We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

patients with mild-to-moderate asthma [1]. In addition, SA can come up concomitantly with other chronic diseases, such as rhinosinusitis and chronic obstructive pulmonary disease (COPD) [2]. Despite the high asthma prevalence worldwide, its pathophysiology, phenotypes, endotypes, biomarkers, and treatment still need to be elucidated, therefore, being of great interest of study for the scientific community [13].

3. Pathophysiology of severe asthma

The main pathophysiological feature of asthma is the bronchial inflammation resulting from interactions between airway structural cells and the innate/adaptive immune system. Structural cells of the lung, among them, epithelial cells, endothelial cells, and fibroblasts, release inflammatory mediators, mainly chemokines, and actively participate in the inflammatory process by attracting blood cells to the inflamed site. Thus, the development of the inflammatory response initially orchestrated by the lung structural cells in asthma also depends on innate immunity cells such as eosinophils, neutrophils, macrophages, mast cells, NKT cells, γδ-Tcells, inactive lymphoid cells (ILCs) and dendritic cells, and also on adaptive immunity cells represented by T and B cells. Interactions among these cells and the release of various inflammatory proteins, including cytokines, chemokines, adhesion molecules, eicosanoids, histamine, and nitric oxide (NO), promote the bronchial inflammatory process [14–16]. This inflammatory process is a common feature to all atopic asthmatic patients including those with the severe phenotype.

Histological addresses indicate that bronchial biopsies of asthmatic individuals reveal tissue structural changes, such as collagen deposition under the epithelium, which is described as the thickening of the basement membrane and of the smooth muscle layer of the airways due to the hyperplasia and the hypertrophy of the smooth muscle, which is most commonly observed in patients with severe asthma [17].

Further, there is an increase if the number of blood vessels (angiogenesis) in response to increased secretion of the vessel-endothelial growth factor (VEGF) [18] as well as an increase in mucus secretion commonly observed in biopsies of asthmatic patients, due to an increase in the number of secreting-mucus goblet cell in the epithelium and in the size of submucosal glands [19].

Once asthma presents a complex inflammatory process regulated by immune cells and structural bronchial cells collaborating for the initiation, exacerbation, and maintenance of the inflammatory process, all of these events might lead to irreversible bronchial structural changes and the airway remodeling which strongly contribute to severe development of asthma [15].

3.1. Airway remodeling

Airway remodeling can be defined as a set of changes in the composition, content and organization of the cellular and molecular constituents of the airway wall. The airway remodeling includes epithelial damage, cilial dysfunction, increased thickness of sub-epithelial basement membrane, angiogenesis, and neuronal proliferation. Also, it increases airway smooth muscle

corticosteroids. Proceedings of the National Academy of Sciences. 2007;**104**:15858-15863. DOI: 10.1073/pnas.0707413104

[36] Spellberg B, Edwards JE. Type 1/type 2 immunity in infectious diseases. Clinical Infectious Diseases. 2001;**32**:76-102. DOI: 10.1086/317537

[37] Ray A, Raundhal M, Oriss TB, Ray P, Wenzel SE. Current concepts of severe asthma. The Journal of Clinical Investigation. 2016;**126**:2394-2403. DOI: 10.1172/JCI84144

[38] Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: Executive summary of the GINA dissemination committee report. Allergy. 2004;**59**:469-478. DOI: 10.1111/j.1398-9995.2004.00526.x

[39] Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. American Journal of Respiratory and Critical Care Medicine. 2008;**178**:218-224. DOI: 10.1164/rccm.200711-1754OC

[40] Just J, Bourgoin-Heck M, Amat F. Clinical phenotypes in asthma during childhood. Clinical and Experimental Allergy. 2017;**47**:848-855. DOI: 10.1111/cea.12939

[41] Bagnasco D, Ferrando M, Varricchi G, Passalacqua G, Canonica GW. A critical evaluation of anti-IL-13 and anti-IL-4 strategies in severe asthma. International Archives of Allergy and Immunology. 2016;**170**:122-131. DOI: 10.1159/000447692

