International Journal of Biochemistry and Cell Biology 112 (2019) 141–144

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Molecules in focus

CD200 in asthma

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ARTICLE INFO

Keywords:
Lung
Immunoregulation
Allergic asthma
CD200Fc
CD200 receptors

ABSTRACT

Constant exposure to foreign particles in the airways requires tight immune regulation in order to maintain sufficient anti-microbial defences, while preventing immunopathological responses that could impair gas exchange. Dysregulation of immunoregulatory pathways has been associated with asthma and allergy. This review will focus on the CD200 regulatory pathway and its role in the asthmatic cascade.

CD200 and its receptors are highly expressed in the lung, on epithelial cells and leukocytes, and emerging evidence links dysregulation of the CD200 pathway with asthma. Moreover, pharmacological modulation of CD200 receptors was shown to improve clinical and inflammatory outcomes of preclinical asthma models. Therefore, the involvement of CD200 in asthma is increasingly recognized and preclinical studies support the contention that it could constitute an additional target to alleviate asthma exacerbation and/or reduce disease severity.

1. Introduction

Asthma is a chronic airway disease characterized by airway hyperreactivity, inflammation and remodeling leading to episodic airflow limitation and breathlessness. Despite a state-of-the-art management with currently available drugs, a significant proportion of asthma patients have poorly controlled symptoms and remain with an evolving inflammatory disease, highlighting our partial understanding of the pathogenesis. In the past decades, there was a great focus on investigating pro-inflammatory mediators involved in asthma pathogenesis, which led to the development of antagonists of those inflammatory pathways with varying degree of success in altering the asthmatic cascade. Nevertheless, it becomes evident that regulatory pathways are also involved and dysregulated in allergic asthma.

The immunoregulatory role of CD200 is well documented in various contexts, including cancer, neuroinflammation, arthritis and transplantation (Holmannova et al., 2012b). CD200 is highly expressed in normal lung (Jiang-Shieh et al., 2010) and increasing evidence supports its critical involvement in pulmonary immunoregulation (Holt and Strickland, 2008). This focussed review will thus summarize the current knowledge of CD200 and CD200 receptor distribution in the lungs, as well as the evidence supporting its involvement in asthma.

2. Pathogenesis: CD200 and its receptors

2.1. CD200

CD200, formerly known as OX-2, is a transmembrane glycoprotein and a member of immunoglobulin (Ig) supergene family (Holmannova et al., 2012a). CD200 has two Ig-like domains, a single transmembrane region and a short cytoplasmic tail with no known signaling motifs (Holmannova et al., 2012a), suggesting that CD200 does not induce signalling in the cells expressing it. Interestingly, a recent study in B-cells chronic lymphocytic leukemia raised the possibility that upon cleavage of membrane CD200 (see section 2.2 below), an intracytoplasmic fragment can relocalize to the nucleus and alter gene expression (Chen et al., 2018). Nevertheless, implications of this novel mechanism of action remain to be investigated in the context of immune responses.

CD200 is highly conserved, with 74% amino acid homology between the human and murine orthologs (Holmannova et al., 2012a). There is cross specificity binding between human CD200 and murine CD200 receptor (CD200R), with a stronger binding with rat CD200R compared to mouse CD200R (Wright et al., 2003). Although discrepancies on CD200 expression might be related to detection techniques and/or the activation state of the cells, it is now well accepted that

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https://doi.org/10.1016/j.biocel.2019.05.003
Received 25 March 2019; Accepted 7 May 2019
Available online 08 May 2019
1357-2725/

Table 1
Cell types expressing CD200 and CD200R in human and mice. ■: expressed consitutively; ■: expressed upon activation or by a cell subset; □: not expressed.

Cell types	CD200	CD200R	References
Macrophages	■	■	(Koning et al., 2010; Mukhopadhyay et al., 2010; Wright et al., 2003; Zhu et al., 2019)
Dendritic cells	■	■	(Akkaya et al., 2013; Koning et al., 2010; Schütz and Hackstein, 2014; Wright et al., 2003)
Monocytes	■	■	(Koning et al., 2010; Krejsek et al., 2010; Steiniger et al., 1990; Wright et al., 2003)
T cells	■	■	(Akkaya et al., 2013; Caserta et al., 2012; Wright et al., 2003)
B cells	■	■	(Akkaya et al., 2013; Snelgrove et al., 2008; Wright et al., 2003)
Neutrophils	■	■	(Akkaya et al., 2013; Koning et al., 2010; Krejsek et al., 2010; Wright et al., 2003)
Eosinophils	■	■	(Akkaya et al., 2013; Blom et al., 2017; Koning et al., 2010)
Mast cells	□	■	(Blom et al., 2017; Cherwinski et al., 2005; Wright et al., 2003)
Natural killer cells	□	■	(Akkaya et al., 2013; Blom et al., 2017; Wright et al., 2003)
Smooth muscle cells	■	□	(Lauzon-Joset et al., 2015; Wright et al., 2001)
Endothelial cells	■	□	(Barclay et al., 2002; Cherwinski et al., 2005; Jiang-Shieh et al., 2010)
Epithelial cells	■	□	(Cherwinski et al., 2005; Jiang-Shieh et al., 2010)
Neurons	■	□	(Barclay et al., 2002; Cherwinski et al., 2005)

