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Current Opinion in Pharmacology

Role of CD38/cADPR signaling in obstructive pulmonary diseases

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The worldwide socioeconomical burden associated with chronic respiratory diseases is substantial. Enzymes involved in the metabolism of nicotinamide adenine dinucleotide (NAD) are increasingly being implicated in chronic airway diseases. One such enzyme, CD38, utilizes NAD to produce several metabolites, including cyclic ADP ribose (cADPR), which is involved in calcium signaling in airway smooth muscle (ASM). Upregulation of CD38 in ASM caused by exposure to cytokines or allergens leads to enhanced calcium mobilization by agonists and the development of airway hyperresponsiveness (AHR) to contractile agonists. Glucocorticoids and microRNAs can suppress CD38 expression in ASM, whereas cADPR antagonists such as 8Br-cADPR can directly antagonize intracellular calcium mobilization. Bronchodilators act via CD38-independent mechanisms. CD38-dependent mechanisms could be developed for chronic airway diseases therapy.

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Current Opinion in Pharmacology 2020, **51**:29–33

This review comes from a themed issue on **Respiratory**

Edited by **Deepak Deshpande**

https://doi.org/10.1016/j.coph.2020.04.007

Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the most common chronic respiratory diseases and are among the leading causes of morbidity and mortality worldwide. In 2015, it was estimated that 358 million people across all ages and ethnicities were affected by asthma and 174 million by COPD, although the death burden from COPD was eight times higher than from asthma [1]. In the United States, chronic obstructive lung diseases (e.g., asthma and COPD) are the 3rd leading cause of death. Among Americans of all age groups, the estimated lifetime asthma prevalence is 8.4% [2] with an associated economic burden of $81.9 billion dollars [3]. Whereas the risk of COPD is largely related to modifiable behaviors (e.g., smoking), risk factors for asthma appear to be substantially more heterogeneous and less understood. Use of symptomatic therapy (e.g., corticosteroids, bronchodilators) has significantly decreased asthma mortality but the overall asthma prevalence is on the rise [1]. A better understanding of underlying causes and mechanisms is necessary to improve disease prevalence. This brief review intends to summarize current knowledge regarding the role of CD38 in the pathogenesis of chronic obstructive pulmonary diseases. The reader is kindly referred to recent, more in depth reviews if interested in more details regarding regulatory mechanisms [4•] and therapeutic potential [5•].

Nicotinamide adenine dinucleotide (NAD) in health and disease

The importance of nicotinamide adenine dinucleotide (NAD) and related metabolic enzymes in health and disease is becoming increasingly appreciated [6]. For example, sirtuins (SIRT) are a family of NAD-dependent enzymes with an increasingly recognized role in metabolism, ageing [7], as well as in airway inflammation during allergic airway diseases [8,9]. Another NAD-consuming enzyme, poly(ADP-ribose) polymerase (PARP), appears to be involved in airway inflammation, hyperresponsiveness and remodeling [10–13]. Finally, CD38 is another NAD-consuming enzyme that has emerged as an important determinant of airway hyperresponsiveness (AHR) associated with allergic airway diseases [14–29,30•,31]. This body of literature suggests that NAD metabolism may be an important determinant of altered airway function in chronic obstructive pulmonary diseases and constitute a feasible therapeutic target.

CD38 protein

CD38 is a type II, 45 kDa glycoprotein with 300 amino acids distributed in three domains comprised by a short

N-terminal cytoplasmic tail (21 amino acids), a single chain transmembrane portion (23 amino acids) and a large C-terminal extracellular domain (256 amino acids) [32]. The short cytoplasmic tail does not appear to contain any known motifs (Src homology domain 2 or 3 — SH2 or SH3, antigen receptor activation — ARAM, or pleckstrin homology — PH) that could mediate interactions with other signaling molecules and no enzymatic activity has been demonstrated [32,33]. The enzymatic activities reside in the extracellular domain whereby CD38 catalyzes the cleavage of the nicotinamide group from NAD (NADase activity) leading to the formation of an enzyme-ADP-ribosyl intermediary complex, which then partitions between two possible pathways. An intramolecular reaction between the ribosyl carbon-1 and the nitrogen-1 of the adenine ring (ADP-ribosyl cyclase activity) yields cyclic adenosine diphosphate ribose (cADPR; ~3% final product) and a macroscopically irreversible hydrolysis reaction (cADPR hydrolase or NAD glycohydrolase) produces adenosine diphosphate ribose (ADPR; ~97% final product). Thus, CD38 is a more efficient NAD glycohydrolase (i.e., direct conversion of NAD to ADPR) than ADP-ribosyl cyclase [34–36]. CD38 is also responsible for the generation of nicotinic acid adenine dinucleotide phosphate (NAADP) from NADP. The cADPR and NAADP products regulate Ca^{2+} signaling and contractility in smooth muscle cells [22].

