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Opinion

PLET1-Expressing Macrophages: An Emerging Player in Asthma Pathogenesis and Airway Repair

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Abstract

Asthma is a heterogeneous chronic inflammatory disease characterized by persistent airway inflammation, epithelial injury, and structural remodeling. While macrophages are among the most abundant immune cells in the lung, their functional diversity in asthma remains incompletely understood. Recent advances in single-cell transcriptomics have identified previously unrecognized macrophage subsets expressing Placenta Expressed Transcript 1 (PLET1), a molecule traditionally associated with epithelial regeneration and tissue repair. Emerging evidence from lung injury and fibrotic disease models suggests that PLET1-expressing macrophages may participate in tissue repair, extracellular matrix remodeling, and immune regulation. However, their contribution to asthma has received little attention. This opinion article proposes that PLET1-expressing macrophages represent an overlooked component of airway immunity that may integrate epithelial repair with inflammatory responses during asthma progression. Potential mechanisms through which these cells could influence airway remodeling, type 2 inflammation, and disease resolution are discussed, together with the major unanswered questions in the field. It is further proposed that investigating PLET1-expressing macrophages may identify novel biomarkers and therapeutic targets, thereby advancing precision medicine strategies for asthma.

Keywords: *Asthma; Placenta Expressed Transcript 1 (PLET1); Type 2 Inflammation*

Introduction

Asthma affects more than 300 million individuals worldwide and remains one of the leading causes of chronic respiratory morbidity. Although advances in biologic therapies have improved outcomes for patients with severe disease, many individuals continue to experience persistent airway inflammation, progressive airway remodeling, and incomplete responses to current treatments [1]. Macrophages constitute the dominant immune population within the lung and perform diverse functions including pathogen clearance, immune regulation, tissue repair, and maintenance of pulmonary homeostasis. Traditionally, macrophages have been classified into pro-inflammatory (M1) and alternatively activated (M2) phenotypes. However, recent single-cell RNA sequencing studies have demonstrated that macrophage biology is considerably more complex, revealing multiple specialized populations with distinct transcriptional programs [2,3]. Among these newly identified subsets, macrophages expressing Placenta Expressed Transcript 1 (PLET1) have emerged as potential regulators of tissue repair [4]. Although these cells have been described in models of lung injury and fibrosis, their role in asthma remains largely unexplored. We believe this represents an important gap in current asthma research.

Why PLET1+ macrophages deserve attention

PLET1 was initially characterized as an epithelial-associated protein involved in tissue regeneration and cellular differentiation [5]. More recently, single-cell studies have identified macrophage populations expressing PLET1 during tissue injury and repair, suggesting that PLET1 is not restricted to epithelial cells. These macrophages appear to emerge in environments characterized by epithelial damage and active tissue remodeling. Their transcriptional signatures indicate involvement in extracellular matrix organization, wound healing, phagocytosis, and interactions with epithelial and stromal cells [4]. This biology closely resembles many of the pathological processes that define chronic asthma. Repeated epithelial injury is considered a central event in asthma. Damage caused by allergens, respiratory viruses, environmental pollutants, and chronic inflammation repeatedly disrupts the airway epithelial barrier, triggering repair responses that frequently become dysregulated. Persistent epithelial injury and aberrant repair contribute to airway remodeling, characterized by goblet cell hyperplasia, subepithelial fibrosis, increased airway smooth muscle mass, and excessive extracellular matrix deposition, ultimately leading to irreversible structural changes and progressive airflow limitation [6]. Moreover, while FABP4$^+$, SPP1$^+$, GPNMB$^+$, and TREM2$^+$ macrophage states have been increasingly characterized in lung homeostasis, fibrosis, and repair [3,7-9], whether the recently described PLET1$^+$ regenerative macrophage population [4] contributes to airway epithelial restoration or disease progression in asthma remains unknown. I therefore propose that PLET1-expressing macrophages may function at the interface between inflammation and tissue repair, influencing whether airway healing proceeds toward restoration of normal tissue architecture or pathological remodeling.

A new perspective on asthma pathogenesis

Rather than acting solely as PLET1+ tissue repair macrophages, they may coordinate multiple biological processes simultaneously. First, they may communicate directly with damaged airway epithelial cells through growth factors and cytokines that promote epithelial regeneration. Failure of this repair program could perpetuate chronic inflammation. Second, these macrophages may regulate extracellular matrix remodeling by interacting with fibroblasts and myofibroblasts. If their repair activity becomes prolonged or dysregulated, they could contribute to excessive collagen deposition and irreversible airway remodeling observed in severe asthma. Third, PLET1+ macrophages may participate in the resolution phase of inflammation by clearing apoptotic cells and limiting excessive immune activation. Impaired function of these macrophages could therefore prolong inflammatory responses and delay tissue recovery after allergen exposure. Finally, their phenotype may be shaped by the type 2 cytokine environment characteristic of allergic asthma. Cytokines such as IL-4, IL-13, IL-33, and Thymic Stromal Lymphopoietin (TSLP) may influence the differentiation or activity of PLET1-expressing macrophages, potentially explaining differences between asthma endotypes and disease severity. Collectively, these possibilities suggest that PLET1+ macrophages represent more than another macrophage subset they may integrate epithelial repair, immune regulation, and structural remodeling within the asthmatic airway.

Future directions

The existence of PLET1-expressing macrophages raises several important questions that deserve immediate investigation. Future studies should determine whether these macrophages are enriched in patients with mild, severe, eosinophilic, neutrophilic, or steroid-resistant asthma. Single-cell RNA sequencing combined with spatial transcriptomics could establish their localization within the airway and define their interactions with epithelial cells, fibroblasts, and other immune populations. Functional studies using experimental asthma models should investigate whether selective depletion or modulation of PLET1+ macrophages alters airway inflammation, mucus production, airway hyperresponsiveness, or tissue remodeling. From a translational perspective, PLET1 expression could potentially serve as a biomarker for active airway remodeling or therapeutic response. If these macrophages are found to promote tissue repair without exacerbating inflammation, strategies aimed at enhancing their beneficial functions may represent an entirely new therapeutic approach for asthma. Recent transcriptomic analyses identify PLET1-expressing macrophages as a regenerative macrophage state that promotes epithelial repair through macrophage-epithelial crosstalk following lung injury [4,6]. Whether these cells also orchestrate extracellular matrix remodeling and communicate with stromal cells during chronic airway diseases such as asthma remains unknown and represents an important area for future investigation

Conclusion

Recent advances in single-cell technologies continue to reshape our understanding of macrophage diversity within the lung. PLET1-expressing macrophages represent an emerging population with potential roles in epithelial repair, extracellular matrix remodeling, and immune regulation. Although direct evidence in asthma remains limited, the biological characteristics of these cells strongly suggest their involvement in processes central to disease pathogenesis. I propose that PLET1+ macrophages constitute an overlooked component of airway immunity deserving focused investigation. Elucidating their function may bridge current gaps between chronic inflammation and tissue remodeling while identifying novel biomarkers and therapeutic targets for precision medicine in asthma. I propose that the regenerative PLET1+ macrophage program identified during viral lung repair may also operate in chronic allergic airway disease, where repeated epithelial injury and dysregulated tissue repair are hallmarks of asthma.

Declarations of Interest

I declare that I have no competing interests.

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