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The C1q-Receptor - Calreticulin - Contributes to the Pathogenesis of Asthma

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Abstract

The C1q-receptor functions as a stress response protein, a cellular calcium regulator, and as a cell death mediator. Thereby it contributes to carcinogenesis and controls innate immunity and. First described as an intracellular protein, the C1q-receptor also integrates into the cell membrane and mediates the response to extracellular stimuli including collagen degradation fragments, bacterial wall proteins and complement proteins. However, its role in chronic inflammatory diseases has not been investigated in details. Recent evidence suggests that in chronic inflammatory lung diseases the C1q-receptor contributes to infection induced exacerbation, which is the major cause of increased morbidity and mortality. In isolated human airway smooth muscle cells, the C1q-receptorregulates translation control and thus, can function on the level of epigenetic protein control. In this function, the C1q-receptor deregulation may lead to hyperplasia of airway smooth muscle cells, which is well documented in asthma. Furthermore, there are studies indicating that the C1q-receptor is a positive regulator for a number of asthma relevant pro-inflammatory cytokines, growth factors, and extracellular matrix compounds. In regard to asthma exacerbation, it is interesting to know that several bacteria and viruses encode for their own specific C1q-receptor or the C1q-receptor -like protein, which interacts with its binding proteins on the host cells just as a host own C1q-receptor. Thereby, the micro-organisms C1q-receptor can hijack the host cellular regulation system.

This review presents supportive data for the hypothesis that deregulation of the C1q-receptor is a major event leading to multiple asthma specific pathologies of the airway.

Introduction

Asthma is the most frequent non-communicable chronic inflammatory lung disease which according to the WHO affects 235 million people, from which 50% are children [1]. The prevalence of asthma is increasing constantly without any known reason(s) and there is no cure available, only symptoms can be controlled by various medications [2-4]. Asthma is the most frequent reason for absence from school, work and social activities. Urbanization is associated with increased asthma prevalence however; the nature of this link is unclear. In general, asthma is under-diagnosed and under-treated according to the newest evaluation of the World Health Organisation [5]. Moreover, a new assessment of asthma diagnosis and management of the WHO indicates that asthma is often neglected, or wrongly diagnosed, and is often ignored by society as it has a relatively low fatality rate compared to other diseases [5].

Asthma is characterized by recurrent breathlessness and wheezing which varies in severity and frequency. These symptoms can occur irregularly, multiple times a day or when triggered by a specific stimulus. Allergic asthma is often accompanied by skin and other allergies, which can be caused by plant pollen, dust (flour), chemicals or toxins. Thus, it was assumed that asthma is the result of a chronic type-2 type inflammation, but there is increasing evidence that there is more to its pathogenesis, and airway wall remodelling precedes or parallels inflammation [6, 7]. However, about 40% of asthma patients suffer from non-allergic asthma which can be caused by physical and psychological stress, by sudden changes in temperature or air humidity [8-10].

The pathogenesis of asthma is not completely understood and new data suggests that the likelyhood to develop asthma increases when a person is the carrier of agenetic pre-disposition and is exposed to specific environmental factors during embryogenesis and in early childhood [11,12]. Environmental factors that can trigger the pathogenesis of asthma by airway irritation include: house dust mite faces in bedding, pet dander, plant pollen, mould spores, tobacco smoke, chemical irritants or air pollution by dust particles. These factors are often causing an allergic response of the lung [12-14]. However, about 40% of asthma cases are due to non-allergic triggers such as cold air,

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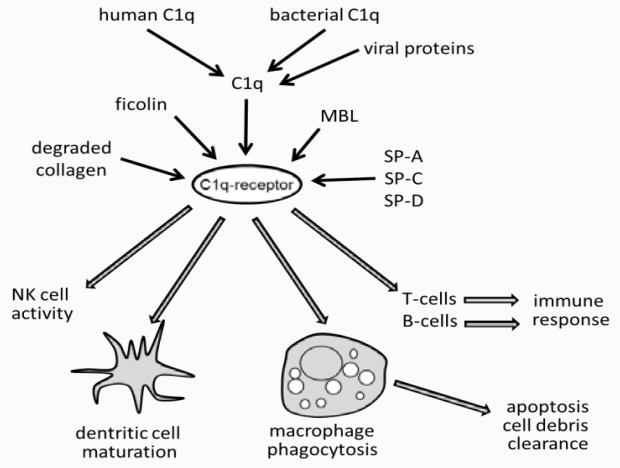

Figure 1: The membranous C1q-receptor functions as the mediator of many extracellular factors, including: manose binding lectin (MBL), surfactant protein (SP), and complement component 1 (C1q).
NK = natural killer cell.

sudden changes of air humidity often occurring in water and winter sport activities, severe anger or fear, and other physical exercise, obesity, or specific medication such as aspirin, non-steroid anti-inflammatory drugs, or β_2-agonists [15-21].

