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Review Article

Mast Cells in Allergy: The Potential Molecular Targets in the Upstream Signalling Pathways

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Abstract

Mast cells (MCs) play a crucial role in the pathogenesis of allergic diseases due to their hypersensitive reaction to non-harmful substances that elicit an allergic response. As such, by interrupting certain signalling proteins within the signalling pathway of a MC, an allergic response may be avoided or inhibited. Compounds that attenuate the release of mediators from MCs are known as MC stabilizers. These drugs are clinically used to prevent MC effector responses towards common allergens. Although commonly prescribed clinical MC stabilizers such as disodium cromoglycate and ketotifen fumarate were used in the preventative treatment of various allergic diseases, there still remains a need of advancement towards the discovery of new MC stabilizing drugs that are able to target specific signalling molecules in order to provide better treatment option against these diseases. Among these newly discovered potential MC stabilizers, much efforts have been given to the inhibition of vital upstream signalling molecules such as spleen tyrosine kinase as well as surface receptors such as the high-affinity IgE receptor (FcεRI) and stem cell factor receptor (KIT). A recent study also reported that linker for activation of T cells (LAT) may also be an excellent molecular target for inhibiting MC degranulation. Although in most cases the exact mode of action of these molecules is yet to be elucidated, all these compounds have shown MC inhibition. Therefore, they might have potential therapeutic use in the treatment of allergies and allergy related diseases where MCs are majorly involved. Thus, this mini review will focus on summarising the potential signalling molecules or receptors that have been targeted to inhibit MC degranulation, particularly those located in the upstream signalling pathway.

Keywords: Mast cell, Molecular targets, Surface receptors, Intracellular signalling, Mini review, Allergy

1.0 Introduction

Mast cell (MC), an immune cell that is derived from the bone marrow's haematopoietic progenitors, plays an important role in both the immediate and late phases of allergic reactions (Metcalfe et al., 1997; Shea-Donohue et al., 2010; Gilfillan and Beaven, 2011). Immature MCs migrate to peripheral tissues, such as mucosa, airways, and skin where they undergo differentiation under the stimulation of various factors from the tissue microenvironment (Kitamura, 1989). Once differentiated, they are able to take part in the modulation of adaptive immune responses (Mekori, 2004; Galli and Nakae et al., 2005). A mature MC plays a major role in host defence mechanisms that are associated with innate immunity such as atopic dermatitis, anaphylaxis and asthma. Antigen-antibody aggregation with FcεRI on MCs initiates multiple signalling pathways that result in degranulation, production of various cytokines and chemokines, and *de novo* synthesis of arachidonic acid metabolites (Metcalfe et al., 1997). Over the years, many studies on MCs have been conducted to understand the signal transduction during degranulation. The studies on MCs are mainly being driven by the fundamental knowledge on the role of these cells in allergic inflammatory responses and the manifestation of MC-driven allergic responses (Metcalfe et al., 1997).

To date, most treatments for allergies focus on either inhibiting the effects of soluble molecules released from activated MCs such as histamine (Zhang et al., 1998; Saitoh et al., 2000), proteinases (Mori et al., 2003), and other mediators, or by hampering the body's overall immune response through the use of steroids. However, both approaches are ineffective. In addition, dampening the immune response produces significant drawbacks. During the last decade, noticeable progress has been shown to increase the treatment effectiveness in MC-driven allergic reactions. These include the discovery of inhibitors that act on the cell surface receptors and signal transduction pathways (Marshall, 2004). For example, FcεRI, a cell surface receptor, together with Syk and PI3K, which are among the upstream signalling molecules, have been reported to inhibit MC activation and might be potential targets for therapy (Mekori, 2004). Therefore, in this mini review, we will focus on discussing the role of selected surface receptors and upstream signalling molecules in MCs, especially those located at the early signalling pathways in antigen-induced degranulation.

