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Mast cell function: Regulation of degranulation by serine/threonine phosphatases

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Abstract

Mast cells play both effector and modulatory roles in a range of allergic and immune responses. The principal function of these cells is the release of inflammatory mediators from mast cells by degranulation, which involves a complex interplay of signalling molecules. Understanding the molecular architecture underlying mast cell signalling has attracted renewed interest as the capacity for therapeutic intervention through controlling mast cell degranulation is now accepted as a viable proposition. The dynamic regulation of signalling by protein phosphorylation is a well-established phenomenon and many of the early events involved in mast cell activation are well understood. Less well understood however are the events further downstream of receptor activation that allow movement of granules through the cytoskeletal barrier and docking and fusion of granules with the plasma membrane. Whilst a potential role for the protein phosphatase family of signalling enzymes in mast cell function has been accepted for some time, the evidence has largely been derived from the use of broad specificity pharmacological inhibitors and results often depend upon the experimental conditions, leading to conflicting views. In this review, we present and discuss the pharmacological and recent molecular evidence that protein phosphatases, and in particular the protein phosphatase serine/threonine phosphatase type 2A (PP2A), have major regulatory roles to play and may be potential targets for the design of new therapeutic agents.

Keywords: Mast cells; Degranulation; Protein phosphorylation; Protein phosphatase; PP2A; Exocytosis

Abbreviations: AHR, airway hyper-reactivity; AKAP, A-kinase anchoring protein; G_M, muscle glycogen-binding subunit of protein phosphatase 1; IL, interleukin; Leu, leucine; NSF, *N*-ethylmaleimide-sensitive factor; PKA, protein kinase A; PKC, protein kinase C; PP1, serine/threonine phosphatase type 1; PP2A, serine/threonine phosphatase type 2A; PP2B, serine/threonine phosphatase type 2B; PP2C, serine/threonine phosphatase type 2C; PP4, serine/threonine phosphatase type 4; PP5, serine/threonine phosphatase type 5; PP6, serine/threonine phosphatase type 6; PP7, serine/threonine phosphatase type 7; PPM, protein phosphatase activated by magnesium; PPP, phosphoprotein phosphatase; PTP, protein tyrosine phosphatase; SNARE, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor; ST, SV 40 virus small T-antigen; Tyr, tyrosine.

Contents

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1. Introduction

Mast cells, which are derived from haematopoetic stem cells, are key effector cells in allergic reactions and IgE associated immune responses. They are also implicated as regulators of adaptive immune responses and this immunoregulatory role has been suggested to be potentially more important than the better established effector role. Attention has therefore begun to re-focus on the mast cell as a potential therapeutic target for asthma and related disorders (Bradding, 2003; Brightling et al., 2003). Mast cells secrete a large number of mediators in response to a diverse range of stimuli with the majority being secreted by regulated exocytosis degranulation (Blank & Rivera, 2004). While significant advances have been made in understanding the basic mechanisms of exocytosis, the key regulatory steps in mast cell degranulation remain unknown. In this review the molecular mechanisms of mast cell degranulation will be reviewed with emphasis on the role of serine/threonine protein phosphatases which we suggest have the potential to be novel targets for the design of new drugs that regulate the degranulation process.

2. Mast cells and asthma

Asthma is a major cause of morbidity and mortality and its prevalence continues to rise (Cantani & Micera, 2005; Butland et al., 2006). At the cellular level, asthma involves a complex interplay between a variety of cell types including mast cells, basophils, eosinophils, neutrophils and lymphocytes with associated increased production of chemokines and cytokines. The precise role(s) played by each cell type and their relative importance in the pleiotropic presentation of asthma and related disorders remains a subject of intense investigation and debate (Bochner & Busse, 2005).

Activation of mast cells represents one of the earliest events in allergic asthma, leading to the release of a range of chemical mediators that recruit other cell types and orchestrate the inflammatory response. Indeed clinical data consistently shows the presence of activated mast cells within the bronchial mucosa of asthmatic patients (Broide et al., 1991; Gibson et al., 1993) and there is a strong correlation between airway hyper-reactivity (AHR) and markers of mast cell activation, including increased cell number and increased histamine concentration (Wardlaw et al., 1988). Contrary to this clinical data, the ineffectiveness of the so-called mast cell stabilizing drugs to modify chronic asthma has historically challenged the view that mast cells contribute substantially to the pathophysiology of asthma. However, these drugs are generally of low potency and bioavailability to tissue compartments where mast cells reside is limited. Thus they do not reliably prevent mast cell activation (Church & Hiroi, 1987; Swystun et al., 2000). More recently, drugs which target products of mast cell activation, such as tryptase or interleukin (IL)-4, have been shown to be effective in the treatment of asthma, reviving interest in the mast cell as a key player in the pathophysiology of asthma (Borish et al., 2001; Krishna et al., 2001). Moreover, recent studies which have compared the pathological characteristics of asthma and eosinophilic bronchitis have shown that the only major difference between the two is the infiltration of airway smooth muscle by mast cells in asthma (Brightling & Bradding, 2005). Since patients with eosinophilic bronchitis do not present with variable airflow obstruction or airway hyper-responsiveness, this suggests that the mast cell infiltration in asthma is central to the development of the characteristic pathology of asthma. These findings have renewed interest in therapy targeted towards the mast cell (Bochner & Busse, 2005; Peachell, 2005; Walsh, 2005; Krishnaswamy et al., 2006). Given the multitude of factors released by mast cells, therapy targeted towards the degranulation process rather than individual products are desirable.

Substantial clinical evidence is also accumulating for a role for mast cells in the chronic features of asthma (Pawankar, 2005), including direct actions on airway smooth muscle and submucosal glands that appear to be independent of recruitment of other inflammatory cell types (Bradding, 2003; Brightling et al., 2003). Bronchial smooth muscle biopsies from asthmatic patients were virtually devoid of other inflammatory cell types suggesting that mast cell infiltration into smooth muscle is a major determinant of the chronic asthmatic phenotype (Brightling et al., 2002). The absence of other inflammatory cell types in these studies suggests that the mast cell has a direct effect on