The main stand of asthma therapy consists of combined anti-inflammatory and muscle relaxing drugs, mainly inhaled corticosteroids (ICS) combined with long acting β_2-agonsist (LABA) [22,23]. The major therapeutic effect of ICS results from their anti-inflammatory action which is achieved by the activation of the intracellular glucocorticoid receptor and by the modification of DNA accessibility through his tone modification [22]. There is controversial data if LABA have any anti-inflammatory effect or if their action is restricted to the relaxation of muscle cells [23]. Studying the effect of these drugs in isolated human airway cells, we were the first to provide the molecular biological mechanism that underlies the beneficial interaction of ICS and LABA [24-26]. This mechanism was later confirmed in tissues of asthma and COPD patients by others [27,28]. However, none of the drug has shown reduction of existing airway wall remodelling and there is data indicating that ICS, if taken in non-acute stages may even worsen remodelling, since under non-inflamed condition, these drugs increase the deposition of different extracellular matrix components [29,30]. This hypothesis was supported by a study in patients with mild asthma, in which airway wall remodelling occurred within 4 days after allergen or cholinergic stimulus inhalation [31]. In this study airway wall remodelling was only reduced in those patients who received inhaled β_2-agonists before the inhalation of the stimulus. In this regard it is of interest that increased levels of extracellular matrix degradation products have been reported in isolated human airway wall cells as well as in tissue and serum samples obtained from asthma patients, but their link to the pathogenesis is still not well understood [32-36]. Since the C1q-receptor has been reported to modify extracellular matrix composition and respond to its degradation products, its contribution to the pathogenesis of asthma is suggested [37].

The C1q-receptor as a regulator of innate immunity

The C1q-receptor, which is also known as calreticulin, surfactant protein receptor, mannan binding ligand receptor, C1qR, CD93 or Aa4, is a ubiquitous, highly conserved calcium-binding protein which is mainly located in the sarcoplasmic and endoplasmic reticulum. In addition, it has been localized as a cell membrane protein. As predicted by its structure the C1q-receptor binds to hormone receptors, heat shock proteins (Hsp), integrins, viral and bacterial proteins, extracellular matrix components such as collagens, cell debris and cytokines [38]. In the nucleus membrane the C1q-receptor controls the in and out of the activated glucocorticoid receptor in other than lung cell types and might therefore be responsible for steroid resistance [39,40]. These studies also showed that the function of the C1q-receptor as a pro- or anti-inflammatory factor depends on its partnering proteins, the cell type, and on its localisation within a cell.

Most often asthma exacerbations are due to viral or bacterial infection [41]. Thus it is important to note that complexes formed by pathogenic organism proteins and the C1q-receptor stimulated phagocytosis, pro-inflammatory response, but also extended the survival of the host cells [42]. Interestingly, the membranous C1q-receptor directly interacts with various proteins that participate in innate immunity and asthma associated exacerbation including collectins such as ficolin [43], and manose binding lectins [44,45]. Furthermore, the interaction of collectins with the C1q-receptor depends on glycosilation [46], which we have reported to be altered in asthma and chronic obstructive pulmonary disease (COPD) [47,48]. Both ficolin and MBLs have been related to increased exacerbation frequencies in asthma [49,50] and frequent infection as well as to oxidative stress in COPD [51].

Collectins and complement components bind and activate the C1q-receptor and have already been linked to the regulation of innate immune response in the late 1990's [52,53].In the lung, collectins have also been shown to modify innate immunity through activation of the C1q-receptor [54]. In a rat model, it was shown that the C1q-receptor is the central regulator of natural killer cell activity [55]. The activation of the C1q-receptor also controls the differentiation of monocyte-derived dendritic cells through modification of innate and acquired immunity [56]. Platelet activation by the action of the C1q-receptor has been linked to collagen-derived peptides which may be relevant for the modification of innate immunity in response to tissue remodelling [57]. A further function of the C1q-receptor is its role as a marker for cells to undergo apoptosis which is resolved by macrophage phagocytosis [58]. Further studies showed that complement activation of the C1q-receptor should be regarded as a unique sensor for "danger signal" which trigger the innate immune response [59]. The known activators of the C1q-receptors are shown in (Figure 1).

The C1q-receptor in the regulation of pro-inflammatory cytokines in asthma

Activation of the C1q-receptor increases IL-6 and IL-8 secretion, which are both important to general immune activation and infiltration of eosinophils into the asthmatic lung [60]. Interestingly, this effect of C1q-receptor seems to be highly conserved through evolution [61]. This action involves TNF-α, another asthma relevant cytokine, which subsequently induces the signalling cascade of mitogen activated protein kinases [62], and their target NF_KB [63,64]. Interestingly, soluble C1q-receptor can also induce the production of TNF-α and IL-6 by macrophages [63], which makes it likely that this pathway represents the activation of the host cells in response to bacterial or viral infections through the micro-organisms own calreticulin [65-70]. Interestingly, the reduction of the C1q-receptor

