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

Michael Roth*
Department of Pulmonary Cell Research and Clinics of Pneumology, University Hospital Basel, Switzerland

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-receptor regulates 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 likelihood 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,
The main stand of asthma therapy consists of combined anti-inflammatory and muscle relaxing drugs, mainly inhaled corticosteroids (ICS) combined with long acting β2-agonist (LABA) [15-21]. 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 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 stimulates 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 triggers 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 NFκB [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...
expression stabilized the inhibitor of NFκB, IκB, 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 deposited 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 the C1q-receptor to the collagenous tail of SP-A and SP-D induced pro-inflammatory mediator production,
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 the C1q-receptor [94]. It is surprising that the function of the C1q-receptor, as a major signal mediator for surfactant proteins, mannann 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**


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