of modulating cell proliferation in both transformed and normal cells [1]. As a ligand for the epidermal growth factor receptor (EGFR), AREG triggers downstream signaling cascades involved in cell survival, proliferation, and differentiation [2–4]. Though initially studied in the context of breast carcinoma,

recent research has broadened understanding of AREG's roles in inflammation, tissue repair, and remodeling [5].

In the lung, these processes are vital for maintaining tissue integrity and responding to injuries. Dysregulated AREG expression or signaling is increasingly recognized in conditions ranging from acute lung injury (ALI) and chronic inflammatory airway diseases, such as asthma, to neonatal disorders like bronchopulmonary dysplasia (BPD) and lung cancers. This review outlines AREG's structure and function, and highlights recent insights into its significance in pulmonary diseases.

2. Structure and Function of Amphiregulin

The human AREG gene is located on chromosome 4 and encodes a transmembrane precursor protein of approximately 252 amino acids [6]. This precursor contains multiple functional domains, including a hydrophobic signal sequence, a heparin-binding region, an EGF-like motif that facilitates EGFR binding, and a transmembrane domain followed by a cytoplasmic tail [7,8]. Cleavage of the membrane-anchored precursor by proteases like TNF-α converting enzyme releases the soluble, mature ligand [9]. As a result, AREG can act in either a juxtacrine or paracrine manner to influence EGFR-driven signaling cascades [10].

AREG promotes cell growth, differentiation, and survival across various cell types, including epithelial and immune cells [2]. In normal physiology, it aids in tissue maintenance and repair; however, in pathological states, aberrant AREG signaling can contribute to chronic inflammation, fibrosis, and oncogenesis [5,11].

3. Amphiregulin in Lung Diseases

3.1. Pulmonary Inflammatory Disorders

AREG expression is upregulated in response to diverse inflammatory stimuli, including viral and bacterial infections [12]. Emerging evidence suggests that AREG production by innate immune cells, including group 2 innate lymphoid cells (ILC2s), mast cells, and macrophages, supports epithelial integrity and repair following influenza infection [13,14]. In chronic inflammatory conditions, such as those induced by persistent irritants or pathogens, sustained AREG signaling may promote pathologic tissue remodeling and fibrotic changes [15]. For example, increased AREG expression was observed in patients recovering from COVID-19, where it may contribute to fibrosis through interplay with immune cells and the extracellular matrix [16,17].

3.2. Acute Lung Injury

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), involve alveolar epithelial damage and inflammatory cell infiltration [18]. Studies demonstrate that mechanical stress or lipopolysaccharide (LPS) exposure can elevate AREG in alveolar epithelial cells, macrophages, and other immune cells [19]. By engaging EGFR-AKT signaling, AREG may limit inflammatory damage and support epithelial cell survival. Pharmacological blockade of EGFR or AKT signaling attenuates AREG's protective effects, highlighting the ligand's potential as a target for modulating ALI severity [20,21].

3.3. Asthma and Airway Remodeling

Asthma is characterized by chronic airway inflammation, hyperresponsiveness, and remodeling. Elevated AREG levels have been found in the airways of asthmatic patients, particularly in epithelial and immune cells [22,23]. AREG can stimulate airway smooth muscle proliferation and contribute to bronchial

hyperplasia [24]. Additionally, it may enhance the release of pro-inflammatory and pro-fibrotic mediators, thus exacerbating airway remodeling. Conversely, controlling AREG activity could mitigate these detrimental changes, potentially improving asthma management [25,26].

3.4. Bronchopulmonary Dysplasia

BPD is a chronic lung disease in preterm infants marked by impaired alveolar development [27]. AREG and EGFR signaling influence alveolar and vascular growth in the developing lung. Elevated AREG expression during mechanical ventilation or prenatal injury may hinder proper alveolarization [28,29]. Interventions that normalize AREG expression or block aberrant EGFR signaling have shown promise in experimental BPD models, suggesting potential therapeutic approaches to preserve alveolar structure in vulnerable neonates [30,31].

3.5. Lung Cancer

AREG overexpression is well documented in various cancers, including non-small cell lung cancer (NSCLC) [32–34]. In lung tumors, AREG can promote cell proliferation, survival, angiogenesis, and resistance to targeted therapies, such as EGFR inhibitors [35,36]. High AREG levels correlate with tumor aggressiveness, poor prognosis, and gefitinib resistance [37]. Targeting AREG or its downstream signaling pathways may enhance the efficacy of existing treatments and improve outcomes for patients with lung cancer.

4. Conclusions and Future Perspectives

AREG plays multifaceted roles in lung biology, shaping the response to injury, infection, inflammation, and tumorigenesis. While it can facilitate tissue repair and regeneration, dysregulated AREG-EGFR signaling drives pathological

remodeling, fibrosis, and oncogenic transformation. The precise contextual cues that determine AREG's dualistic roles remain to be fully elucidated.

Future research should focus on dissecting the molecular networks controlling AREG expression and activity in specific lung cell populations. Moreover, developing therapeutics that selectively modulate AREG-EGFR signaling could offer new strategies for managing lung diseases. Improved understanding of AREG's involvement in lung pathophysiology promises to guide the design of more effective and targeted interventions for patients suffering from a range of respiratory disorders.

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Conflicts of Interest

The authors declare no competing interests.