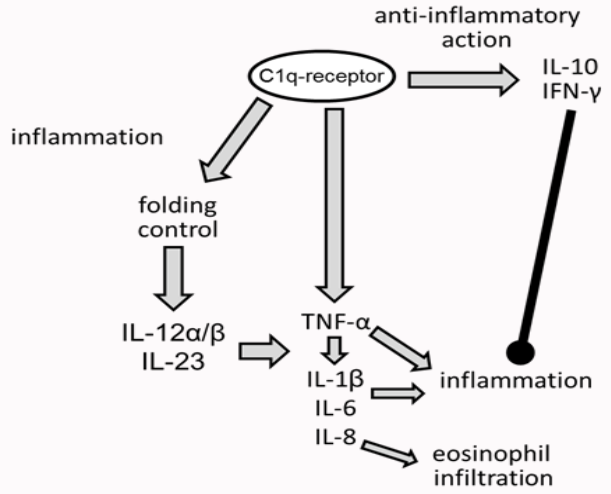

Figure 2: The C1q-receptor can act as an anti-inflammatory factor or as a pro-inflammatory factor. The conditions under which it acts have to be further defined. Arrows indicate stimulating effects, while round end indicate inhibitory effects.

expression stabilized the inhibitor of NF_KB, I_KB, thereby reducing histone modification and cytokine secretion [64]. In cardio-myocytes of mice, it has been observed that glutathione depletion increased the C1q-receptor expression and thereby enhanced myocyte proliferation [71].

The C1q-receptor controls protein folding when it is located in the endoplasmic reticulum where it has been shown to modify the structure of IL-12α and β [72]. A similar effect of the C1q-receptor was reported on IL-23 [73]. Furthermore, C1q-receptor affects the expansion of B-cells and the secretion of IL-10 [74]. In T-cells, the C1q-receptor enhanced IFN-γ secretion and the expression of CD40 on dendritic cells [75]. Finally in macrophages, the C1q-receptor induced autophagy through the activation of IL-1β [76]. A summary of the effects of the C1q-receptor on cytokine release is shown in (Figure 2).

The role of the C1q-receptor in airway wall remodelling

Beside chronic inflammation, asthma is characterised by extensive airway wall remodelling, presenting as increased mass of smooth muscle bundles, sub-epithelial fibrosis, and extracellular matrix deposition, which were first described in 1922 [77]. This major pathology was believed to increase with the duration of the disease but it has recently been demonstrated that it can be induced within days and is independent of inflammation and was related to constrictive forces in the airway wall [31]. Once established, the remodelled airway wall is largely resistant to therapy and the increased airway smooth muscle bundles are responsible for the hyper-constrictive force, airway narrowing, and the increased deposed extracellular matrix that together stiffens the airways and reduces its flexibility, thereby limiting the patient's breathing capacity [78]. However, in a complex disease such as asthma, the malfunction of a single cell type is unlikely the exclusive cause. In order to understand what causes asthma, we need to regard the network between the airways tissue forming cells with the infiltrating immune cells as an inseparable unit as it has been suggested by Holgate in 2000 [79]. Interestingly, the C1q-receptor has been shown to promote fibrotic responses when released from epithelial cells in other diseases [80].

New studies indicate that bronchial epithelial cells control the airway wall structure and the function of sub-epithelial smooth muscle cells and fibroblasts through secreted growth factors and cytokines [81-83]. In conditions other than asthma, the C1q-receptor has been linked to tissue remodelling mediating and regulating TGF-β expression and function, as well as pro-inflammatory extracellular matrix synthesis [84,85]. In this context, the interaction between thrombospondin and the C1q-receptor plays an important role in wound repair and chronic inflammatory tissue remodelling [86], both events are important to airway wall remodelling in asthma. In renal fibrosis, it was the C1q-receptor produced by tubular epithelial cells that induced sub-epithelial fibrosis, through TGF-β synthesis, extracellular matrix production, and fibroblast proliferation [87]. There is no information if a similar mechanism involving the C1q-receptor occurs in sub-epithelial fibrosis in asthma.

In regard to asthma, the function of the C1q-receptor has been studied in isolated human airway smooth muscle cells. We have reported that the increased expression of the C1q-receptor was strongly associated with the decreased translation of the cell differentiation regulating transcription factor C/EBP-α [88]. This reduced C/EBP-α expression was cell type and disease specific and increased the proliferation of airway smooth muscle cells [26,89]. Furthermore, the C1q-receptor was up-regulated by the most power full asthma trigger - house dust mite allergens [90]. In healthy airway smooth muscle cells up-regulation of the C1q-receptor down-regulated C/EBP-α expression and thereby increased cell proliferation [91]. Others reported that the C1q-receptor is up-regulated in airway smooth muscle cells by IL-13, an asthma relevant pro-inflammatory mediator [92]. In murine tracheal smooth muscle cells the C1q-receptor was associated with caveolin and activated calcium pump proteins, suggesting a new role of the membranous C1q-receptor [93].