CD38 and immunity

CD38 is a pleiotropic cell surface molecule within the immune system, acting as a multifunctional enzyme and receptor. CD38 generates transmembrane signals upon engagement with its counter-receptor, CD31, with agonistic monoclonal antibodies and during G-protein coupled receptor activation. The effects mediated include production of pro-inflammatory and regulatory cytokines by monocytes, NK cells, activated B and T lymphocytes, proliferation of T lymphocytes and protection of mature B lymphocytes from apoptosis. Defective CD38 signaling in neutrophils impairs innate immunity to bacterial infection, and inadequate dendritic cell priming of B-cells and T-cells affect humoral immune responses to antigens [37].

CD38 and airway function

Our laboratory was the first to demonstrate the contribution of CD38 to the regulation of airway hyperresponsiveness (AHR). We first determined the airway phenotype of CD38 knockout mice as compared to that of the wild-type mice. Airway challenge with inhaled methacholine resulted in significantly attenuated changes in resistance to airflow and dynamic compliance in the CD38 knockout mice compared to wild-type controls [27]. Additionally, ASM cells isolated from CD38 knockout mice developed significantly lower intracellular calcium responses to acetylcholine and endothelin-1 than wild-type controls. In ASM cells, CD38 utilizes NAD to form cADPR and ADPR, but the release of calcium in response to agonist activation is cADPR-dependent as it can be antagonized by the competitive cADPR antagonist 8Br-cADPR [27]. These evidences suggested that the attenuated airway responsiveness to inhaled methacholine likely stemmed from decreased intracellular calcium responses in ASM cells due to the loss of CD38 activity and cADPR production in these cells.

Since asthma is an inflammatory disease, in which pro-inflammatory cytokines have a role in inducing abnormal ASM function and in the development of AHR, we determined the methacholine responsiveness of CD38 knockout and wild-type mice exposed to the asthma-relevant cytokines IL-13 and TNF-α [25,26]. It was previously known that the pro-inflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, interferon (IFN)-γ or the T helper type 2 (TH2) cytokine IL-13 significantly upregulate CD38 expression, cADPR production and intracellular calcium responsiveness in ASM cells [23,24,38–41]. Intranasal challenge with IL-13 induced robust AHR to inhaled methacholine in wild-type mice whereas AHR was significantly lower in the CD38 knockout mice. The ASM reactivity to inhaled methacholine was significantly lower in the CD38 knockout mice than in wild-type controls. Using tracheal ring preparations, we showed that CD38 within ASM mediated the IL-13-associated increase in isometric force generation to carbachol stimulation whereas absence of CD38 did not affect relaxation of ASM to the β-adrenergic receptor agonist isoproterenol [25]. A single intranasal challenge with TNF-α caused AHR to inhaled methacholine in wild-type but not in CD38 knockout mice whereas the differences in airway phenotype were no longer present following more prolonged exposure to TNF-α [26]. Together, these results provided evidence that CD38 expressed in ASM cells plays a significant role in AHR to two asthma-relevant cytokines. More recent findings showed that the CD38 signaling pathway mediated AHR due to high-fat diet in mice, thus extending its possible role to obese asthma phenotype [30•].

Earlier studies suggested that CD38 knockout mice developed attenuated T cell-dependent humoral immune response to protein antigens [42]. The underlying mechanisms for this attenuated allergen-induced antibody response were complex and included inefficient migration of CD38-deficient dendritic cells from sites of inflammation to the draining lymph nodes and defective priming of T cells [37]. Interestingly, airway inflammation in response to IL-13 was similarly robust in both wild-type and CD38 knockout mice, yet AHR was significantly lower in the former [25]. The role of CD38 in the responses to intranasal challenge with TNF-α also seemed disconnected from the development of airway inflammation [26]. Since asthma is triggered by allergen exposure leading to airway inflammation and release of cytokines and chemokines, we investigated

whether CD38 knockout mice would develop an attenuated airway phenotype following allergen sensitization and challenge [14]. We compared the airway responsiveness of CD38 knockout and wild-type mice following intranasal sensitization and intranasal challenge with fungal antigens as well as following intraperitoneal sensitization followed by intranasal challenge with ovalbumin antigen. Regardless of the route of allergen sensitization, the CD38 knockout mice developed significantly attenuated AHR to inhaled methacholine compared to wild-type mice. Once again, the airway inflammatory response characterized by the number and types of inflammatory cells in the bronchoalveolar lavage (BAL) fluid was comparable in the two groups of mice. Furthermore, the changes in BAL fluid content of IL-5 and IL-13 were similar between CD38 knockout and wild-type mice in both allergen models. However, the magnitude of increase in eotaxin-2 levels in BAL fluid was significantly less in the CD38 knockout mice following fungal allergen challenge but not following ovalbumin. These findings indicated that CD38 expression is relevant for the development of heightened AHR following allergen sensitization and challenge, but appears to be a less important determinant of airway inflammation.