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2.0 Upstream signal transduction pathways in mast cells

As shown in Fig. 1, mast cell activation is modulated by a wide network of intracellular signalling cascade that is initiated following engagement of ligand towards their respective receptors (Gilfillan and Tkaczyk, 2006). There are several surface receptors that are located on the membrane surface of MCs such as high affinity IgE receptors (FcεRI), IgG receptors (FcγRIII), complement receptors, stem cell factor receptors (KIT) and Toll-like receptors (TLRs) (Gilfillan and Tkaczyk, 2006; Galli and Tsai, 2012). Each of these receptors requires different ligands to bind and interact with them in order for the MC to be activated (Galli et al., 2005; Gilfillan and Tkaczyk, 2006). For example, studies have shown that a stem cell factor is needed for the activation of a KIT receptor in order to potentiate the degranulation effect initiated by the antigen-IgE bound FcεRI receptor (Gilfillan and Tkaczyk, 2006). Although the direct receptor-proximal signalling events seem to be the same for the release of all types of mediators, the receptor-distal signalling events must diverge to modulate the diverse mechanisms by which these mediators are produced (Gilfillan and Tkaczyk, 2006). Over the years, the roles of signalling molecules in the events that modulate MC response have been extensively studied (Gilfillan and Tkaczyk, 2006; Rivera and Gilfillan, 2006; Kraft and Kinet, 2007). Here we will concentrate on several upstream cytoplasmic signalling proteins and surface receptors that may be the targets for potential pharmacologic inhibitors in the future. Depending on their roles in allergen-induced MC activation, signalling proteins such as phosphatidylinositol 3-kinases (PI3Ks), linker for activation of T cell (LAT), and spleen tyrosine kinase (Syk) as well as MC surface receptors such as FcεRI and KIT will be discussed in detail in this mini review.

