

Research Advance

Autocrine motility factor receptor as a therapeutic target for asthma: *comments on ‘AMFR drives allergic asthma development by promoting alveolar macrophage-derived GM-CSF production’*

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Asthma is a chronic inflammatory disease characterized by airway hyper-responsiveness and tissue remodeling (Nobs et al., 2021). Although explorations into the pathogenesis of asthma are increasing, the underlying molecular and cellular mechanisms of asthma remain indistinct, and existing targeted therapy strategies are still limited and ineffective. Therefore, it is necessary to explore the mechanisms of asthma and identify new therapeutic targets for asthma treatment.

Alveolar macrophages (AMs), one of the prominent immune system cells in the lung, have been implicated in the development and progression of asthma (Evren et al., 2020). Accumulating evidence suggests that AMs can promote the differentiation and proliferation of T helper 2 (Th2) cells, mediate the recruitment, accumulation, and degranulation of eosinophils within inflamed sites, and regulate epithelial integrity and smooth muscle responses (Evren et al., 2020). However, the detailed mechanism by which AMs regulate cell–cell crosstalk in asthma is still a knowledge gap regarding the roles of AMs in asthma pathogenesis.

In our recent publication (Zhang et al., 2022), we reported that autocrine motility factor receptor (AMFR) was upregulated in AMs of asthma by conducting a transcriptomic analysis. As a membrane-bound protein, AMFR was initially identified as a cell surface receptor for cytokines (Liu et al., 2021). Later, researchers found that AMFR was an endoplasmic reticulum-resident E3 ubiquitin ligase mediating the endoplasmic reticulum-associated degradation pathway (Fang et al., 2001) and participating in immune response (Wang et al., 2014). However, its role in asthma has never been studied.

Based on the upregulation of AMFR in AMs in asthma, we established myeloid cell-restricted AMFR-deficient mice and found that AMFR deficiency significantly decreased allergy-induced Th2 and eosinophilic inflammation with less granulocyte–macrophage colony-stimulating factor (GM-CSF) production in AMs. Mechanistically, we identified that under thymic stromal lymphopoietin (TSLP) stimulation, elevated AMFR in AMs could promote K48-linked ubiquitination and degradation of cytokine-inducible SH2-containing protein (CIS) on Lys98, consequently blocking the inhibitory effect of CIS on STAT5 phosphorylation and its downstream GM-CSF production (Figure 1).

GM-CSF was first identified as the hematopoietic growth factor for myeloid

cell development and maturation. However, growing evidence supports the notion that GM-CSF has a major role in some inflammatory diseases (Dougan et al., 2019). GM-CSF has also been implicated as a mediator in asthmatic pathogenesis. For example, it was demonstrated that overexpression of GM-CSF in the sputum and the bronchial mucosa was a particular feature of severe asthma (Saha et al., 2009). GM-CSF receptor alpha-deficient (*Csf2ra*^{-/-}) mice were shown to have less asthmatic inflammation compared with wild-type mice (Nobs et al., 2021). Here, our study illustrated that AM-derived GM-CSF was essential for mediating the crosstalk between AMs and eosinophils and Th2 cells. A previous study reported that alveolar epithelial type 2 cell-derived GM-CSF and AM-derived GM-CSF were different in mediating AM development and homeostasis (Gschwend et al., 2021), and thus, we speculate that GM-CSF can regulate the function of various types of cells in asthma, and targeting GM-CSF will be a new direction for asthma treatment.

TSLP is an alarmin cytokine in asthma. Accordingly, targeting TSLP and TSLP-mediated signaling is considered as an attractive therapeutic strategy for asthma, and the FDA has recently approved tezepelumab (a human monoclonal antibody that binds to TSLP)

