



Targeting airway macrophages for inflammatory lung diseases – insights from traditional Chinese medicine

Ruowen Ge

Department of Biological Sciences, National University of Singapore, Singapore, Singapore

Correspondence to: Ruowen Ge. Department of Biological Sciences, National University of Singapore, Singapore 117558, Singapore.

Email: dbsgerw@nus.edu.sg.

Comment on: Yu X, Chen D, Wang L, *et al.* Wogonoside inhibits inflammatory cytokine production in lipopolysaccharide-stimulated macrophage by suppressing the activation of the JNK/c-Jun signaling pathway. *Ann Transl Med* 2020;8:532.

Submitted Sep 30, 2022. Accepted for publication Oct 12, 2022.

doi: [10.21037/atm-22-4845](https://doi.org/10.21037/atm-22-4845)

View this article at: <https://dx.doi.org/10.21037/atm-22-4845>

Inflammatory lung diseases, both acute and chronic, are critical respiratory diseases with huge global impact. The current COVID-19 pandemic due to the coronavirus SARS-COV-2 infection caused pneumonia is a prime example of acute inflammatory lung disease which has infected nearly 600 million people worldwide with more than 6 million death (as of Aug 25, 2022) (1). Dysregulated inflammation is the dominant underlying pathological mechanism for all inflammatory lung diseases including acute lung injury/acute respiratory distress syndrome (ALI/ARDS), asthma, chronic obstructive pulmonary disease (COPD), and pneumonia.

Pulmonary inflammation arises following respiratory exposure to pathogens, allergens, pollutants, toxins, mechanical stress, and other forms of injury. Upon pathogen infection or environmental irritation, the respiratory tract mounts a localized inflammatory immune response, first with airway macrophage activation, followed by cytokine/chemokine release by activated macrophages, and then leukocytes infiltration into the airway and lung. Lung macrophages include alveolar macrophages (AMs) that reside on the alveolar epithelial surface in the alveolar space, and interstitial macrophages (IMs) that reside in the alveolar wall. Both AMs and IMs are sentinel phagocytic immune cells for the airway and the lung. In addition, macrophages that reside on the epithelial surface of the airways are likely a separate type of macrophages, but are particularly poorly characterized, albeit presumably relevant in asthma. Airway macrophages isolated from bronchoalveolar lavage fluid (BALF) would contain both AMs and the macrophages from the airway epithelial surfaces, but not IMs. Up to now,

macrophages from BALF have been used as AMs.

Lung tissue resident AMs (TR-AMs) are derived from precursors in the embryos and are anti-inflammatory under physiological conditions, providing the first line of immune defense upon respiratory infection by phagocytosing and neutralizing many inhaled pathogens to protect lung homeostasis. Only when the pathogens surpass the AM phagocytosis, AMs become activated and initiate inflammation by releasing pro-inflammatory cytokines/chemokines to trigger neutrophil influx (2,3). Meanwhile, inflammation also triggers the recruitment of circulating monocytes to the lung, and these recruited monocytes become AMs in the local alveolar environment (Mo-AMs or RecAMs). These Mo-AMs are strongly pro-inflammatory and help to release signals to fight infection and promote tissue repair in ALI. However, Mo-AMs are also pro-fibrotic and if excessive or persist can contribute to lung fibrosis (4,5).

Macrophages are critical players for chronic inflammatory lung diseases such as COPD and asthma. AMs have long been known to be in an activated state and function as orchestrators of COPD (6). In the case of asthma, both immuno-suppressive and pro-inflammatory roles of AMs have been reported, likely due to the different roles of TR-AMs and Mo-AMs played and the functional changes of TR-AMs under the influence of the inflammatory environment (3,7). TR-AMs initially play a predominant suppressive role upon allergen exposure, along with the rapid recruitment of monocytes into the alveolar space. The recruited monocytes become Mo-AMs and promote acute lung inflammation. After repeated allergen exposures, AMs