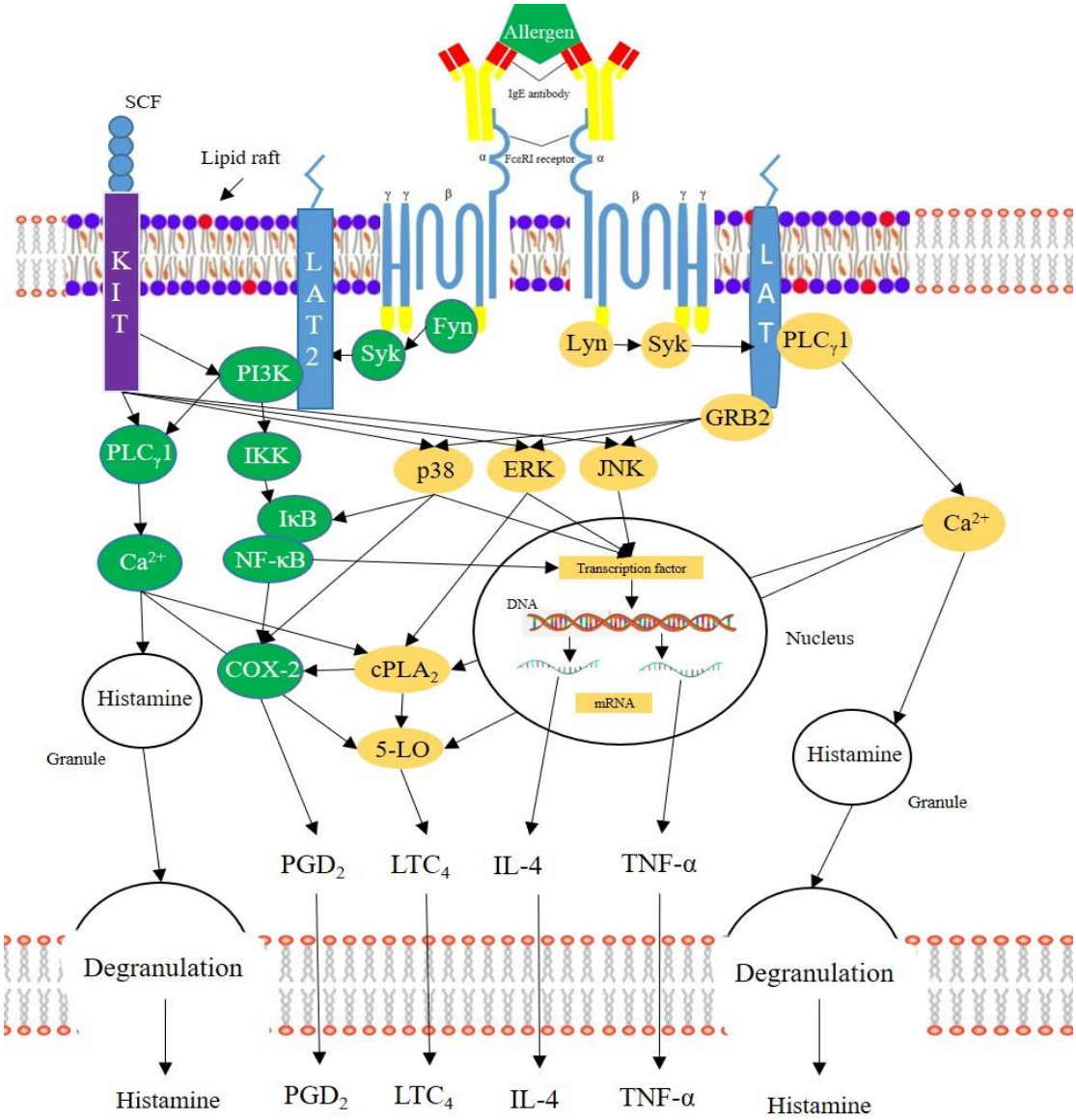

Figure 1: The complex signalling pathways involved during MC activation.

2.1 FcεRI

FcεRI is a tetrameric receptor consisting of an IgE-binding α-chain, a single 4-transmembrane-containing β-chain and a disulphide-linked γ-chain homodimer, which are responsible for initiating signalling (Gilfillan and Tkaczyk, 2006; Harvima et al., 2014). Aggregation of antigen-IgE immune complexes with FcεRI on allows the receptor on MCs to be activated, which results in the immediate explosive release of mediators such as chymase, histamine, and tryptase that are preformed inside the cytoplasmic granules (Harvima et al., 2014). Prolonged or continuous exposure of allergens through this receptor causes the MC to synthesis and release *de novo* mediators, for example PGD_2, LTC_4, IL-4 and TNF-α, from their cellular components (Marshall, 2004; Gilfillan and Tkaczyk, 2006; Harvima et al., 2014) due to the activation of

specific genes (Harvima et al., 2014). Therefore, one of the main goals of the researches associated with the treatment of allergy is to find ways to interfere with the activity of this receptor with antigen-IgE immune complexes.

The protein-protein interaction (PPI) between FcεRI receptor and IgE is a crucial component of allergic responses (Smith et al., 2013). Inhibiting the IgE:FcεRI PPI is a strategic therapeutic intervention in the treatment of allergic diseases (Smith et al., 2013). Currently, the only specific inhibitor being used clinically which targets IgE:FcεRI PPI is the humanized monoclonal antibody (mAb) omalizumab (Corren et al., 2009). Omalizumab acts by binding to an antigenic epitope on IgE that overlaps with the site to which FcεRI binds (Chang and Shiung, 2006). It also decreases cell surface FcεRI expressions on MCs as well as plasma IgE levels (Chang, 2000; Chang et al., 2007). Omalizumab has been proven to be effective and safe for the treatment of moderate and severe asthma (Corren et al., 2009). Other studies also reported that it is effective in treating other allergic diseases such as food allergies, atopic dermatitis and idiopathic anaphylaxis (Lieberman et al., 2013). However, the major limitation of such therapy is the high treatment cost (Galli and Tsai, 2012) and its inability to bind with IgE that is already bound to the FcεRI receptor on the surface of MCs (Chang et al., 2007). Unfortunately, other than omalizumab, there is no other low molecular weight compound that can interrupt the binding of IgE to the FcεRI receptor (Smith et al., 2013) or can modulate MC degranulation through FcεRI inhibition.