CD200 is broadly distributed on cells from both hematopoietic and non-hematopoietic origin (Table 1 and Fig. 1), and is conserved between humans and rodents.

2.2. Post translational modifications of CD200

A naturally-occurring truncated splice variant of CD200 was documented to act as an antagonist of CD200R (Holmannova et al., 2012a). In addition, the ectodomain of membrane-bound CD200 can be cleaved by metalloproteases resulting in a soluble form of CD200, sCD200 (Wong et al., 2016). Yet, sCD200 displays a limited ability to activate CD200 receptors (Cherwinski et al., 2005), and its biological role remains misunderstood.

Although the role of sCD200 is still unclear, sCD200 was identified as a potential biomarker in multiple diseases. Elevated level of serum sCD200 is an early positive prognostic factor after engraftment (Gorczynski, 2012), supporting the involvement of sCD200 in the control and resolution of inflammation. On the other hand, CD200 shedding correlates with disease severity in advanced stage of breast cancer and inflammatory skin disorders (Gorczynski, 2012), as well as in uncontrolled asthma (Tural Onur et al., 2015); supporting an inflammatory role for sCD200. Alternatively, sCD200 levels could increase during inflammation in an attempt to reduce the inflammatory cascade. Thus, the levels of sCD200 are modified under pathological conditions, but the impact of this modulation remains unclear and might depend on the pathophysiological context.

2.3. CD200 receptors

The structure of CD200 receptor shares similarities with CD200, both containing two Ig superfamily extracellular domains and a single transmembrane region. In contrast with CD200, the receptors have a longer cytoplasmic domain with signaling capacity (Wright et al., 2003). CD200 receptors are unusual inhibitory receptors that do not contain any ITIM (immunoreceptor tyrosine-based inhibitory motifs). Instead, there is a phosphotyrosine-binding (PTB) domain-recognition motif (NPXY) (Holmannova et al., 2012a). Engagement of CD200R induces tyrosine phosphorylation of the PTB domain recruiting adaptor proteins Dok1 and Dok2. The anti-inflammatory signal of CD200R is mediated via Dok2 and activation of Ras p21 protein activator 1 (RasGAP), whereas Dok1 would act as a negative regulator of CD200R signaling by recruiting CrkL (Holmannova et al., 2012a).

CD200 receptor expression is limited to lymphoid and myeloid cell lineages (see Table 1 and Fig. 1). In human and rat, there are only two CD200R isoforms, CD200R1 and CD200R2, whereas there are at least 5 isoforms in mouse, numbered CD200R1 to CD200R5. In mouse, the

