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Mast cell adenosine receptors function: a focus on the A3 adenosine receptor and inflammation

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Adenosine is a metabolite, which has long been implicated in a variety of inflammatory processes. Inhaled adenosine provokes bronchoconstriction in asthmatics or chronic obstructive pulmonary disease patients, but not in non-asthmatics. This hyper responsiveness to adenosine appears to be mediated by mast cell activation. These observations have marked the receptor that mediates the bronchoconstrictor effect of adenosine on mast cells (MCs), as an attractive drug candidate. Four subtypes (A1, A2a, A2b, and A3) of adenosine receptors have been cloned and shown to display distinct tissue distributions and functions. Animal models have firmly established the ultimate role of the A3 adenosine receptor (A3R) in mediating hyper responsiveness to adenosine in MCs, although the influence of the A2b adenosine receptor was confirmed as well. In contrast, studies of the A3R in humans have been controversial. In this review, we summarize data on the role of different adenosine receptors in mast cell regulation of inflammation and pathology, with a focus on the common and distinct functions of the A3R in rodent and human MCs. The relevance of mouse studies to the human is discussed.

Keywords: mast cells, adenosine, A3 adenosine receptor, HMC-1, RBL-2H3

THE MAST CELL

Mast cells (MCs) are hematopoietic-derived cells that play important physiological roles in innate and adaptive immunity, as well as in wound healing (Galli, 1997; Metcalfe et al., 1997; Noli and Miolo, 2001; Weller et al., 2006; Metz and Maurer, 2007; Shelburne and Abraham, 2011). Arising from committed progenitors ($CD34^+$, c-kit positive cells) in the bone marrow (Rodewald et al., 1996), MCs progenitors pass through the vascular space, entering the tissues, where they complete their differentiation and maturation process *in situ* (Metcalfe et al., 1981, 1997; Galli, 1997). Mature MCs typically present widespread plasma membrane processes, round nuclei, and numerous electron-dense cytoplasmic secretory granules. Growth, survival, differentiation, and homing are dependent on SCF-dependent c-kit signaling (Metcalfe et al., 1981, 1997) and accordingly, gain of functions mutations in the c-kit receptor result in mastocytosis (Lim et al., 2008; Fritsche-Polanz et al., 2010; Valent et al., 2011).

Human and rodent mature MCs are classified into one of two categories, based on phenotypic, biochemical, and functional differences. In rodents, MCs are classified as connective tissue type MCs (CTMCs), and include primarily skin MCs and cells of the peritoneal cavity, and mucosal MCs (MMCs), which are associated with the mucosa of the digestive tract or lungs (Welle, 1997; Bischoff and Krämer, 2007). In human, two types of MCs have been categorized based on their neutral protease compositions: MC_{TC} contain the neutral proteases tryptase and chymase, whereas MC_T contain only tryptase (Irani et al., 1986; Welle, 1997). Both types of MCs express on their plasma membrane FcεRI receptors, the high-affinity receptors for the Fc region of monomeric Immunoglobulin E (IgE). In tissues, MCs are distributed at interfaces between the outside world and the internal milieu, consistent with their immune tasks in host defense mechanisms. MCs are also found near blood and lymphatic vessels (Kunder et al., 2011) as well as in close proximity to nerves (Bienenstock et al., 1991; Theoharides et al., 2006).

Mature MCs store in their cytoplasmic secretory granules inflammatory mediators, including vasoactive amines such as histamine and serotonin, multiple proteases such as tryptase and chymase, mentioned above, and lysosomal hydrolases such as β-hexosaminidase and cathepsin D (Schwartz and Austen, 1980). MCs secretory granules also contain proteoglycans, such as heparin and chondroitin sulfate E, and polyamines, which play a role in proteases storage in secretory granules (Garcia-Faroldi et al., 2010). Some cytokines, including tumor necrosis factor (TNF-α) and basic fibroblast growth factor (bFGF) are also prestored in the secretory granules (Ribatti et al., 2002; Olszewski et al., 2007).

MCs AS MEDIATORS OF ALLERGIC AND INFLAMMATORY DISEASES

Despite their beneficial physiological roles in immunity and wound healing, MCs are best known for their involvement in allergic and inflammatory diseases, including autoimmune and neurodegenerative diseases and cancer, where they contribute significantly to the complexity of these diseases (Galli, 1997; Theoharides and Kalogeromitros, 2006; Bischoff, 2007). Allergy involves the activation and subsequent degranulation of MCs,

where activation can be triggered by a variety of external stimuli (**Figure 1**). The immune trigger involves production of IgE class antibodies, specific for a wide range of allergens, IgE binding to the FcεRI, followed by their allergen-induced cross-linking and receptor aggregation leading to cell activation (Turner and Kinet, 1999; Siraganian, 2003; Gilfillan and Tkaczyk, 2006; Rivera and Gilfillan, 2006; Wilson et al., 2011). In addition, MCs can be triggered in an IgE-independent fashion, by a variety of soluble stimuli (see below), as well as through cell interactions with neighboring cells including fibroblasts, eosinophils, T cells, and nerve cells (Askenase et al., 1980; Baram et al., 2001; Garbuzenko et al., 2002; Puxeddu et al., 2005; **Figure 1**). These interactions are complex involving feedback loops. For example, MCs activate eosinophils, which in turn release proteins that further activate MCs (Puxeddu et al., 2005).