[42] Fitzpatrick AM, Baena-Cagnani CE, Bacharier LB. Severe asthma in childhood: Recent advances in phenotyping and pathogenesis. Current Opinion in Allergy and Clinical Immunology. 2012;**12**:193-201. DOI: 10.1097/ACI.0b013e32835090ac

[43] Zhao J, Lloyd CM, Noble A. Th17 responses in chronic allergic airway inflammation abrogate regulatory T-cell-mediated tolerance and contribute to airway remodeling. Mucosal Immunology. 2013;**6**:335-346. DOI: 10.1038/mi.2012.76

[44] Loutsios C, Farahi N, Porter L, Lok LS, Peters AM, Condliffe AM, Chilvers ER. Biomarkers of eosinophilic inflammation in asthma. Expert Review of Respiratory Medicine. 2014;**8**:143-150. DOI: 10.1586/17476348.2014.880052

[45] Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, Liu X. National surveillance of asthma: United States, 2001–2010. Vital & Health Statistics. Series 3, Analytical and Epidemiological Studies. 2012:1-58 http://www.ncbi.nlm.nih.gov/pubmed/24252609 [Accessed: January 12, 2018

[46] Tsai C-L, Lee W-Y, Hanania NA, Camargo CA. Age-related differences in clinical outcomes for acute asthma in the United States, 2006–2008. Journal of Allergy and Clinical Immunology. 2012;**129**:1252-1258.e1. DOI: 10.1016/j.jaci.2012.01.061

[47] Gonzalez-Garcia M, Caballero A, Jaramillo C, Maldonado D, Torres-Duque CA. Prevalence, risk factors and underdiagnosis of asthma and wheezing in adults 40 years and older: A population-based study. The Journal of Asthma. 2015;**52**:823-830. DOI: 10.3109/02770903.2015.1010733

[48] Dykewicz MS. Occupational asthma: Current concepts in pathogenesis, diagnosis, and management. The Journal of Allergy and Clinical Immunology. 2009;**123**:519-528. DOI: 10.1016/j.jaci.2009.01.061

[49] Melgert BN, Ray A, Hylkema MN, Timens W, Postma DS. Are there reasons why adult asthma is more common in females? Current Allergy and Asthma Reports. 2007;**7**:143-150 http://www.ncbi.nlm.nih.gov/pubmed/17437685 [Accessed: January 12, 2018

[50] Jenkins MA, Dharmage SC, Flander LB, Douglass JA, Ugoni AM, Carlin JB, Sawyer SM, Giles GG, Hopper JL. Parity and decreased use of oral contraceptives as predictors of asthma in young women. Clinical and Experimental Allergy. 2006;**36**:609-613. DOI: 10.1111/j.1365-2222.2006.02475.x

[51] Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. American Journal of Respiratory and Critical Care Medicine. 1995;**152**:1183-1188. DOI: 10.1164/ajrccm.152.4.7551368

[52] Romieu I, Fabre A, Fournier A, Kauffmann F, Varraso R, Mesrine S, Leynaert B, Clavel-Chapelon F. Postmenopausal hormone therapy and asthma onset in the E3N cohort. Thorax. 2010;**65**:292-297. DOI: 10.1136/thx.2009.116079

[53] van den Berge M, Heijink HI, van Oosterhout AJM, Postma DS. The role of female sex hormones in the development and severity of allergic and non-allergic asthma. Clinical and Experimental Allergy. 2009;**39**:1477-1481. DOI: 10.1111/j.1365-2222.2009.03354.x

[54] Koczulla AR, Vogelmeier CF, Garn H, Renz H. New concepts in asthma: Clinical phenotypes and pathophysiological mechanisms. Drug Discovery Today. 2017;**22**:388-396. DOI: 10.1016/j.drudis.2016.11.008

[55] Heller F, Florian P, Bojarski C, Richter J, Christ M, Hillenbrand B, Mankertz J, Gitter A, Burgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. Gastroenterology. 2005;**129**:550-564. DOI: 10.1016/j.gastro.2005.05.002

[56] Hoshino T, Kato S, Oka N, Imaoka H, Kinoshita T, Takei S, Kitasato Y, Kawayama T, Imaizumi T, Yamada K, Young HA, Aizawa H. Pulmonary inflammation and emphysema. American Journal of Respiratory and Critical Care Medicine. 2007;**176**:49-62. DOI: 10.1164/rccm.200603-316OC