In lung fibroblasts, the C1q-receptor expression was increased by stress such as heat [38], and together with other epithelial cell specific proteins, surfactant proteins (SP-A, SP-D), the C1q-receptor enhanced or suppressed inflammatory mediator production depending on its binding sites. Binding of thecC1q-receptor to the collagenous tail of SP-A and SP-D induced pro-inflammatory mediator production,

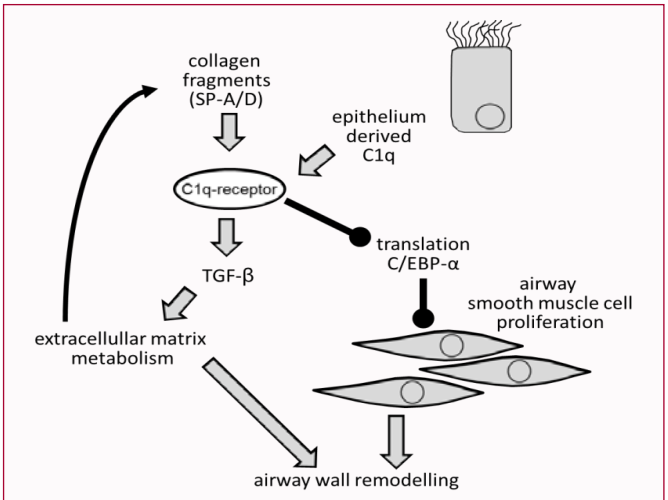

Figure 3: The C1q-receptor as a promoter of airway wall remodelling in asthma. Arrows indicate stimulating effects, while round end indicate inhibitory effects.
TGF = tumor growth factor, C/EBP = CCAAT/enhancer binding protein.

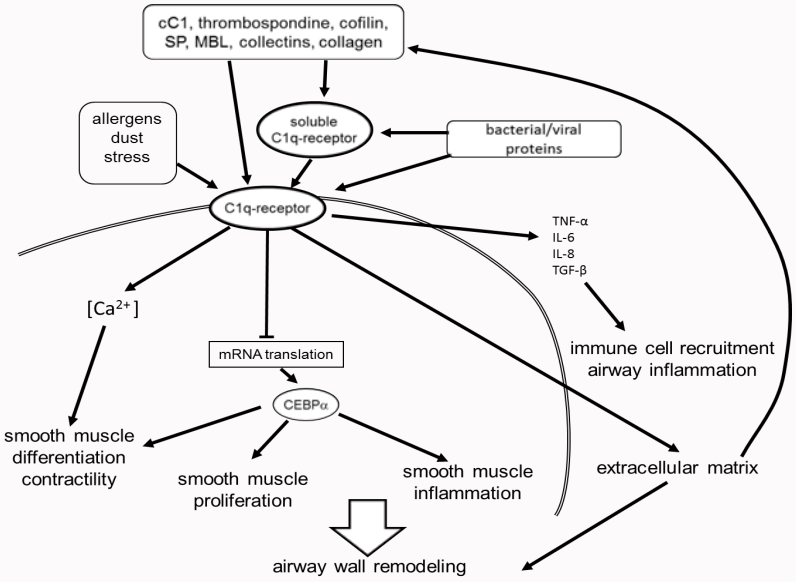

Figure 4: The hypothesized role of the C1q-receptor in the pathogenesis of asthma.

while binding with other site was anti-inflammatory [38]. Airway epithelial cells are the major source of SPs which are fundamental to the control of airway function and may be linked to embryonal pre-dispositioning to asthma through their interaction with thecC1q-receptor [94]. It is surprising that the function of the C1q-receptor, as a major signal mediator for surfactant proteins, mannan binding proteins and other collectins, has been neglected in the past 10 years [95-99]. (Figure 3) shows the known effects of the C1q-receptor in tissue remodelling.

Conclusion and Hypothesis

In conclusion, asthma remains a major burden for social life and health care systems worldwide and new curative therapeutic targets are needed [1]. The dogma that asthma results from chronic airway inflammation has recently been challenged and it is indicated that airway wall remodelling is an independent pathology of asthma which may even cause inflammation.

Based on the above presented evidence, it can be postulated that the malfunction of the C1q-receptor is causatively linked to the pathogenesis of asthma. The C1q-receptor can be regarded as a major initiating factor of asthma which activates tissue remodelling, inflammation and innate immunity. Furthermore, the role of the C1q-receptor in asthma exacerbation caused by infections should be further analysed. Referring to the above studies, it can be suggested that neutralising the C1q-receptor will resolve many pathologies of asthma and help to develop novel curative drugs.

The hypothesis that the increased expression of the C1q receptor in asthma is the cause of increased airway wall remodelling and increased secretion of pro-inflammatory cytokines is illustrated in (Figure 4).