To further explore this mechanism, we developed bone marrow chimeras to assess if reciprocal transfer of bone marrow-derived cells from wild-type and CD38 knockout mice would restore the airway phenotype in the hosts. The airway phenotype under naïve conditions was unchanged by reciprocal bone marrow transfer. Following ovalbumin challenge, the airway phenotype in CD38 knockout mice was partially reversed by bone marrow transfer from either source whereas the airway phenotype of WT hosts was preserved [14]. These results thus confirm that loss of CD38 in hematopoietic cells is insufficient to prevent AHR to allergen and thus the contribution of CD38 to AHR stems from its presence and activity in resident airway cells. Altogether, the above findings in the cytokine and allergen models are consistent with the role of CD38 in ASM calcium responses and contractility to agonists and suggest that this CD38 mechanism is an important contributor to heightened bronchoconstriction in allergic airway diseases. Interestingly, injection of dendritic cells overexpressing CD38 into ovalbumin-immunized female mice before ovalbumin challenge led to lower airway inflammation compared to controls as well as increased in the levels of the Th1 cytokine IFN-γ concurrently with a decrease in the Th2 cytokine IL-4 [43•]. Thus, it is possible that CD38 expression in dendritic cells and ASM cells has opposing roles in terms of inflammation and AHR during allergic airway disease.

The presence of increased CD38 expression in the lungs of asthmatic human patients was first reported in a study analyzing its distribution in human tissues [44]. Since then, the role of CD38 in human ASM cell function has been extensively investigated in cells obtained from patients with asthma and healthy controls [15–21,23,28,29]. In human ASM from asthmatics, CD38 amplifies calcium signaling and inflammatory response to pro-inflammatory cytokines via mechanisms involving both transcriptional and post-transcriptional regulation [16–21,24]. Glucocorticoids, which are commonly used in both asthma and COPD therapy [45,46], significantly suppress TNF-α-induced CD38 expression in human ASM from asthmatics [15,17,20]. Treatment of human ASM with microRNAs with (miRNAs) miR-140-3p and miR-708 negatively regulate CD38 expression by mechanisms that involve translational repression as well as indirectly by transcriptional mechanisms [19]. This results in profound anti-inflammatory effect as evidenced by significant decreases in the expression and release of several chemokines and asthma related genes [47]. Thus, there is good understanding of the role of CD38 in ASM from human asthmatics.

The role of CD38 on COPD is less clear. In COPD patients, expression of CD38 occurs in both alveolar and interstitial macrophages (small and large), although expression is greater in the small macrophages [48•]. 'Small' and 'large' macrophage subpopulations have been identified in the sputum of COPD patients based on pattern of forward scatter during flow cytometry analysis. Compared to large macrophages, COPD small macrophages show higher levels of TNF-α, both constitutively and in response to lipopolysaccharide challenge [49]. Current smoking on COPD patients is associated with lower CD38 expression in large interstitial macrophages compared to ex-smokers [48•]. Levels of a soluble form of CD38 (sCD38) in the serum and exhaled breath condensate of patients with moderate COPD were higher than in healthy non-smoker controls [50], but the significance of this finding is unclear. In addition, patients with significant smoking history (>25 pack years) had significantly higher CD38 expression in epithelium-denuded bronchial smooth muscle when compared to lifetime non-smokers. *In vitro*, cigarette smoke extract concentration-dependently increased CD38 expression and calcium responsiveness in human ASM, as well as enhanced TNF-α release and proliferative capacity [51]. Lastly, *in vitro* evidence suggests that CD38 might play a role in the response to respiratory viral infections [52], which are known to worsen the symptoms of asthma and COPD patients. In that study, the inflammatory response of human monocyte-derived dendritic cells infected with respiratory syncytial virus was significantly reduced by inhibiting CD38 enzymatic activity with the flavonoid kuromanin, as well as by inhibiting CD38 downstream signaling with the cADPR antagonist 8Br-cADPR [52].

Conclusions and future directions

This review outlines the current understanding of the role of CD38/cADPR signaling in chronic obstructive

pulmonary diseases. Cytokines, glucocorticoids, and miRNAs modulate CD38 expression in human ASM, especially in asthmatics. Furthermore, CD38 significantly contributes to the asthmatic phenotype in mice challenged with inhaled allergens. The role CD38 in the pathophysiology of COPD appears to be emerging, but additional studies are necessary to elucidate this possibility. Studies are warranted to better understand the epigenetic interactions between the CD38 signaling system and factors such as viral infections, cigarette smoking and ozone, which contribute to or exacerbate obstructive pulmonary diseases such as asthma and COPD.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Alonso GP Guedes: Conceptualization, Writing - review & editing. **Mythili Dileepan:** Writing - review & editing. **Joseph A Jude:** Writing - review & editing. **Deepak A Deshpande:** Writing - review & editing. **Timothy F Walseth:** Writing - review & editing. **Mathur S Kannan:** Writing - review & editing.

Acknowledgement

Mathur S. Kannan and Deepak A. Deshpande received support through grants from the National Institutes of Health.

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