[57] Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, Bleecker ER, National Heart, Lung, and Blood Institute Severe Asthma Research Program. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. Journal of Allergy and Clinical Immunology. 2010;**125**:1028-1036.e13. DOI: 10.1016/j.jaci.2010.02.008

[58] Ciepiela O, Ostafin M, Demkow U. Neutrophils in asthma—A review. Respiratory Physiology & Neurobiology. 2015;**209**:13-16. DOI: 10.1016/J.RESP.2014.12.004

[59] Fahy JV. Type 2 inflammation in asthma—Present in most, absent in many. Nature Reviews Immunology. 2015;**15**:57-65. DOI: 10.1038/nri3786

[60] Manni ML, Trudeau JB, Scheller EV, Mandalapu S, Elloso MM, Kolls JK, Wenzel SE, Alcorn JF. The complex relationship between inflammation and lung function in severe asthma. Mucosal Immunology. 2014;**7**:1186-1198. DOI: 10.1038/mi.2014.8

[61] Pelaia C, Vatrella A, Busceti MT, Gallelli L, Terracciano R, Savino R, Pelaia G. Severe eosinophilic asthma: From the pathogenic role of interleukin-5 to the therapeutic action of mepolizumab. Drug Design, Development and Therapy. 2017;**11**:3137-3144. DOI: 10.2147/DDDT.S150656

[62] Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. Nature Medicine. 2013;**19**:977-979. DOI: 10.1038/nm.3300

[63] Yousefi S, Simon D, Simon H-U. Eosinophil extracellular DNA traps: Molecular mechanisms and potential roles in disease. Current Opinion in Immunology. 2012;**24**:736-739. DOI: 10.1016/j.coi.2012.08.010

[64] Possa SS, Leick EA, Prado CM, Martins MA, Tibério IFLC. Eosinophilic inflammation in allergic asthma. Frontiers in Pharmacology. 2013;**4**:46. DOI: 10.3389/fphar.2013.00046

[65] Louis R, Lau LCK, Bron AO, Roldaan AC, Radermecker M, Djulanovic R. The relationship between airways inflammation and asthma severity. American Journal of Respiratory and Critical Care Medicine. 2000;**161**:9-16. DOI: 10.1164/ajrccm.161.1.9802048

[66] Fahy JV. Eosinophilic and neutrophilic inflammation in asthma: Insights from clinical studies. Proceedings of the American Thoracic Society. 2009;**6**:256-259. DOI: 10.1513/pats.200808-087RM

[67] George L, Brightling CE. Eosinophilic airway inflammation: Role in asthma and chronic obstructive pulmonary disease. Therapeutic Advances in Chronic Disease. 2016;**7**:34-51. DOI: 10.1177/2040622315609251

[68] Pelaia G, Vatrella A, Busceti MT, Gallelli L, Calabrese C, Terracciano R, Maselli R. Cellular mechanisms underlying eosinophilic and neutrophilic airway inflammation in asthma. Mediators of Inflammation. 2015;**2015**:879783. DOI: 10.1155/2015/879783

[69] Shimoda T, Obase Y, Nagasaka Y, Asai S. Phenotype classification using the combination of lung sound analysis and fractional exhaled nitric oxide for evaluating asthma treatment. Allergology International. 2017:1-6. DOI: 10.1016/j.alit.2017.09.004

[70] Nagasaki T, Matsumoto H, Izuhara K, Kanemitsu Y, Tohda Y, Horiguchi T, Kita H, Tomii K, Fujimura M, Yokoyama A, Nakano Y, Hozawa S, Ito I, Oguma T, Izuhara Y, Tajiri T, Iwata T, Yokoyama T, Niimi A, Mishima M. Utility of serum periostin in combination with exhaled nitric oxide in the management of asthma. Allergology International. 2017;**66**:404-410. DOI: 10.1016/j.alit.2017.02.003