2.2 KIT

KIT is a single-chain MC surface receptor associated with protein tyrosine kinase activity (Harvima et al., 2014). Its ligand stem cell factor (SCF) binds to it and causes MC differentiation, proliferation, activation, and survival (Bischoff and Dahinden, 1992; Columbo et al., 1992; Coleman et al., 1993; Ali et al., 2004). Numerous signals that are initiated by the IgE bound antigen with FcεRI in MCs can also be initiated by KIT (Galli and Tsai, 2012), for example PLCγ, PI3K, and MAPK-cascade activation, as well as calcium mobilization. However, the signals produced by SCF are lower in magnitude and slower compared to those initiated by FcεRI aggregation (Hundley et al., 2004). The possible explanation of this phenomenon is the inability of SCF to induce a significant increase in the activation of PKC and tyrosine phosphorylation of LAT (Hundley et al., 2004; Tkaczyk et al., 2004). Nevertheless, the activation of KIT is crucial and reports have shown that FcεRI-mediated MC activation is likely to occur in the background of this receptor's activation (Gilfillan and Tkaczyk, 2006). In other words, the signalling pathways that are elicited by both FcεRI and KIT receptors must be synchronized in order to induce the synergistic responses from an activated MC (Gilfillan and Tkaczyk, 2006).

Some small inhibitors of KIT have been considered for the treatment of asthma, systemic mastocytosis or anaphylaxis. Among which, Imatinib was found to inhibit KIT-mediated MC activation in clinical trials involving patients with severe refractory asthma (KIA) (Cahill et al., 2017). However, this compound is not suitable for the treatment of mastocytosis carrying mutated c-KIT (D816V) (Verstovsek et al., 2006; Vega-Ruiz et al., 2009). Other potential inhibitory compounds such as Dasatinib, Masitinib and Midostaurin are proven to be efficient in controlling MC activity in both preclinical studies and clinical trials. However, these inhibitors are not specific towards KIT (Kneidinger et al., 2008; Humbert et al., 2009; Gotlib et al., 2010; Paul et al., 2010). Therefore, more effort should be taken in the search of suitable candidate compounds for the inhibition of MC activation by modulating this surface receptor as there is still no clinically approved drug that is capable of targeting KIT specifically in MCs.

2.3 Spleen tyrosine kinase (Syk)

Syk, along with Zap-70, is a member of the Syk family of tyrosine kinases. These non-receptor cytoplasmic tyrosine kinases are expressed in the cytoplasm of hematopoietic cells (Rivera and Gilfillan, 2006) and structurally consist of two Src-homology 2 domains separated by a kinase domain (Kraft and Kinet, 2007). Syk is recruited to the FcεRI after antigen aggregation with the receptor and it is mostly autophosphorylated with some degree of contribution by other tyrosine kinases such as Lyn (Mocsai et al., 2010). Once activated, Syk is involved in the tyrosine phosphorylation of other downstream signalling molecules particularly the PI3K, linker for activation of T cell (LAT) and Non-T Cell activation linker (NTAL). This will ultimately lead to the production and release of various pro-inflammatory mediators such as histamine, IL-4, TNF-α, PGD_2 and LTC_4 (Siraganian et al., 2010). In comparison to the other signalling molecules, Syk could be a desirable molecular target as its deletion will lead to suppressed allergic responses without affecting the migration of neutrophils and monocytes (Wex et al., 2011).

