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Short communication

Curdlan induces selective mast cell degranulation without concomitant release of LTC_4, IL-6 or CCL2

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ABSTRACT

Mast cells are sentinel cells with a tissue-specific localization in the interface between the host and the external environment. Their quick and selective response upon encountering pathogens is part of the innate host response and typically initiates the following adaptive immune response. Among several pattern recognition receptors (PRRs) involved in the recognition of pathogens by mast cells, the C-type lectin receptor Dectin-1 has been associated with the recognition of fungi. Our previous studies have shown that mast cells are the predominant cell type expressing Dectin-1 in human skin, and they also recognize and respond to *Malassezia sympodialis* by producing cytokines connected to the innate host response and upregulating the expression of Dectin-1. In the present study, we investigated mast cell responses to Curdlan, a β-glucan that acts as an agonist for the fungi receptor Dectin-1, and found a unique response pattern with induced degranulation, but surprisingly without synthesis of Leukotriene C_4, IL-6 or CCL2. Since mast cells are the predominant Dectin-1 expressing cell in the human skin, this study suggests that mast cell degranulation in response to fungi is an important part of the first line of defense against these pathogens.

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1. Introduction

Mast cells are particularly localized in tissues at the interface between the host and the external environment, placing them in a privileged position acting as sentinel cells. Through their quick response to external signals, they release their stored granule mediators and secrete *de novo*-synthesized lipid mediators, and newly-synthesized cytokines and growth factors (Metz and Maurer, 2007). The initial recognition of microorganisms is mediated mainly by a series of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs), and retinoic acid-inducible gene-I-like receptors (RLRs) (Kumagai and Akira, 2010). Mast cells are equipped with a large number of these PRRs making these cells an important part of the front line protection system against pathogens (Abraham and St. John, 2010). Mast cells are the predominant cell type in human skin expressing Dectin-1 (Ribbing et al., 2011), a CLR that recognizes β-glucan and has been associated with the recognition of fungi (Dambuza and Brown, 2015). Our previous studies have shown that mast cells recognize and respond to *Malassezia sympodialis,* a skin-colonizing fungi associated with atopic eczema (Saunders et al., 2012), by producing cytokines connected to the innate host response and upregulating the expression of the CLRs Dectin-1 and Mincle (Ribbing et al., 2011; Selander et al., 2009). Our intriguing finding that the majority of the Dectin-1 expressing cells in the skin are mast cells (Ribbing et al., 2011), led us to investigate the response of mast cells to Curdlan, a β-(1 → 3)-glucan and agonist for Dectin-1. We found a unique response pattern of mast cells to Curdlan with induced degranulation (release of histamine and β-hexosaminidase), but without concomitant synthesis of Leukotriene C_4, (LTC_4), IL-6 or CCL2. These results demonstrate how mast cells respond very specifically through one type of a PPR, a CLR, in contrast to e.g., TLR that generates eicosanoid and cytokine release independent of degranulation (McAlpine et al., 2011).

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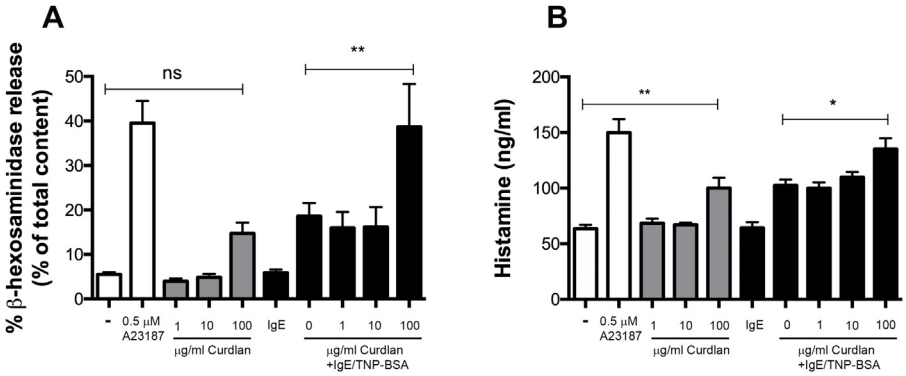

Fig. 1. Curdlan induces degranulation in BMMCs. (A and B) 1×10^6 BMMCs were stimulated with different concentrations of Curdlan (1–100 μg/ml) for 30 min then the cell-free supernatant was harvested, and the amounts of β-hexosaminidase (A) and histamine (B) released were measured. Data are expressed as mean ± SEM of five independent experiments, and the samples were run in triplicate. $^*p < 0.05$, $^{**}p < 0.01$. White bars correspond to the different controls performed; gray bars correspond to Curdlan stimulus; black bars correspond to IgE sensitized cells, or IgE receptor cross-linking stimulated cells along with or without Curdlan.