[71] Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SAA, Bleecker E, Busse W, Calhoun WJ, Castro M, Chung KF, Israel E, Jarjour N, Moore W, Peters S, Teague G, Gaston B, Erzurum SC, National Heart, Lung, and Blood Institute Severe Asthma Research Program. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. American Journal of Respiratory and Critical Care Medicine. 2010;**181**:1033-1041. DOI: 10.1164/rccm.200905-0695OC

[72] McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, Fahy JV, Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. American Journal of Respiratory and Critical Care Medicine. 2012;**185**:612-619. DOI: 10.1164/rccm.201109-1640OC

[73] Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. The Journal of Allergy and Clinical Immunology. 2015;**135**:299-310. DOI: 10.1016/j.jaci.2014.12.1871

[74] Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, Irvin CG. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. Journal of Allergy and Clinical Immunology. 2011;**128**:508-515.e2. DOI: 10.1016/j.jaci.2011.06.009

[75] Rasmussen F, Hancox RJ. Mechanisms of obesity in asthma. Current Opinion in Allergy and Clinical Immunology. 2014;**14**:35-43. DOI: 10.1097/ACI.0000000000000024

[76] Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, Stream AR, Fahy JV, Leung DYM. Asthma clinical research network, cluster analysis of obesity and asthma phenotypes. PLoS One. 2012;**7**:e36631. DOI: 10.1371/journal.pone.0036631

[77] Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, Fitzpatrick AM, Gaston B, Israel E, Jarjour NN, Moore WC, Peters SP, Yonas M, Teague WG, Wenzel SE. Obesity and asthma: An association modified by age of asthma onset. Journal of Allergy and Clinical Immunology. 2011;**127**:1486-1493.e2. DOI: 10.1016/j.jaci.2011.03.036

[78] Gomez-Llorente M, Romero R, Chueca N, Martinez-Cañavate A, Gomez-Llorente C. Obesity and asthma: A missing link. International Journal of Molecular Sciences. 2017; **18**:1490. DOI: 10.3390/ijms18071490

[79] Wenzel SE, Szefler SJ, Leung DYM, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. American Journal of Respiratory and Critical Care Medicine. 1997;**156**:737-743. DOI: 10.1164/ajrccm.156.3.9610046

[80] Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persistent asthma. American Journal of Respiratory and Critical Care Medicine. 1999;**160**:1532-1539. DOI: 10.1164/ajrccm.160.5.9806170

[81] Kato T, Takeda Y, Nakada T, Sendo F. Inhibition by dexamethasone of human neutrophil apoptosis in vitro. Natural Immunity. 1995;**14**:198-208. http://www.ncbi.nlm.nih.gov/pubmed/8696009 [Accessed: January 12, 2018

[82] Busacker A, Newell JD, Keefe T, Hoffman EA, Granroth JC, Castro M, Fain S, Wenzel S. A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis. Chest. 2009;**135**:48-56. DOI: 10.1378/chest.08-0049

[83] Gupta S, Siddiqui S, Haldar P, Raj JV, Entwisle JJ, Wardlaw AJ, Bradding P, Pavord ID, Green RH, Brightling CE. Qualitative analysis of high-resolution CT scans in severe asthma. Chest. 2009;**136**:1521-1528. DOI: 10.1378/chest.09-0174

[84] Gounni AS, Lamkhioued B, Koussih L, Ra C, Renzi PM, Hamid Q. Human neutrophils express the high-affinity receptor for immunoglobulin E (Fc epsilon RI): Role in asthma. The FASEB Journal. 2001;**15**:940-949. http://www.ncbi.nlm.nih.gov/pubmed/11292654 [Accessed: January 12, 2018]

[85] Alphonse MP, Saffar AS, Shan L, HayGlass KT, Simons FER, Gounni AS. Regulation of the high affinity IgE receptor (Fc epsilonRI) in human neutrophils: Role of seasonal allergen exposure and Th-2 cytokines. PLoS One. 2008;**3**:e1921. DOI: 10.1371/journal.pone.0001921

[86] Lavinskiene S, Bajoriuniene I, Malakauskas K, Jeroch J, Sakalauskas R. Sputum neutrophil count after bronchial allergen challenge is related to peripheral blood neutrophil chemotaxis in asthma patients. Inflammation Research. 2014;**63**:951-959. DOI: 10.1007/s00011-014-0770-0