Currently, there are many Syk inhibitors undergoing extensive research to understand their pharmaceutical properties (Weinblatt et al., 2013). However, none of these tested compounds are clinically available yet. Recent studies reported that Syk inhibitors, including fostamatinib, PRT062607 and R343, were being withdrawn as a result of not passing phase two clinical trials (Lusková and Dráber, 2004; Braselmann et al., 2006; Riccaboni et al., 2010; Simmons, 2013; Weinblatt et al., 2013). Recently, one novel Syk inhibitor known as CC-509 has been reported to potentially inhibit IgE-mediated β-hexosaminidase from LAD2 cells (IC_{50} = 0.22 μM) (Ferguson et al., 2016). Another inhibitor known as NVP-QAB205 has also been reported to inhibit both histamine release and the production of LTC_4/LTD_4/LTE_4 and PGD_2 in MCs collected from patients with nasal polyposis who underwent sinus surgery (Ali et al., 2008). Apart from that, many potential MC stabilizers from natural sources have been extensively identified over the years. Among which, Streptochlorin and Spiraeoside have been shown to attenuate IgE-mediated MC degranulation using rat basophilic leukemia (RBL) 2H3 cell line and IgE-mediated passive cutaneous anaphylaxis (PCA) in mice (Kim et al., 2015; Lee et al., 2013). Specifically, these two compounds attenuate the phosphorylation of Syk in RBL-2H3 cells which eventually inhibit the downstream signalling molecules such as Lyn, Fyn, and MAPK proteins (Kim et al., 2015; Lee et al., 2013).

2.4 Phosphoinositide 3-kinase (PI3K)

PI3K is an enzyme essential for intermediary signalling in MCs. It regulates multiple processes in MCs including degranulation, cytokine production, proliferation, differentiation and survival (Kim et al., 2008). The major role of PI3K during MC activation is to catalyze the ATP-dependent phosphorylation of phosphoinositides and to generate lipid-based second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP_3) from phosphatidylinositol 4,5-bisphosphate (PIP_2) (Foster et al., 2012). This enzymatic step is very important for the development of inflammatory responses in MCs as it involves the subsequent activation of phospholipase Cγ (PLCγ), VAV and Bruton's tyrosine kinase (BTK) (Tkaczyk et al., 2005; Rivera and Gilfillan, 2006; Blunt and Ward, 2012). Although PI3K is involved in the early signalling cascade in MC degranulation, there are studies reported that this enzyme is likely to be in charge of its maintenance rather than the calcium signal initiation that is required for optimal degranulation (Tkaczyk et al., 2003; Ali et al., 2004). PI3K can be divided into several classes and MC activation is primarily regulated by class 1B (p110γ) and class 1A (P110δ) PI3Ks (Kim et al., 2008). Class 1B PI3Ks are associated to G protein-coupled receptors (GPCRs) whereas class 1A PI3Ks are linked to receptors that signal through tyrosine kinases such as FcεRI (Metcalfe et al., 2009).

The naturally occurring Wortmannin and the synthetic LY294002 are the two classical PI3K inhibitors that have been widely reported to inhibit cytokine production in both rodent and human MCs as well as to attenuate antigen-mediated degranulation (Okayama et al., 2003; Tkaczyk et al., 2005; Lee et al., 2013). However, these inhibitors fail to completely inhibit degranulation, at least in human MCs (Ali et al., 2004; Kim et al., 2008). Polydatin (3, 4′, 5-trihydroxystibene-3-β-mono-D-glucoside; (PD)), a natural component extracted from perennial herb *Polygonum cuspidatum*, has been recently reported to dramatically inhibit the activity of Lyn kinases and attenuate downstream signalling molecules including NF-kB, MAPK, and PI3K/AKT (Ye et al., 2017). In addition, PD also attenuates MC-derived allergic inflammatory reactions by targeting the Nrf2/HO-1 pathway (Ye et al., 2017). Nevertheless, all these compounds are still undergoing pre-clinical studies to evaluate their efficacies in treating allergic diseases. In terms of clinically approved drugs, there is still no successful candidate drug that is capable of specifically targeting PI3K in MCs.

