

PUBLISHED VERSION

Hodge, Sandra Joy

[Pulmonary macrophage-targeted therapies-the way forward in chronic inflammatory lung diseases?](#)

Journal of Pulmonary & Respiratory Medicine, 2012; 2(1):1000e105

As a member of Publishers International Linking Association, PILA, Journal of Pulmonary and Respiratory Medicine (of OMICS Publishing Group) follows the Creative Commons Attribution License and Scholars Open Access publishing policies.

The electronic version of this article is the complete one and can be found online at:

<http://dx.doi.org/10.4172/2161-105X.1000e105>

PERMISSIONS

Open Access License

No Permission Required

The OMICS Publishing Group applies the Creative Commons Attribution License (CCAL) to all works we publish (read the human-readable summary or the full license legal code). Under the CCAL, authors retain ownership of the copyright for their article, but authors allow anyone to download, reuse, reprint, modify, distribute, and/or copy articles in OMICS journals, so long as the original authors and source are cited. **No permission is required from the authors or the publishers.** The broad license was developed to facilitate open access to, and free use of, original works of all types. Applying this standard license to your own work will ensure your right to make your work freely and openly available. Learn more about [open access](#). For queries about the license, please [contact us](#). All Published content, except where otherwise noted, is licensed under a [Creative Commons Attribution License](#).

24th April 2013

<http://hdl.handle.net/2440/77191>

Pulmonary Medicine deals with the diseases of the respiratory tract and respiratory disease. It is called chest medicine and respiratory medicine in some countries and areas. Pulmonology is generally considered a branch of internal medicine. Chest medicine is not a specialty in itself but is an inclusive term which pertains to the treatment of diseases of the chest and contains the fields of pulmonology, thoracic surgery, and intensive care medicine. Effective disease treatment physician specializing in this area are called Pulmonologists.

The Journal of Pulmonary & Respiratory Medicine under open access category aims to advance our understanding of the diagnosis and treatment of lung diseases, as well as secondary prevention (Tuberculosis). The Journal of Pulmonary & Respiratory Medicine is an international, peer-reviewed journal, publishing an overview of Pulmonary Medicine which includes the contents geared towards the fields of pulmonology, thoracic surgery, and intensive care medicine.



ISSN:2161-105X

Journal of Pulmonary & Respiratory Medicine

Editors & Editorial Board

<http://www.omicsonline.org/jprmhome.php>

 John E Repine University of Colorado Denver, USA	 Vincent Cottin University of Lyon France	 Curtis N. Sessler Virginia Commonwealth University, Virginia	 Peter Gibson John Hunter Hospital Newcastle, UK	 Richard Loh Medicine in Penang Medical College Malaysia	 Panettieri RA University of Penn- sylvania Philadelphia, PA	 Frank Mazza Seton Family of Hospitals, USA	 Ibrahim Faruqi University of Florida USA
 Machado RF University of Illinois Chicago Chicago, IL	 Solomidou MC University of Pennsylvania Medical Center, USA	 Denis Hadjiladis University of Pennsylvania Medical Center, PA	 Chris Russian Texas State University-San Marcos	 Alexander Sy Wake Forest University Health Sciences USA	 Sharafkhaneh A Baylor College of Medicine Houston, TX, USA	 Crossno JT University of Colorado CO	 Zeenat Safdar Baylor College of Medicine Houston, Texas
 Krymskaya VP Translational Research Laboratories, USA	 Natarajan R Internal Medicine Pulmonary Disease	 Kiyoyasu K Yokohama City University Medical Center, Japan	 Verceles AC Sleep Medicine Baltimore, USA	 Khan Mubarak K University of Florida USA	 Mohammed KA University of Florida USA	 Hans J Lee Virginia Commonwealth University, VA	 Irena Levitan University of Illinois Chicago
 Charlie Lan Baylor College of Medicine, Texas	 Qi Qian Mayo Clinic Rochester, MN, USA	 Wei Zhang University of Illinois Chicago	 Modrykamien AM Creighton University Medical Center, USA		 Sandra Hodge University of Adelaide South Australia		 Bhavin D Dalal University of Missis- sippi Medical Center USA
 Guervilly C Hôpital Nord, Chemin des Bourrelly Marseille, France	 Gianni Pala Allergy and Immunology Unit, Italy	 Yungjae Lee E Harvard Medical School Boston, USA	 Florian Lang University of Tübingen Germany	 Elizabeth Sapey University of Birmingham, UK	 Al-Jumaily A Auckland University of Technology, New Zealand		 Alan Fujii Boston University USA

Journal of Pulmonary & Respiratory Medicine Open Access is using online manuscript submission.
Submit your manuscript at <http://www.omicsonline.org/submission/>

OMICS Publishing Group

5716 Corsa Ave., Suite 110, Westlake, Los Angeles, CA 91362-7354, USA, Phone: +1-650-268-9744, Fax: +1-650-618-1414, Toll free: +1-800-216-6499

Pulmonary Macrophage-Targeted Therapies-The Way Forward in Chronic Inflammatory Lung Diseases?