[87] Macdowell AL, Peters SP. Neutrophils in asthma. Current Allergy and Asthma Reports. 2007;**7**:464-468. http://www.ncbi.nlm.nih.gov/pubmed/17986378 [Accessed: January 12, 2018]

[88] Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, Ceuppens JL. IL-17 mRNA in sputum of asthmatic patients: Linking T cell driven inflammation and granulocytic influx? Respiratory Research. 2006;**7**:135. DOI: 10.1186/1465-9921-7-135

[89] Cosmi L, Annunziato F, MIG G, RME M, Nagata K, Romagnani S. CRTH2 is the most reliable marker for the detection of circulating human type 2 Th and type 2 T cytotoxic cells in health and disease. European Journal of Immunology. 2000;**30**:2972-2979. DOI: 10.1002/1521-4141(200010)30:10<2972::AID-IMMU2972>3.0.CO;2-#

[90] Monteseirín J, Camacho MJ, Bonilla I, De la Calle A, Guardia P, Conde J, Sobrino F. Respiratory burst in neutrophils from asthmatic patients. The Journal of Asthma. 2002;**39**:619-624. http://www.ncbi.nlm.nih.gov/pubmed/12442951 [Accessed: January 12, 2018]

[91] Bourgeois EA, Levescot A, Diem S, Chauvineau A, Bergès H, Milpied P, Lehuen A, Damotte D, Gombert J-M, Schneider E, Girard J-P, Gourdy P, Herbelin A. A natural protective function of invariant NKT cells in a mouse model of innate-cell-driven lung inflammation. European Journal of Immunology. 2011;**41**:299-305. DOI: 10.1002/eji.201040647

[92] Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, Patalano F, Fogel R, Kostikas K. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: A systematic review and meta-analysis. International Journal of Chronic Obstructive Pulmonary Disease. 2017;**12**:907-922. DOI: 10.2147/COPD.S130482

[93] Wynn TA. Type 2 cytokines: Mechanisms and therapeutic strategies. Nature Reviews. Immunology. 2015;**15**:271-282. DOI: 10.1038/nri3831

[94] Beeh K-M, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, Korn S. Tiotropium Respimat® in asthma: A double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respiratory Research. 2014;**15**:61. DOI: 10.1186/1465-9921-15-61

[95] Leung JS, Johnson DW, Sperou AJ, Crotts J, Saude E, Hartling L, Stang A. A systematic review of adverse drug events associated with administration of common asthma medications in children. PLoS One. 2017;**12**:e0182738. DOI: 10.1371/journal.pone.0182738

[96] Bengtson LGS, Yu Y, Wang W, Cao F, Hulbert EM, Wolbeck R, Elliott CA, Buikema AR. Inhaled corticosteroid-containing treatment escalation and outcomes for patients with asthma in a U.S. Health Care Organization. Journal of Managed Care & Specialty Pharmacy. 2017;**23**:1149-1159. DOI: 10.18553/jmcp.2017.23.11.1149

[97] Navinés-Ferrer A, Serrano-Candelas E, Molina-Molina G-J, Martín M. IgE-related chronic diseases and anti-IgE-based treatments. Journal of Immunology Research. 2016; **2016**:1-12. DOI: 10.1155/2016/8163803

[98] Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefler SJ, Kattan M, Kianifard F, Ortiz B, Haselkorn T, Iqbal A, Rosén K, Trzaskoma B, Busse WW. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. The Journal of Allergy and Clinical Immunology. 2017;**139**:1431-1444. DOI: 10.1016/j.jaci.2017.03.002

[99] Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, Zangrilli J, Castro M. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. Journal of Allergy and Clinical Immunology: In Practice. 2017;**5**:1572-1581.e3. DOI: 10.1016/j.jaip.2017.08.024

[100] Fahy JV. Type 2 inflammation in asthma—Present in most, absent in many. Nat. Rev. Immunol. 2015;**15**:57-65. DOI: 10.1038/nri3786

[101] Kohn CM, Paudyal P. A systematic review and meta-analysis of complementary and alternative medicine in asthma. European Respiratory Review. 2017;**26**:160092. DOI: 10.1183/16000617.0092-2016