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Editorial

Adenosine: Key Link between Allergy and Asthma?

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Mast cells are the main effector cell type of immunoglobulin E (IgE) -dependent immediate hypersensitivity responses manifested as seasonal rhinitis, urticaria and life threatening anaphylaxis-inducing food allergies [1]. The causative agents are pre-formed inflammatory mediators stored within cytoplasmic granules that are released immediately (degranulation) following activation, and lipid mediators such as prostaglandins and leukotrienes that are rapidly biosynthesized and secreted. Prolonged activation also results in delayed secretion of *de novo* produced cytokines that contribute to chronic disease by further activating and recruiting other cell types to the site of inflammation. In recent years, mast cells have been implicated in numerous other diseases in various mouse models. Whether mast cells are critical for disease development in all of these pathophysiological states, or if their involvement is artifactual to particular experimental animal models remains to be determined. In humans, however, considerable evidence exists to implicate mast cells in asthma pathogenesis [2,3]. Mast cells are known to infiltrate asthmatic smooth muscle, and are found in greater numbers in lungs of patients with asthma compared to non-asthmatics [3]. Moreover, it is now widely accepted that allergy is a major component of asthma. A recent clinical study showing that treatment with Omalizumab, an antibody against IgE, prevented nearly all increases in seasonal asthma and decreased allergy symptoms demonstrates the interwoven relationship between allergies and asthma [4]. This and other studies underscore the clinical significance of understanding the mechanisms that regulate mast cells and their role in allergy and asthma. Adenosine, a purine nucleoside and product of ATP metabolism, is a modulator of mast cell degranulation that has been implicated in asthma. The discovery over 30 years ago that adenosine could enhance the degranulation of rodent mast cells [5], and subsequent finding that inhalation or intravenous administration of adenosine induces mast cell-dependent bronchoconstriction in asthmatics [6-8] ignited a strong interest in adenosine as a possible link to asthma pathogenesis. Over the years, numerous studies have attempted to understand the mechanism (s) by which adenosine potentiates mediator release from mast cells and its involvement in pulmonary diseases. Yet, many issues remain unresolved and many questions unanswered. One major question is: Why does administered adenosine induce bronchoconstriction only in asthmatics with no pulmonary effects observed in non-asthmatic individuals? If adenosine acting on mast cells to enhance degranulation was solely responsible for inducing bronchospasm it would be expected that non-asthmatics would respond similarly to administered adenosine as asthmatics. However, this is not the case.

Adenosine is intimately connected to cellular metabolism, and concentrations are highest under conditions of cellular stress when energy demand is high, such as during inflammation. In fact, adenosine levels are reportedly much higher in bronchoalveolar lavage fluid from asthmatic lungs compared to that from "normal" lungs [9]. Therefore, inhalation or intravenous administration of adenosine, which occurs daily in clinical settings for the purpose of cardiac stress testing, would further increase the amount of adenosine. It can be argued that the additional adenosine is necessary to potentiate mast cell degranulation. Interestingly, however, *in vitro* studies with human lung mast cells consistently show that relatively high concentration of adenosine, such as that reportedly found in asthmatic lungs, strongly inhibits rather than enhances IgE-dependent mast cell degranulation. Moreover, the potentiating effect on FcεRIinduced degranulation of human lung mast cells *in vitro* appears to generally occur within a narrow concentration range of adenosine (10-6 – 10-5 M), and in less than impressive fashion. For example, three independent studies, including our own, using impure to highly purified lung mast cells report increases in mediator release of only 19% [10], 25% [11] and 33% [12]. On the other hand, the inhibition of degranulation at relatively high concentrations of adenosine is dosedependent over a wide range of adenosine and a consistent finding. One recent study reported no enhancement, only inhibition, of human lung mast cell degranulation by adenosine [13]. Based on these reports, mast cell degranulation in the asthmatic lung should be inhibited rather than enhanced, and adenosine should block, rather than induce, bronchoconstriction in asthmatics. Rather, the opposite is true: Adenosine induces mast cell-mediated (histamine-dependent) bronchospasms. Importantly, in most physiological systems, adenosine acts to inhibit inflammation rather than promote it [14]. Thus, how and why adenosine acts as it does in the asthmatic lung remains enigmatic.

Another area of significant research interest has been the identification of the adenosine receptor (s) (ADORs) responsible for potentiating mast cell degranulation and inducing bronchoconstriction. Four ubiquitously expressed G protein-coupled ADORs have been identified [15]. Human and mouse

mast cells express A2aAR, A2bAR and A3AR, but not A1AR. Studies with knockout mice have demonstrated clearly that A3AR is a potentiating receptor

required for enhancing murine mast cell degranulation [16,17]. Moreover, we recently demonstrated that direct triggering of A3AR with an A3AR-specific agonist enhances degranulation of human lung mast cells [11]. On the other hand, degranulation of human skin mast cells, which express 3 – 5 fold lower amounts of A3AR compared to human lung mast cells, was not enhanced with adenosine, the adenosine analogue NECA, or A3AR-specific agonist. Thus, the data overwhelmingly supports the notion that A3AR is the ADOR responsible for potentiating mast cell degranulation. In addition, the demonstration that inhaled adenosine induces airway hyper-responsiveness upon methacholine challenge in normal but not A3AR-null mice [18] also implicate A3AR as a mediator of adenosine-induced bronchoconstriction.

Interestingly, our study showing that human mast cells from lung, but not those from skin, respond to adenosine with enhanced degranulation provide a possible explanation as to why systemically administered adenosine induces a pulmonary response but not urticaria in humans. It should be noted, that A2bAR has also been implicated in these processes [19,20], though mostly through indirect evidence. Treatment of adenosine deaminase (ADA) -deficient mice with an A2bAR-specific antagonist reportedly reduced pulmonary inflammation associated with increased adenosine due to ADA-deficiency *in vivo* [21], indicating an involvement of A2bAR in chronic inflammation in the lung. However, direct assessment of A2bAR in mast cells is hindered by the fact that A2bAR deficiency itself results in enhanced antigen-mediated degranulation of mouse mast cells [22], and by the lack of commercially available A2bAR-specific agonists with which to analyze its role in human mast cells. Thus, the currently available data indicate that enhanced mediator release leading to bronchoconstriction occurs through triggering of A3AR on mast cells. Despite the countless studies that have been performed, the enigmatic role of adenosine in mast cell activation and asthma continues to intrigue and perplex us. Is it primarily a positive or negative regulator of mast cell mediator release? What role does it play in asthma? More than 30 years after its discovery as a modulator of mast cells, we still don't have all the answers. The empirically driven realization that allergy and asthma are intertwined demand a greater understanding of the cellular components of these diseases and of the mechanisms that regulate them. Whether adenosine is the key component that links allergy and asthma remains to be determined.

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