2. Results & discussion

2.1. Curdlan induces degranulation and augments IgE-receptor mediated exocytosis

Mast cells recognize and respond to fungi such as *Malassezia* through the expression of PRRs including the CLRs Dectin-1 and Mincle (Ribbing et al., 2011). We first examined by flow cytometry the expression of Dectin-1 on the bone marrow-derived cultured mast cells (BMMCs) used for the study. In agreement with previously published data (Yang and Marshall, 2009) we found a low surface expression of Dectin-1 on resting cells and on those that had been stimulated with Curdlan (data not shown). To further investigate if mast cells recognize fungal products through Dectin-1, BMMCs were subjected to the Dectin-1 agonist Curdlan (Palma et al., 2006). Treatment of BMMCs with Curdlan at a higher concentration (100 μg/ml) for 30 min induced degranulation and release of β-hexosaminidase, though not statistically significant different compared to the medium control (Fig. 1A), and significantly enhanced release of histamine ($p < 0.01$) (Fig. 1B). Since mast cells are activated mainly through cross-linking of IgE receptors in allergic processes, we also analyzed the effect of Curdlan in combination with IgE receptor cross-linking. A prominent response with significantly increased release of both β-hexosaminidase ($p < 0.01$) and histamine ($p < 0.05$) was obtained compared to that induced by each stimuli used separately (Fig. 1A and B). In our previously published studies, where both human and mouse mast cells have been exposed to *M. sympodialis* extract, we could not observe any degranulation (Ribbing et al., 2011; Selander et al., 2009). Although this might appear in contrast to our findings in this study it could possibly be explained by the structure of Curdlan. Curdlan is a linear polymer consisting of β-(1,3)-linked glucose residues (Saito et al., 1977) a form that has only been found in trace amounts in the *M. sympodialis* cell wall which contains (1 → 6)-β-D-glucan as the major carbohydrate component (Kruppa et al., 2009). Also, zymosan, another β-glucan, that might at least in part mediate its effect through Dectin-1 in combination with TLR-2, does not cause mast cell degranulation (Selander et al., 2009; Enoksson et al., 2011). In contrast, mast cells treated with *Candida albicans* are able to both degranulate and release chemokines and cytokines by a mechanism that involves Dectin-1 recognition (Nieto-Patlan et al., 2015; Pinke et al., 2016). Thus, it appears that dependent on the combination of involved ligands and receptors, Dectin-1 induces mast cell activation leading to either degranulation or release of mediators independent of degranulation. The mechanisms for this are not known but might be dependent on other receptors, e.g., TLR-2, or specific epitopes on the glucans.

2.2. Curdlan does not induce de novo synthesis of LTC_4, IL-6 or CCL2

It has previously been reported that Zymosan induces the synthesis and secretion of LTC_4 from human mast cells partially through the activation of Dectin-1 (Olynych et al., 2006). We therefore investigated whether Curdlan is able to induce the synthesis and secretion of the *de novo*-synthesized lipid mediator LTC_4, the newly-synthesized cytokine IL-6 and the chemokine CCL2, which are often released from PRR-activated mast cells (McAlpine et al., 2011; Lunderius-Andersson et al., 2012). Curdlan by itself did not induce the release of LTC_4 (Fig. 2A), IL-6 (Fig. 2B) or CCL2 (Fig. 2C).

When BMMCs were subjected to Curdlan in combination with IgE receptor cross-linking no further increased levels of either LTC_4 (Fig. 2A), IL-6 (Fig. 2B) or CCL2 (Fig. 2C) were found compared to that induced by only IgE receptor cross-linking. Olynych et al. used the same concentration of Zymosan as we have used of Curdlan (100 μg/ml) (Olynych et al., 2006). When they used laminarin, a Dectin-1 inhibitor, the secretion of LTC4 induced by Zymosan was reduced to 60%, suggesting a partly Dectin-1 mediated induction of LTC_4 synthesis. Similar to our findings they did not observe any Dectin-1 mediated cytokine release (IL-1β and GM-CSF), although they did not measure IL-6, neither CCL2 (Olynych et al., 2006). Even more, Kimura et al. showed that Curdlan induces secretion of MCP-1, IL-4 and TNF-α in the rat mast cell line RBL-2H3, which response was mediated by Dectin-1 via Syk, although they have not assessed degranulation on these cells (Kimura et al., 2014).

Mast cells are versatile cells able to recognize a wide variety of exogenous and endogenous agents, and respond to these by selective release of mediators by three means: immediate degranulation, rapid enzymatic synthesis of lipid mediators and delayed *de novo* synthesis of cytokines. Some stimuli induce all three types of release, e.g., IgE-receptor activation, whereas others induce degranulation-independent release of lipid mediators and/or cytokines, chemokines etc (Enoksson et al., 2011; Kandere-Grzybowska et al., 2003; Abdel-Majid and Marshall, 2004; Fischer et al., 2006). The ability of mast cells to respond to challenges in a custom-made fashion places them as important key-cells in the innate immune response, since they lead to specific activation of other immune cells amplifying the immune response.

In the present study we demonstrate a unique activation pathway of mast cells leading to a specific induction of degranulation, without concomitant synthesis of LTC_4, IL-6 or CCL2. Mast cell recognition of pathogens through PRRs leads most commonly to degranulation-independent release of lipid mediators and cytokines (McAlpine et al., 2011). Our results demonstrate that exposure of BMMCs to Curdlan, a Dectin-1 ligand, induces only

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