lose their suppressive functions and become polarized to pro-inflammatory phenotype. The highly heterogeneous nature of AM population has been revealed in recent single-cell RNA sequencing (scRNA-seq) studies of human AMs, with 4 superclusters encompassing many subclusters discovered (8). The varied AM functions in different asthma studies could be attributed to the high heterogeneity of AM populations in different experimental settings. Notably, due to the intense focus on the central importance of eosinophil-dominant type 2 immune-response in allergic asthma, the roles of AMs in asthma have been relatively overlooked. However, macrophages are essential components of the innate immunity, and their roles in asthma warrant more rigorous investigations, particularly in “low type 2” inflammation subset of asthma patients (7).

Traditional Chinese medicine (TCM) have long been used to modulate immunity and suppress inflammation. *Radix Scutellariae* (Huang-Qin), the dried root of the medicinal plant *Scutellaria baicalensis* Georgi, have been used in TCM for thousands of years to suppress inflammation and bacterial/viral infection including for the treatment of respiratory tract infections, pneumonia and allergic diseases (9,10). Flavonoids are the main bioactive compounds extracted from *Radix Scutellariae* and are also the main mediators of the anti-inflammatory and immune-suppressive functions of this medicinal plant. All these bioactive flavonoids can significantly inhibit inflammation and proinflammatory cytokine production such as TNF- α , IL-6 and IL-1 β (9,10). Wogonoside is one of the six main bioactive flavonoids that has been reported to suppress inflammation in various disease settings including lipopolysaccharide (LPS)-induced ALI, traumatic spinal cord injury, ischemia-reperfusion induced myocardial injury, nonalcoholic fatty liver disease, colitis, and colorectal cancer. In 2014, Zhang *et al.* reported that Wogonoside can potently reduce lung infiltration of macrophages and neutrophils in an LPS-induced mouse model of ALI and that Wogonoside likely achieved this function by suppressing LPS-induced production of pro-inflammatory factors including TNF- α , IL-6 and IL-1 β (11). However, whether Wogonoside directly target airway macrophages and how does it interfere with these cells' function remain unresolved.

In 2020, Yu *et al.* reported in this journal that Wogonoside potently inhibits LPS-stimulated production of proinflammatory cytokines in mouse macrophages (12). Using primary AMs isolated from BALF in LPS-treated mice (most likely a mixture of TR-AMs and Mo-AMs), they

demonstrated that Wogonoside dose-dependently suppressed LPS-stimulated production of multiple proinflammatory factors. Using the mouse peritoneal macrophage cell line RAW264.7, they went on to demonstrate that Wogonoside potently suppressed LPS-induced phosphorylation of the cytosolic signaling kinase JNK (c-Jun N-terminal kinase), with the corresponding downstream reduction of binding of the transcription factor c-Jun to the promoters of multiple proinflammatory genes including IL-6, IL-1 β , TNF- α , iNOS and COX-2 via ChIP assay. c-Jun is a critical component of the transcription factor complex AP-1 and a substrate of JNK. These findings in conjunction with previous reports supported a critical role AM plays in LPS-induced acute lung inflammation and ALI. Inhibiting JNK is a new mechanism of action by Wogonoside in its suppression of pulmonary inflammation. Nevertheless, the data on JNK inhibition were only obtained using RAW264.7 macrophages, a mouse peritoneal macrophage cell line, not of AM origin.

Macrophages are known to be deeply influenced by the tissue microenvironment they reside in (3). AMs are the only type of macrophages that reside in the alveolar space and are directly exposed to the outside environment. Hence, whether Wogonoside can indeed suppress pulmonary inflammation by targeting JNK signaling in AMs require further experimental investigation using primary AMs as well as in animals. In addition, which AM subpopulation is targeted by Wogonoside, TR-AMs or Mo-AMs, and how Wogonoside suppress JNK signaling remain unknown. Furthermore, whether human AMs also function in similar fashion as their mouse counterparts needs to be investigated.