Sandra Hodge*

Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, South Australia

It is becoming increasingly evident that pulmonary macrophage dysfunction contributes to disease pathogenesis in a variety of chronic lung diseases including chronic obstructive pulmonary disease (COPD) [1], bronchiolitis obliterans syndrome (BOS) following lung transplantation [2], cystic fibrosis (CF) [3] and severe asthma (NEA) [4]. An abnormal accumulation of apoptotic bronchial epithelial cells with an associated defect in the phagocytic ability of neighboring macrophages (efferocytosis) can lead to secondary necrosis of the uncleared apoptotic material with pro-inflammatory effects [5,6]. Specific therapeutic targeting of the macrophage dysfunction is being increasingly studied. The actual progression of this strategy to clinical use is however still very much in the early stages and much of our knowledge of the potential impact of macrophage-targeted therapies has evolved in retrospect rather than from a direct developmental approach.

The emerging body of evidence suggests that the use of long-term macrolide therapy is both feasible and may offer useful clinical outcomes in chronic lung diseases, including COPD, BOS and NEA [6-8], while results in CF have been inconclusive [9,10]. The mechanism of action of macrolides in this regard may be through their effects on macrophage function [6-8]. In a small uncontrolled study using low-dose azithromycin in COPD subjects the principal findings were a significant increase in the efferocytosis capacity of alveolar macrophages and a reduction in the percentage of apoptotic airway epithelial cells obtained by airway brushing [7]. A role for phosphatidylserine (PS) in these effects was shown [8].

Pulmonary macrophages may contribute to the relative insensitivity to corticosteroids in chronic lung diseases [11,12]. Dexamethasone has been shown to improve efferocytosis [13] while in patients with severe asthma, defective efferocytosis was improved after a course of high dose steroids [14]. In COPD, lung macrophages have reduced expression of the epigenetic modifying enzyme histone deacetylase 2 (HDAC2) and this is associated with increased expression of inflammatory genes and also resistance to corticosteroids [12].

Statins also have been shown to improve macrophage phagocytic function mediated in part by their inhibitory effects on RhoA [15]. In COPD, there is evidence of an improved mortality rate following treatment with statins [16]; however, whether the effects of statins on macrophage function will translate to human clinical benefit is uncertain, as the doses used to achieve the *in vitro* effects were higher than those typically used clinically.

The process of efferocytosis involves signaling through macrophage surface receptors that include MER tyrosine kinase (MERTK), GAS6, milk fat globule epidermal growth factor 8 (MFG-E8) and several putative PS receptors including a G protein-coupled receptor, BA11 (brain-specific angiogenesis 1), TIM-1 and TIM-4. Activation of protein kinase C β II is required for efferocytosis. Scavenger receptors (mannose receptor, SRA11 (type AII), MARCO (class A) CD36 (class B)) facilitate the phagocytosis of modified protein on apoptotic cells. Dysregulated expression of macrophage receptors in COPD has been reported [6,7,17-19] and these may provide suitable targets for macrophage-targeted therapies. Whether epigenetic regulation of the various receptors alters their ligand-binding properties also remains unclear,

and there is a need for characterizing epigenetic signatures of relevant genes in macrophages isolated from the various patient groups.

More recently, strategies are being pursued that are more specifically directed towards macrophage function, such as the use of mannose-binding lectin (MBL). MBL plays a key role in regulating efferocytosis and it is expressed at reduced levels in the airway in COPD or BOS [2,20]. Human and animal studies support the potential role for MBL in improving phagocytosis and reducing inflammation as a therapeutic strategy for airways disease [20]. Further studies using anti-oxidants with a resultant improvement in macrophage function in smoke exposed mice have also been reported [21].

Compelling evidence is thus emerging for the role of defective pulmonary macrophage function in the pathogenesis of chronic inflammatory airways diseases, and it is also becoming clear that several therapies with established clinical efficacy for various conditions may be exerting some of their beneficial effects via modulation of macrophage function. Greater understanding of the clinical consequences of defective macrophage function and its modulation by therapeutic agents will progress the development of specific macrophage-targeted therapies with complementary or synergistic benefits to established therapies.

References

1. Hodge S, Hodge G, Scicchitano R, Reynolds PN, Holmes M (2003) Alveolar macrophages from subjects with COPD are deficient in their ability to phagocytose apoptotic airway epithelial cells. *Immunol Cell Biol* 81: 289-296.
2. Hodge S, Dean M, Hodge G, Holmes M, Reynolds PN (2011) Decreased efferocytosis and mannose binding lectin in the airway in bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 30: 589-595.
3. Vandivier RW, Richens TR, Horstmann SA, deCathelineau AM, Ghosh M, et al. (2009) Dysfunctional cystic fibrosis transmembrane conductance regulator inhibits phagocytosis of apoptotic cells with proinflammatory consequences. *Am J Physiol Lung Cell Mol Physiol* 297: 677-686.
4. Bhavsar P, Hew M, Khorasani N, Torrego A, Barnes PJ, et al. (2008) Relative corticosteroid insensitivity of alveolar macrophages in severe asthma compared with non-severe asthma. *Thorax* 63: 784-790.
5. Vandivier RW, Henson PM, Douglas IS (2006) Burying the dead: the impact of failed apoptotic cell removal (efferocytosis) on chronic inflammatory lung disease. *Chest* 129: 1673-1682.
6. Katoh S, Matsubara Y, Taniguchi H, Fukushima K, Mukae H, et al. (2001) Characterization of CD44 expressed on alveolar macrophages in patients with diffuse panbronchiolitis. *Clin Exp Immunol* 126: 545-550.