References

1. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. Int J Tuberc Lung Dis. 2015; 19: 10-20.
2. Patel M, Shaw D. A review of standard pharmacological therapy for adult asthma- Steps 1 to 5. Chron Respir Dis. 2015; 12: 165-176.
3. Olin JT, Wechsler ME. Asthma: pathogenesis and novel drugs for treatment. BMJ. 2014; 349: 5517.
4. Ortega VE, Meyers DA, Bleecker ER. Asthma pharmacogenetics and the development of genetic profiles for personalized medicine. Pharmgenomics Pers Med. 2015; 8: 9-22.
5. WHO up-date. 2013.
6. Fahy JV. Type 2 inflammation in asthma-present in most, absent in many. Nat Rev Immunol. 2015; 15: 57-65.
7. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of bronchoconstriction on airway remodeling in asthma. N Engl J Med. 2011; 364: 2006-2015.
8. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014; 140: 774-815.
9. Carlsen KH. Sports in extreme conditions: the impact of exercise in cold temperatures on asthma and bronchial hyper-responsiveness in athletes. Br J Sports Med. 2012; 46: 796-799.
10. Wang W. Progress in the impact of polluted meteorological conditions on the incidence of asthma. J Thorac Dis. 2016; 8: 57-61.
11. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015; 385: 899-909.
12. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. Nat Rev Immunol. 2015; 15: 57-65.
13. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. J Allergy ClinImmunol. 2015; 135: 299-310.
14. Pyun BY. Natural history and risk factors of atopic dermatitis in children. Allergy Asthma Immunol Res. 2015; 7: 101-105.
15. Bonfield TL, Ross KR. Asthma heterogeneity and therapeutic options from the clinic to the bench. Curr Opin Allergy Clin Immunol. 2012; 12: 60-67.
16. Hackett TL, Singhera GK, Shaheen F, Hayden P, Jackson GR, Hegele RG, et al. Intrinsic phenotypic differences of asthmatic epithelium and its inflammatory responses to respiratory syncytial virus and air pollution. Am J Respir Cell Mol Biol. 2011; 45: 1090-1100.
17. Kim HY, DeKruyff RH, Umetsu DT. The many paths to asthma: phenotype shaped by innate and adaptive immunity. Nat Immunol. 2010; 11: 577-584.

18. Peters SP. Asthma phenotypes: nonallergic (intrinsic) asthma. J Allergy Clin Immunol Pract. 2014; 2: 650-652.

19. Sacha JJ, Quinn JM. The environment, the airway, and the athlete. Ann Allergy Asthma Immunol. 2011; 106: 81-87.

20. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Respir Med. 2014; 108: 1723-1732.

21. Vandenplas O. Occupational asthma: etiologies and risk factors. Allergy Asthma Immunol Res. 2011; 3: 157-167.

22. Barnes PJ. Biochemical basis of asthma therapy. J Biol Chem. 2011; 286: 32899-32905.

23. Giembycz MA, Kaur M, Leigh R, Newton R. A Holy Grail of asthma management: toward understanding how long-acting beta (2)-adrenoceptor agonists enhance the clinical efficacy of inhaled corticosteroids. Br J Pharmacol. 2008; 153: 1090-1104.

24. Eickelberg O, Roth M, Lörx R, Bruce V, Rüdiger J, Johnson M, et al. Ligand-independent activation of the glucocorticoid receptor by beta2-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. J Biol Chem. 1999; 274: 1005-1010.

25. Roth M, Johnson PR, Rüdiger JJ, King GG, Ge Q, Burgess JK, et al. Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. Lancet. 2002; 360: 1293-1299.

26. Roth M, Johnson PR, Borger P, Bihl MP, Rüdiger JJ, King GG, et al. Dysfunctional interaction of C/EBPalpha and the glucocorticoid receptor in asthmatic bronchial smooth-muscle cells. N Engl J Med. 2004; 351: 560-574.

27. Haque R, Hakim A, Moodley T, Torrego A, Essilfie-Quaye S, Jazrawi E, et al. Inhaled long-acting β_2 agonists enhance glucocorticoid receptor nuclear translocation and efficacy in sputum macrophages in COPD. J Allergy Clin Immunol. 2013; 132: 1166-1173.

28. Usmani OS, Ito K, Maneechotesuwan K, Ito M, Johnson M, Barnes PJ, et al. Glucocorticoid receptor nuclear translocation in airway cells after inhaled combination therapy. Am J Respir Crit Care Med. 2005; 172: 704-712.

29. Goulet S, Bihl MP, Gambazzi F, Tamm M, Roth M. Opposite effect of corticosteroids and long-acting beta (2)-agonists on serum- and TGF-beta(1)-induced extracellular matrix deposition by primary human lung fibroblasts. J Cell Physiol. 2007; 210: 167-176.

30. Degen M, Goulet S, Ferralli J, Roth M, Tamm M, Chiquet-Ehrismann R. Opposite effect of fluticasone and salmeterol on fibronectin and tenascin-C expression in primary human lung fibroblasts. Clin Exp Allergy. 2009; 39: 688-699.

31. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of bronchoconstriction on airway remodeling in asthma. N Engl J Med. 2011; 364: 2006-2015.

32. Burgess JK, Boustany S, Moir LM, Weckmann M, Lau JY, Grafton K, et al. Reduction of tumstatin in asthmatic airways contributes to angiogenesis, inflammation, and hyperresponsiveness. Am J Respir Crit Care Med. 2010; 181: 106-115.

33. Van der Velden J, Harkness LM, Barker DM, Barcham GJ, Ugalde CL, Koumoundouros E, et al. The Effects of Tumstatin on Vascularity, Airway Inflammation and Lung Function in an Experimental Sheep Model of Chronic Asthma. Sci Rep. 2016; 6: 26309.

34. Nihlberg K, Andersson-Sjöland A, Tufvesson E, Erjefält JS, Bjermer L, Westergren-Thorsson G. Altered matrix production in the distal airways of individuals with asthma. Thorax. 2010; 65: 670-676.

35. Weitoft M, Andersson C, Andersson-Sjöland A, Tufvesson E, Bjermer L, Erjefält J, et al. Controlled and uncontrolled asthma display distinct alveolar tissue matrix compositions. Respir Res. 2014; 15: 67.