2.5 Linker for activation of T cell (LAT)

LAT is a transmembrane protein with the molecular weight of 36-38 kDa (Zhang et al., 1998). It acts as an adapter molecule which plays a pivotal role in antigen receptor-mediated activation of immune cells such as MCs and T cells (Rivera, 2002; Samelson, 2002; Lindquist et al., 2003). In MC degranulation, LAT is central to FcεRI-mediated signalling and effector function in MCs (Saitoh et al, 2000). As such, it is important for the organization of downstream signalling cascades that are needed for the production of various pro-inflammatory mediators (Saitoh et al, 2000). Upon FcεRI receptor activation, LAT will be phosphorylated by the tyrosine kinase, Syk. An activated LAT serves as a docking site for interacting with several SH2 domain containing proteins, such as Grb2, Gads, and PLCγ1 (Zhang et al., 1998; Liu and McGlade; 1998). This will lead to the formation of a macromolecular signalling complex that allows the diversification of downstream signalling for the pro-inflammatory mediators' production (Gilfillan and Tkaczyk, 2006). Both degranulation and cytokine production will be impaired if loss of the LAT occurs in MCs (Kitamura, 1989; Galli et al., 2005). This defect is due to the inability of LAT to bind with its downstream signalling molecules, such as Grb2, SLP-76, Gads, and PLCγ1 (Rivera, 2005).

Another transmembrane adaptor molecule, known as LAT2, can be found in the lipid rafts within MCs (Galli and Tsai, 2012). LAT2 contains a palmitoylation site for some of the important signalling molecules such as PI3K, GAB2, and GRB2 (Galli and Tsai, 2012). Together with LAT, both of these transmembrane adaptor molecules have been proposed to function in a complementary manner during regulation of MC activation (Galli and Tsai, 2012). Given the balancing act between LAT and LAT2 in MC activation, any potential inhibitory compound that targets LAT in MC degranulation may be considered as an alternative to combating allergic diseases in the future. A recent study published by Tan et al. (2017a) demonstrated that 2,4,6-Trihydroxy-3-geranylacetophenone (tHGA), which is an active compound originally found in *Melicope ptelefolia*, exerted MC stabilizing activity by attenuating IgE-mediated MC degranulation *in vitro* and *in vivo*. At the molecular level, tHGA reduced the phosphorylation of signalling molecules located along both LAT and LAT2 axis pathways without interfering with the activation of PI3K and Syk. Another more in depth study by Tan et al. (2017b) reported that tHGA specifically targeted the activation of LAT in IgE-mediated MC activation without any involvement of LAT2. As LAT does not have any obvious role in MC development, the inhibitory action of tHGA on MC activation will not cause any lethal effects towards the cell, in comparison to Syk which is required for the development and function of various tissues (Saitoh et al, 2000). To the best of our knowledge, there is still no available drug or compound that specifically targets LAT in IgE-mediated MC degranulation.

3.0 Conclusion

MCs remain a viable target for molecular biologists due to its continuous expanding role in the pathological conditions of allergic diseases. Significant progress has been made in the development of targeted therapies for receptors or signalling molecules in MCs ever since the discovery of Khellin and Cromolyn sodium. However, these potential compounds are often not specific to the MCs and as a result, the possible off target actions of these new drug candidates must be taken into account if they were to undergo clinical development. Although the multi-modal action of some of these compounds cast doubt on their molecular target's specificity during MC activation, large amounts of interesting data continue to be generated from various synthetic/natural products as potential MC stabilizers. Nevertheless, the effort to find a compound that specifically targets MCs is encouraging and is still on its way, especially against those signalling molecules that are located on the upstream signalling pathways, as attenuation of these molecules will ensure the complete arrest of mediators' release at the receptor-distal signalling events. Finally, it should be noted that the real potential of any new compound with its proposed molecular target(s) can only be realized once its properties have been studied in an extended range of preclinical *ex vivo*, *in vitro*, and *in vivo* models of efficacy.

4.0 Declaration

The authors declare no conflicts of interest in this work.

5.0 Acknowledgements

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