*Corresponding author: Sandra Hodge, Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, South Australia, E-mail: Sandra.Hodge@health.sa.gov.au

Received February 29, 2012; Accepted March 03, 2012; Published March 05, 2012

Citation: Hodge S (2012) Pulmonary Macrophage-Targeted Therapies-The Way Forward in Chronic Inflammatory Lung Diseases?. *J Pulmonar Respirat Med* 2:e105. doi:10.4172/2161-105X.1000e105

Copyright: © 2012 Hodge S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

7. Hodge S, Hodge G, Jersmann H, Matthews G, Ahern J, et al. (2008) Azithromycin Improves Macrophage Phagocytic Function and Expression of Mannose Receptor in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 178: 139-148.
8. Yamaryo T, Oishi K, Yoshimine H, Tsuchihashi Y, Matsushima K, et al. (2003) Fourteen-member macrolides promote the phosphatidylserine receptor-dependent phagocytosis of apoptotic neutrophils by alveolar macrophages. *Antimicrob Agents Chemother* 47: 48-53.
9. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, et al. (2011) Macrolides: from *in vitro* anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. *Eur J Clin Pharmacol*.
10. Robinson P, Schechter MS, Sly PD, Winfield K, Smith J, et al. (2012) Clarithromycin therapy for patients with cystic fibrosis: A randomized controlled trial. *Pediatr Pulmonol*.
11. Barnes PJ (2011) Glucocorticosteroids: current and future directions. *Br J Pharmacol* 163: 29-43.
12. Marwick JA, Adcock IM, Chung KF (2010) Overcoming reduced glucocorticoid sensitivity in airway disease: molecular mechanisms and therapeutic approaches. *Drugs* 70: 929-948.
13. McColl A, Bourmazos S, Franz S, Perretti M, Morgan BP, et al. (2009) Glucocorticoids induce protein S-dependent phagocytosis of apoptotic neutrophils by human macrophages. *J Immunol* 183: 2167-2175.
14. Huynh ML, Malcolm KC, Kotaru C, Tilstra JA, Westcott JY, et al. (2005) Defective apoptotic cell phagocytosis attenuates prostaglandin E2 and 15-hydroxyeicosatetraenoic acid in severe asthma alveolar macrophages. *Am J Respir Crit Care Med* 172: 972-979.
15. Morimoto K, Janssen WJ, Fessler MB, McPhillips KA, Borges VM, et al. (2006) Lovastatin enhances clearance of apoptotic cells (efferocytosis) with implications for chronic obstructive pulmonary disease. *J Immunol* 176: 7657-7665.
16. Ishida W, Kajiwara T, Ishii M, Fujiwara F, Taneichi H, et al. (2007) Decrease in mortality rate of chronic obstructive pulmonary disease (COPD) with statin use: a population-based analysis in Japan. *Tohoku J Exp Med* 212: 265-273.
17. Kazeros A, Harvey BG, Carolan BJ, Vanni H, Krause A, et al. (2008) Overexpression of apoptotic cell removal receptor MERTK in alveolar macrophages of cigarette smokers. *Am J Respir Cell Mol Biol* 39: 747-757.
18. Hanayama R, Tanaka M, Miyasaka K, Aozasa K, Koike M, et al. (2004) Autoimmune disease and impaired uptake of apoptotic cells in MFG-E8-deficient mice. *Science* 304: 1147-1150.
19. Hodge S, Hodge G, Ahern J, Jersmann H, Holmes M, et al. (2007) Smoking alters alveolar macrophage recognition and phagocytic ability: implications in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 37: 748-755.
20. Hodge S, Matthews G, Dean MM, Ahern J, Djukic M, et al. (2009) Is there a therapeutic role for mannose binding lectin in cigarette smoke-induced lung inflammation? Evidence from a murine model. *Am J Respir Cell Mol Biol* 42: 235-242.
21. Hodge S, Matthews G, Mukaro V, Ahern J, Shivam A, et al. (2011) Cigarette smoke-induced changes to alveolar macrophage phenotype and function are improved by treatment with procysteine. *Am J Respir Cell Mol Biol* 44: 673-681.
22. Hodge S, Hodge G, Holmes M, Reynolds PN (2005) Increased apoptosis in the airways in COPD persists after smoking cessation. *Eur Resp J* 25: 447-454.

Submit your next manuscript and get advantages of OMICS Group submissions

Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:

- 200 Open Access Journals
- 15,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submission/>