36. Bougault V, Loubaki L, Joubert P, Turmel J, Couture C, Laviolette M, et al. Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools. J Allergy Clin Immunol. 2012; 129: 351-358.

37. Zimmerman KA, Graham LV, Pallero MA, Murphy-Ullrich JE. Calreticulin regulates transforming growth factor-β-stimulated extracellular matrix production. J Biol Chem. 2013; 288: 14584-14598.

38. Conway EM, Liu L, Nowakowski B, Steiner-Mosonyi M, Ribeiro SP, Michalak M. Heat shock-sensitive expression of calreticulin. J Biol Chem. 1995; 270: 17011-17016.

39. Olkku A, Mahonen A. Calreticulin mediated glucocorticoid receptor export is involved in beta-catenin translocation and Wnt signalling inhibition in human osteoblastic cells. Bone. 2009; 44: 555-565.

40. Walther RF, Lamprecht C, Ridsdale A, Groulx I, Lee S, Lefebvre YA, et al. Nuclear export of the glucocorticoid receptor is accelerated by cell fusion-dependent release of calreticulin. J Biol Chem. 2003; 278: 37858-37864.

41. Graham LM, Eid N. The impact of asthma exacerbations and preventive strategies. Curr Med Res Opin. 2015; 9: 1-11.

42. Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, et al. By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell. 2003; 115: 13-23.

43. Lacroix M, Dumestre-Pérard C, Schoehn G, Houen G, Cesbron JY, Arlaud GJ, et al. Residue Lys57 in the collagen-like region of human L-ficolin and its counterpart Lys47 in H-ficolin play a key role in the interaction with the mannan-binding lectin-associated serine proteases and the collectin receptor calreticulin. J Immunol. 2009; 182: 456-465.

44. Bohlson SS, Fraser DA, Tenner AJ. Complement proteins C1q and MBL are pattern recognition molecules that signal immediate and long-term protective immune functions. Mol Immunol. 2007; 44: 33-43.

45. Pagh R, Duus K, Laursen I, Hansen PR, Mangor J, Thielens N, et al. The chaperone and potential mannan-binding lectin (MBL) co-receptor calreticulin interacts with MBL through the binding site for MBL-associated serine proteases. FEBS J. 2008; 275: 515-526.

46. Rudd PM, Wormald MR, Dwek RA. Sugar-mediated ligand-receptor interactions in the immune system. Trends Biotechnol. 2004; 22: 524-530.

47. Klagas I, Goulet S, Karakiulakis G, Zhong J, Baraket M, Black JL, et al. Decreased hyaluronan in airway smooth muscle cells from patients with asthma and COPD. Eur Respir J. 2009; 34: 616-628.

48. Papakonstantinou E, Roth M, Tamm M, Eickelberg O, Perruchoud AP, Karakiulakis G. Hypoxia differentially enhances the effects of transforming growth factor-beta isoforms on the synthesis and secretion of glycosaminoglycans by human lung fibroblasts. J Pharmacol Exp Ther. 2002; 301: 830-837.

49. Cedzynski M, Atkinson AP, St Swierzko A, MacDonald SL, Szala A, Zeman K, et al. L-ficolin (ficolin-2) insufficiency is associated with combined allergic and infectious respiratory disease in children. Mol Immunol. 2009; 47: 415-419.

50. Koponen P, He Q, Helminen M, Nuolivirta K, Korppi M. Association of MBL2 polymorphism with asthma after bronchiolitis in infancy. Pediatr Int. 2012; 54: 619-622.

51. Tran HB, Ahern J, Hodge G, Holt P, Dean MM, Reynolds PN, et al. Oxidative stress decreases functional airway mannose binding lectin in COPD. PLoS One. 2014; 9: 98571.

52. Nicholson-Weller A, Klickstein LB. C1q-binding proteins and C1q receptors. Curr Opin Immunol. 1999; 11: 42-46.

53. Reid KB, Colomb MG, Loos M. Complement component C1 and the

collectins: parallels between routes of acquired and innate immunity. Immunol Today. 1998; 19: 56-59.

54. Kuroki Y, Takahashi M, Nishitani C. Pulmonary collectins in innate immunity of the lung. Cell Microbiol. 2007; 9: 1871-1879.

55. Løvik G, Vaage JT, Dissen E, Szpirer C, Ryan JC, Rolstad B. Characterization and molecular cloning of rat C1qRp, a receptor on NK cells. Eur J Immunol. 2000; 30: 3355-3362.

56. Hosszu KK, Santiago-Schwarz F, Peerschke EI, Ghebrehiwet B. Evidence that a C1q/C1qR system regulates monocyte-derived dendritic cell differentiation at the interface of innate and acquired immunity. Innate Immun. 2010; 16: 115-127.

57. Skoglund C, Wetterö J, Tengvall P, Bengtsson T. C1q induces a rapid up-regulation of P-selectin and modulates collagen- and collagen-related peptide-triggered activation in human platelets. Immunobiology. 2010; 215: 987-995.