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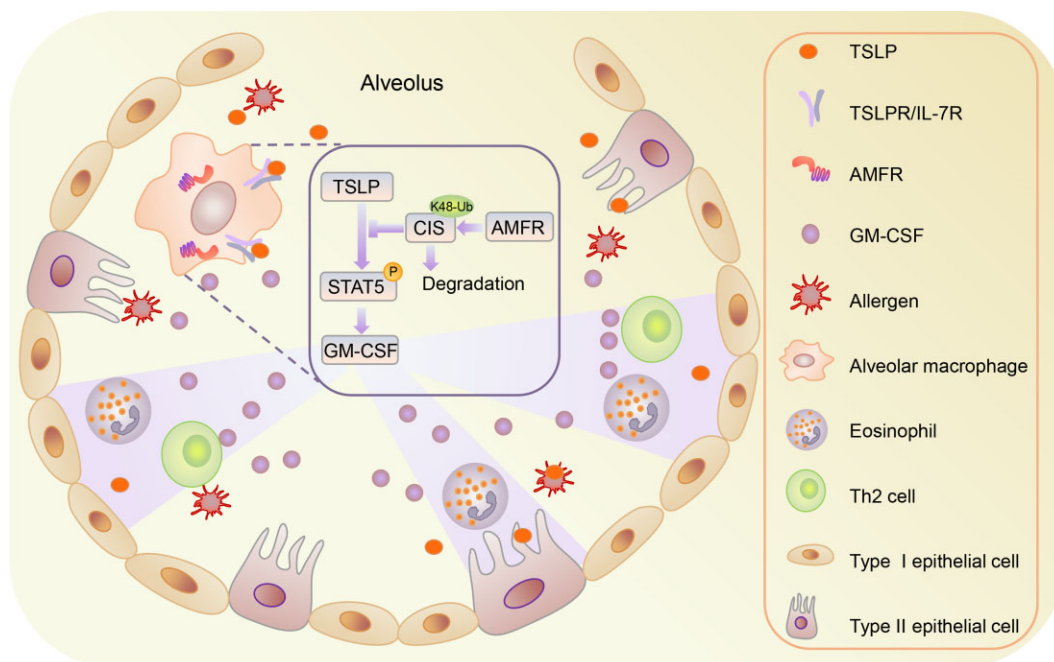


Figure 1 Illustration of the role of AMFR in AMs in asthma. In allergic asthma, TSLP induces the upregulation of AMFR in AMs, and this in turn promotes K48-linked ubiquitination and degradation of CIS, resulting in augmented activation of STAT5 and GM-CSF production. The elevated GM-CSF promotes eosinophil accumulation and Th2 reactions in the airway.

as a first-in-class treatment for severe asthma (Mullard, 2022). In our study, we found that AMFR regulated the TSLP signaling in AMs by mediating the degradation of CIS in asthma (Zhang et al., 2022). As CIS belongs to the suppressor of cytokine signaling family, and it can regulate several intracellular cytokine signal cascades such as IL-2, IL-3, and IL-5 (Delconte et al., 2016), it is worthwhile to explore whether AMFR also modulates the degradation of CIS in these signaling cascades. In addition, targeting essential cytokines in asthma and finding novel regulatory molecules of their pathways will provide more directions for the treatment of the disease.

Significant progress has been made in identifying the role of AMs in the pathogenesis of asthma. Targeting and modulating the functions of AMs, combined with reducing airway inflammation, would be of clinical significance to asthma. However, considering the fact that macrophages show significant heterogeneity in function, identifying novel biomarkers and targeting certain protein molecules relevant to individual phenotypes in AMs are still limited. Here,

we found that the E3 ubiquitin ligase AMFR was upregulated in AMs in asthma. We also identified its intricate regulatory mechanism in regulating the TSLP signaling in asthma. Due to this intricate network of cellular and marker interplay, our study opens up an array of therapeutic targets for the future to modulate macrophage function and immune responses in asthma. Also, we believe that through further clinical research and correlation analysis with various types of asthma, modulation of macrophage function through molecular intervention by targeting some of the potential macrophage regulators, such as AMFR, may have therapeutic potential in the treatment of allergic asthma and other allergic diseases.

In conclusion, our research linked the ubiquitin pathway to the function of AMs in the development and exacerbation of asthma. Furthermore, we identified that the expression of AMFR in AMs could be used as a clinical prognostic biomarker of asthma development and progression to evaluate the risk of asthma (Zhang et al., 2022). This study not only expands our insight into AMFR biological function but

also provides a new potential drug target for allergic disease therapies in the future.

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