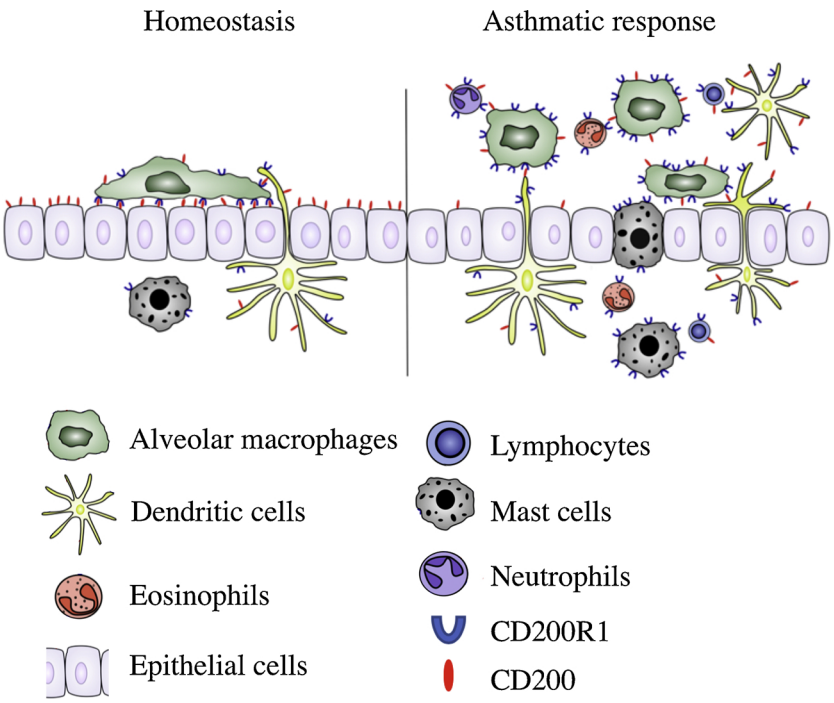

Fig. 1. CD200 and CD200 receptor expression in the airways. Under homeostatic conditions, airway epithelial cells express high levels of CD200. Correspondingly, resident lung immune cells, including mast cells, dendritic cells and alveolar macrophages, express CD200 receptor (CD200R1). Lung CD200 expression is not restricted to the epithelium, and is also found on some immune cells, including alveolar macrophages and dendritic cells. In asthma pathogenesis, CD200 is down-regulated on the airway epithelium, whereas lung resident immune cells display increased CD200R1 levels. Moreover, many inflammatory cells recruited to the airways during asthma pathogenesis also express either CD200R1, such as eosinophils, or varying levels of CD200 and CD200R1, including neutrophils and lymphocytes.

receptors CD200R2 to CD200R5 are also named CD200 “receptor-like”, respectively CD200RLc, b, a, e. CD200R1 is an inhibitory receptor whereas CD200R2 (or CD200R4/La in mouse) is an activating receptor. Although the activating receptor is closely related to CD200R1, it does not bind CD200 and has no known ligand (Holmannova et al., 2012a).

3. CD200/CD200R in asthma

3.1. The interplay between CD200 and CD200R in the lung

The microenvironment of the lung is particular given its exposure to a plethora of foreign particles and microbes. The presence of inhibitory modulators to avoid unnecessary inflammation is thus crucial. Accordingly, airway epithelial cells are actively involved in maintaining lung homeostasis. Airway epithelium express many immonumodulatory molecules, including CD200, which binds CD200R1 on alveolar macrophages and dendritic cells, preventing their activation in absence of inflammatory stimuli (Snelgrove et al., 2008) (Fig. 1). Of note, airway epithelial cells were also shown to influence the level of CD200R1 on dendritic cells (Rate et al., 2012), and alveolar macrophages express high basal levels of CD200R1, compared with macrophages from other tissues (Snelgrove et al., 2008). Recently, CD200 expression by alveolar macrophages was also reported, highlighting their unique capacity to regulate and be regulated by CD200/CD200R pathway (Lauzon-Joset et al., 2018).

During inflammation, CD200 expression on the epithelium is rapidly, but transiently reduced (Jiang-Shieh et al., 2010), whereas CD200R1 expression on macrophages increases gradually (Snelgrove et al., 2008) (Fig. 1), consistent with the role of alveolar macrophages in resolving inflammation. Absence of CD200 increased the inflammatory response to influenza infection and prevented its resolution, although the viral load was reduced (Snelgrove et al., 2008). Interestingly, the administration of CD200Fc lowered the inflammatory response to influenza without compromising viral clearance. This highlights the critical role of CD200 in resolving lung inflammation while preserving anti-microbial capacities, whereas a defect in CD200/CD200R pathway may result in inflammatory diseases.

3.2. CD200 in asthma

Dysregulation of CD200 in asthma was first mentioned in a gene expression study investigating factors involved in asthma exacerbation (Aoki et al., 2009). Peripheral blood mononuclear cells of children during an asthma exacerbation have reduced expression of CD200 compared with those from controlled asthmatics. In addition, serum levels of sCD200 are higher in uncontrolled asthmatic subjects compared with controlled subjects (Tural Onur et al., 2015). Interestingly, asthmatics treated with anti-IgE have improved pulmonary functions and reduced inflammation, concomitant with lower sCD200 levels (Yalcin et al., 2013). It is probable that during asthma pathogenesis, CD200 is shed from multiple circulating or lung resident cells, including activated leukocytes and lung epithelial cells, which could ultimately increase plasma levels of sCD200. Our understanding of sCD200 mode-of-action is very limited, and it remains unclear how it can activate CD200R1 or have anti-inflammatory proprieties. Yet, CD200 (and maybe sCD200) could constitute meaningful regulatory mechanisms of lung inflammation, since CD200R1 is instrumental to control the activation of alveolar macrophages and pulmonary dendritic cells (Lauzon-Joset et al., 2015; Snelgrove et al., 2008).