58. Verneret M, Tacnet-Delorme P, Osman R, Awad R, Grichine A, Kleman JP, et al. Relative contribution of c1q and apoptotic cell-surface calreticulin to macrophage phagocytosis. J Innate Immun. 2014; 6: 426-434.

59. Gasque P. Complement: a unique innate immune sensor for danger signals. Mol Immunol. 2004; 41: 1089-1098.

60. van den Berg RH, Faber-Krol MC, Sim RB, Daha MR. The first subcomponent of complement, C1q, triggers the production of IL-8, IL-6, and monocyte chemoattractant peptide-1 by human umbilical vein endothelial cells. J Immunol. 1998; 161: 6924-6930.

61. Sukkurwala AQ, Martins I, Wang Y, Schlemmer F, Ruckenstuhl C, Durchschlag M, et al. Immunogenic Calreticulin exposure occurs through a phylogenetically conserved stress pathway involving the chemokine CXCL8. Cell Death Differ. 2014; 21: 59-68.

62. Singh U, Kumar A, Sinha R, Manral S, Arora S, Ram S, et al. Calreticulintransacetylasecatalyzed modification of the TNF-alpha mediated pathway in the human peripheral blood mononuclear cells by polyphenolic acetates. Chem Biol Interact. 2010; 185: 263-270.

63. Duo CC, Gong FY, He XY, Li YM, Wang J, Zhang JP, et al. Soluble calreticulin induces tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 production by macrophages through mitogen-activated protein kinase (MAPK) and NFκBsignaling pathways. Int J Mol Sci. 2014; 1: 2916-2928.

64. Massaeli H, Jalali S, Viswanathan D, Mesaeli N. Loss of calreticulin function decreases NFκB activity by stabilizing IκB protein. Biochim Biophys Acta. 2014; 1843: 2385-2393.

65. Ghebrehiwet B, Peerschke EI. CC1q-R (calreticulin) and gC1q-R/p33: ubiquitously expressed multi-ligand binding cellular proteins involved in inflammation and infection. Mol Immunol. 2004; 41: 173-183.

66. Oresic K, Tortorella D. Endoplasmic reticulum chaperones participate in human cytomegalovirus US2-mediated degradation of class I major histocompatibility complex molecules. J GenVirol. 2008; 89: 1122-1130.

67. Limjindaporn T, Wongwiwat W, Noisakran S, Srisawat C, Netsawang J, Puttikhunt C, et al. Interaction of dengue virus envelope protein with endoplasmic reticulum-resident chaperones facilitates dengue virus production. Biochem Biophys Res Commun. 2009; 379: 196-200.

68. Yue X, Wang H, Zhao F, Liu S, Wu J, Ren W, et al. Hepatitis B virus-induced calreticulin protein is involved in IFN resistance. J Immunol. 2012; 189: 279-286.

69. Castillo C, Ramírez G, Valck C, Aguilar L, Maldonado I, Rosas C, et al. The interaction of classical complement component C1 with parasite and host calreticulin mediates Trypanosoma cruzi infection of human placenta. PLoS Negl Trop Dis. 2013; 7: 2376.

70. Sosoniuk E, Vallejos G, Kenawy H, Gaboriaud C, Thielens N, Fujita T, et al. Trypanosoma cruzicalreticulin inhibits the complement lectin pathway activation by direct interaction with L-Ficolin. Mol Immunol. 2014; 60: 80-85.

71. Ren J, Privratsky JR, Yang X, Dong F, Carlson EC. Metallothionein alleviates glutathione depletion-induced oxidative cardiomyopathy in murine hearts. Crit Care Med. 2008; 36: 2106-2116.

72. Alloza I, Baxter A, Chen Q, Matthiesen R, Vandenbroeck K. Celecoxib inhibits interleukin-12 alphabeta and beta2 folding and secretion by a novel COX2-independent mechanism involving chaperones of the endoplasmic reticulum. Mol Pharmacol. 2006; 69: 1579-1587.

73. McLaughlin M, Alloza I, Quoc HP, Scott CJ, Hirabayashi Y, Vandenbroeck K. Inhibition of secretion of interleukin (IL)-12/IL-23 family cytokines by 4-trifluoromethyl-celecoxib is coupled to degradation via the endoplasmic reticulum stress protein HERP. J Biol Chem. 2010; 285: 6960-6969.

74. Hong C, Zhang T, Gao XM. Recombinant murine calreticulin fragment 39-272 expands CD1d(hi)CD5+ IL-10-secreting B cells that modulate experimental autoimmune encephalomyelitis in C57BL/6 mice. Mol Immunol. 2013; 55: 237-246.

75. Baruah P, Dumitriu IE, Malik TH, Cook HT, Dyson J, Scott D, et al. C1q enhances IFN-gamma production by antigen-specific T cells via the CD40 costimulatory pathway on dendritic cells. Blood. 2009; 113: 3485-3493.

76. Petrovski G, Ayna G, Majai G, Hodrea J, Benko S, Mádi A, et al. Phagocytosis of cells dying through autophagy induces inflammasome activation and IL-1β release in human macrophages. Autophagy. 2011; 7: 321-330.

77. Huber HL, Koessler KK. The pathology of bronchial asthma Arch Intern Med (Chic).1922; 30: 689-760.

78. Gosens R, Grainge C. Bronchoconstriction and airway biology: potential impact and therapeutic opportunities. Chest. 2015; 147: 798-803.