Beside Wogonoside, other major bioactive flavonoids from *Radix Scutellariae* have also been reported to have anti-inflammatory and immune-suppressive functions in various diseases including reducing pulmonary inflammation as have been reviewed previously (9,10). In the area of inhibition of pulmonary inflammation by bioactive flavonoids from *Radix Scutellariae*, most studies share similar limitations with the study by Yu *et al.* in 2020 in that they all largely used the mouse macrophage cell line RAW264.7 which are very different from airway macrophages or AMs. These studies also mostly limited their investigations to LPS-activated RAW264.7 macrophages and the effect of these flavonoids on the production of pro-inflammatory cytokines/chemokines under a rather narrow experimental condition, limiting the significance for their findings in relation to the many types of inflammatory lung diseases in human. Future research

needs to be expanded into investigations of primary AMs (both mouse and human) to reveal the anti-inflammatory mechanisms of these bioactive flavonoids in lung relevant macrophages. In particular, the anti-inflammatory mechanisms at the molecular and cellular levels need to be studied under various pulmonary disease models in animals. Advancements in these directions are critical for the modernization and internationalization of TCM.

Nevertheless, it is envisioned that Wogonoside and other anti-inflammatory flavonoids from *Radix Scutellariae*, either alone or in combination, have the potential to become modern drugs for inflammatory lung diseases. The rich resources harbored in TCM should be fully tapped to generate modern drugs for the benefits of mankind.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4845/coif>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;20:533-4.
- Westphalen K, Gusarova GA, Islam MN, et al. Sessile alveolar macrophages communicate with alveolar epithelium to modulate immunity. *Nature* 2014;506:503-6.
- Aegerter H, Lambrecht BN, Jakubzick CV. Biology of lung macrophages in health and disease. *Immunity* 2022;55:1564-80.
- McCubbrey AL, Barthel L, Mohning MP, et al. Deletion of c-FLIP from CD11bhi Macrophages Prevents Development of Bleomycin-induced Lung Fibrosis. *Am J Respir Cell Mol Biol* 2018;58:66-78.
- Gibbons MA, MacKinnon AC, Ramachandran P, et al. Ly6Chi monocytes direct alternatively activated profibrotic macrophage regulation of lung fibrosis. *Am J Respir Crit Care Med* 2011;184:569-81.
- Barnes PJ. Alveolar macrophages as orchestrators of COPD. *COPD* 2004;1:59-70.
- Draijer C, Peters-Golden M. Alveolar Macrophages in Allergic Asthma: the Forgotten Cell Awakes. *Curr Allergy Asthma Rep* 2017;17:12.
- Mould KJ, Moore CM, McManus SA, et al. Airspace Macrophages and Monocytes Exist in Transcriptionally Distinct Subsets in Healthy Adults. *Am J Respir Crit Care Med* 2021;203:946-56.
- Liao H, Ye J, Gao L, et al. The main bioactive compounds of *Scutellaria baicalensis* Georgi. for alleviation of inflammatory cytokines: A comprehensive review. *Biomed Pharmacother* 2021;133:110917.
- Li C, Lin G, Zuo Z. Pharmacological effects and pharmacokinetics properties of *Radix Scutellariae* and its bioactive flavones. *Biopharm Drug Dispos* 2011;32:427-45.
- Zhang L, Ren Y, Yang C, et al. Wogonoside ameliorates lipopolysaccharide-induced acute lung injury in mice. *Inflammation* 2014;37:2006-12.
- Yu X, Chen D, Wang L, et al. Wogonoside inhibits inflammatory cytokine production in lipopolysaccharide-stimulated macrophage by suppressing the activation of the JNK/c-Jun signaling pathway. *Ann Transl Med* 2020;8:532.

Cite this article as: Ge R. Targeting airway macrophages for inflammatory lung diseases—insights from traditional Chinese medicine. *Ann Transl Med* 2022;10(20):1086. doi: 10.21037/atm-22-4845