3.3. CD200R1 in asthma

Multiple cells involved in asthma pathogenesis express various levels of CD200R1. Amongst the lung resident immune cells, alveolar macrophages, dendritic cells and mast cells have high levels of CD200R1 (Fig. 1). Moreover, these cell types overexpress CD200R1 under allergic and/or inflammatory conditions (Rate et al., 2012; Snelgrove et al., 2008), supporting their role in maintaining lung immune homeostasis (Fig. 1). Interestingly, many inflammatory cells recruited to the airways during asthma also express CD200R1, including eosinophils, Th2 cells, and innate lymphoid cells type 2 (Blom et al., 2017; Wright et al., 2003). The role of CD200R1 on inflammatory cells is poorly understood, although it is expected that CD200R1 expression by these cells should dampen inflammatory response and/or enable the resolution of inflammation. Alternatively, recent evidence suggests that CD200R1 activation could favor the production of Th2 cytokines, via the inhibition of ERK pathway (Blom et al., 2017). Further studies are required to understand cell specific functions of CD200 receptors in homeostatic and inflammatory conditions.

3.4. CD200 receptors as therapeutic targets in asthma

Although no current asthma therapies target the CD200/CD200R1 pathway, Moodley et al showed that corticosteroid, a common anti-inflammatory treatment of asthma, increases CD200 expression of bronchial epithelial cells (Moodley et al., 2013). Furthermore, formoterol, a long-acting β2 agonist, and roflumilast, an inhibitor of phosphodiesterase 4, synergize with corticosteroids to activate genes under glucocorticoid response elements, including CD200 (Moodley et al., 2013). Thus, restoring CD200/CD200R1 pathway in asthma is an attractive target that could improve control and reduce disease severity.

A proof-of-concept study to activate CD200R1 pathway in asthma was carried out in an animal model of acute allergic asthma using CD200Fc (Lauzon-Joset et al., 2015). Airway delivery of CD200Fc before allergen exposure reduces some features of lung Th2 inflammation, including bronchoalveolar lavage levels of IL-13 and airway hyperreactivity. There is also a downregulation of dendritic cell accumulation, mirrored by a lower Th2 activation of lung $CD4^+$ T cells. However, CD200R1 activation does not alter eosinophil recruitment to the lungs nor does it modulate cellular accumulation in the airway draining lymph node in this acute model. Similar data were observed using an aptamer activating CD200R1 in a mouse model of allergic asthma (Prodeus et al., 2018).

The mechanisms involved in CD200Fc modulation of asthma pathogenesis are not completely understood and probably implicate numerous cell types, given the presence of CD200R1 on many lung immune cells (Fig. 1). Lung administration of CD200Fc will most likely bind to alveolar macrophages that express a very high level of CD200R. The resulting activation of CD200R1 on alveolar macrophages may potentiate their anti-inflammatory role in limiting dendritic cell activation and recruitment (Lauzon-Joset et al., 2014). Eosinophils also express high levels of CD200R1 (Fig. 1), and CD200Fc may downregulate the inflammatory functions of eosinophils, but it does not alter their recruitment (Lauzon-Joset et al., 2015). Given the presence of CD200R1 on mast cells and dendritic cells, CD200Fc can also directly inhibit mast cell degranulation and dampen the ability of dendritic cells to capture and present allergens (Akkaya et al., 2013). Thus, local administration of CD200Fc or other CD200R1 agonists may be a new therapeutic avenue in asthma since it could act simultaneously on multiple inflammatory pathways.

4. Conclusion

Immune regulation in the airways is a fine balance between pro-inflammatory anti-microbial defense and homeostatic anti-inflammatory responses. High level expression of CD200 and CD200R1 on epithelial cells and alveolar macrophages respectively is an important feature of lung unique microenvironment. This regulation seems to be lost during asthma pathogenesis, although it is not clear at this stage whether the CD200 pathway is deficient in asthmatic patient or whether asthma inflammatory response dysregulates CD200 pathway. Further studies are needed to understand the function of

sCD200, as well as the role (and ligands) of the activating CD200 receptor (CD200R2) in lung immune response and asthma pathology.

Current pre-clinical/animal models support the benefit of targeting CD200/CD200R pathway to restore lung homeostasis/reduce airway inflammation in asthma. Yet, we have to confirm that CD200Fc and aptamers targeting CD200R1 would not impair lung anti-microbial defenses while dampening the excessive inflammatory response observed in asthma.

Funding

EB and DM are supported by grants from Canadian Institutes of Health Research (CIHR) and Quebec Respiratory Health Network. DM has a fellowship from the *Fond de Recherche du Québec - Santé* (FRQS).

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