79. Holgate ST, Davies DE, Lackie PM, Wilson SJ, Puddicombe SM, Lordan JL. Epithelial-mesenchymal interactions in the pathogenesis of asthma. J Allergy ClinImmunol. 2000; 105: 193-204.

80. Prakoura N, Politis PK, Ihara Y, Michalak M, Charonis AS. Epithelial calreticulin up-regulation promotes profibrotic responses and tubulointerstitial fibrosis development. Am J Pathol. 2013; 183: 1474-1487.

81. Grainge C, Dennison P, Lau L, Davies D, Howarth P. Asthmatic and normal respiratory epithelial cells respond differently to mechanical apical stress. Am J Respir Crit Care Med. 2014; 190: 477-480.

82. Green BJ, Wiriyachaiporn S, Grainge C, Rogers GB, Kehagia V, Lau L, et al. Potentially pathogenic airway bacteria and neutrophilic inflammation in treatment resistant severe asthma. PLoS One. 2014; 9: 100645.

83. Hostettler KE, Roth M, Burgess JK, Gencay MM, Gambazzi F, Black JL, et al. Airway epithelium-derived transforming growth factor-beta is a regulator of fibroblast proliferation in both fibrotic and normal subjects. Clin Exp Allergy. 2008; 38: 1309-1317.

84. Sweetwyne MT, Pallero MA, Lu A, Van Duyn Graham L, Murphy-Ullrich JE. The calreticulin-binding sequence of thrombospondin 1 regulates collagen expression and organization during tissue remodeling. Am J Pathol. 2010; 177: 1710-1724.

85. Zimmerman KA, Graham LV, Pallero MA, Murphy-Ullrich JE. Calreticulin regulates transforming growth factor-β-stimulated extracellular matrix production. J Biol Chem. 2013; 288: 14584-145698.

86. Sweetwyne MT, Murphy-Ullrich JE. Thrombospondin1 in tissue repair and fibrosis: TGF-β-dependent and independent mechanisms. Matrix Biol. 2012; 31: 178-186.

87. Prakoura N, Politis PK, Ihara Y, Michalak M, Charonis AS. Epithelial calreticulin up-regulation promotes profibrotic responses and tubulointerstitial fibrosis development. Am J Pathol. 2013; 183: 1474-1487.

88. Borger P, Miglino N, Baraket M, Black JL, Tamm M, Roth M. Impaired translation of CCAAT/enhancer binding protein alpha mRNA in bronchial smooth muscle cells of asthmatic patients. J Allergy Clin Immunol. 2009; 123: 639-645.

89. Borger P, Matsumoto H, Boustany S, Gencay MM, Burgess JK, King GG, et al. Disease-specific expression and regulation of CCAAT/enhancer-binding proteins in asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2007; 119: 98-105.

90. Miglino N, Roth M, Tamm M, Borger P. House dust mite extract downregulates C/EBPα in asthmatic bronchial smooth muscle cells. Eur Respir J. 2011; 38: 50-58.

91. Miglino N, Roth M, Lardinois D, Tamm M, Borger P. Calreticulin is a negative regulator of bronchial smooth muscle cell proliferation. J Allergy. 2012; 2012: 783290.

92. He YF, Hua L, Bao YX, Liu QH, Chu Y, Fang DZ. IL-13 R110Q, a Naturally Occurring IL-13 Polymorphism, Confers Enhanced Functional Activity in Cultured Human Bronchial Smooth Muscle Cells. Allergy Asthma Immunol Res. 2013; 5: 377-382.

93. Darby PJ, Kwan CY, Daniel EE. Caveolae from canine airway smooth muscle contain the necessary components for a role in Ca (2+) handling. Am J Physiol Lung Cell Mol Physiol. 2000; 279: 1226-1235.

94. Whitsett JA, Wert SE, Weaver TE. Diseases of pulmonary surfactant homeostasis. Annu Rev Pathol. 2015; 10: 371-393.

95. Malhotra R. Collectin receptor (C1q receptor): structure and function. Behring Inst Mitt. 1993; 93: 254-261.

96. Megidish T, Takio K, Titani K, Iwabuchi K, Hamaguchi A, Igarashi Y, et al. Endogenous substrates of sphingosine-dependent kinases (SDKs) are chaperone proteins: heat shock proteins, glucose-regulated proteins, protein disulphide isomerase, and calreticulin. Biochemistry. 1999; 38: 3369-3378.

97. Vandivier RW, Ogden CA, Fadok VA, Hoffmann PR, Brown KK, Botto M, et al. Role of surfactant proteins A, D, and C1q in the clearance of apoptotic cells in vivo and in vitro: calreticulin and CD91 as a common collectin receptor complex. J Immunol. 2002; 169: 3978-3986.

98. Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, et al. By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell. 2003; 115: 13-23.

99. Kishore U, Greenhough TJ, Waters P, Shrive AK, Ghai R, Kamran MF, et al. Surfactant proteins SP-A and SP-D: structure, function and receptors. Mol Immunol. 2006; 43: 1293-315.