MCs MECHANISMS OF SECRETION

When activated, MCs release the contents of their secretory granules within seconds to minutes of trigger. Depending on the strength of the external signal or the stimulus type, release may occur by kiss-and-run exocytosis that partially releases the secretory granule cargo through a relative narrow and transient fusion pore; full exocytosis, when fusion of plasma membrane docked secretory granules, with the plasma membrane, allows complete expulsion of their contents, and thirdly, compound exocytosis, also termed anaphylactic degranulation, the most extensive mode of cargo release, that involves fusion of the secretory granule membrane with the plasma membrane and release of secretory granule contents, as well as homotypic fusion between secretory granules by mechanisms whose details are still largely unresolved (Alvarez De Toledo and Fernandez, 1990; Blank, 2011; Woska and Gillespie, 2012). In addition, upon activation, MCs also produce and release arachidonic acid (AA) metabolites including leukotrienes and prostaglandins as well as multiple cytokines and chemokines (Metcalfe et al., 1981, 1997; Wasserman, 1983; Galli et al., 1991; Ogawa and Grant, 2007). Also formed are growth factors such as Vascular endothelial growth factor (VEGF), a cytokine crucial to angiogenesis, and the growth of blood vessels (Detoraki et al., 2009; García-Román et al., 2010) and NGF (Xiang and Nilsson, 2000; Cantarella et al., 2011). Notably, the repertoire of mediators released by MCs as well as their responsiveness to external ligands may vary dependently on the MC type or stimulus nature. Indeed, MCs are tunable cells (Galli et al., 2005) and under specified conditions can be programmed to selectively release a subset of mediators with no massive degranulation. Such selective secretion, termed piecemeal degranulation (PMD), is primarily linked with chronic inflammation and accounts for MCs involvement in inflammatory diseases and cancer (Dvorak and Kissell, 1991; Crivellato et al., 2003; Theoharides et al., 2007; Ribatti, 2011). Unlike exocytosis, PMD involves budding of vesicles, carrying the selective cargo to be released, from the secretory granule, and their transport and fusion with the plasma membrane. This type of secretion is also characterized by crosstalk with the endocytic system, whereby following their fusion with the plasma membrane and release of contents, these vesicles recycle to the secretory granule by means of endocytosis and subsequent fusion (Dvorak et al., 1992; Crivellato et al., 2003; Ribatti and Crivellato, 2009; Ribatti, 2011). The molecular mechanisms of PMD remain largely elusive.

Upon their release to the extracellular milieu, preformed and newly synthesized mediators affect multiple target organs and cells giving rise to an immediate inflammatory response followed by the progression of a tremendously amplified late-phase inflammatory response, which may acquire a chronic nature. The wide spectrum of biologically active substances produced and released by MCs thus contributes to the complexity of the allergic diseases. Moreover, an appreciable fraction of mediators released by activated MCs, acts in an autocrine manner to activate MCs and amplify their signaling outputs (Gilfillan et al., 2009). Such is also the case of adenosine, whose function in MCs is the focus of the present review.

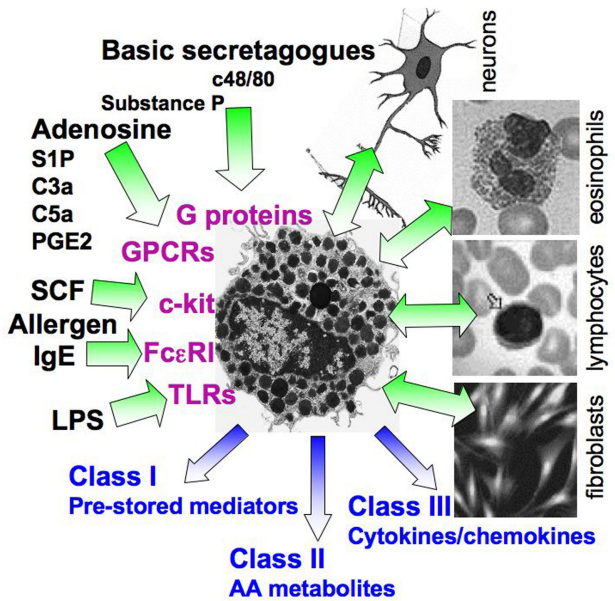

FIGURE 1 | Complexity of MC activation. A scheme illustrating the multiple stimuli that can activate MCs. The latter include the immunological, IgE-mediated pathway, interactions with neighboring cells, such as eosinophils, T cells, and fibroblasts, pathogens that act through TLRs, the c-kit ligand SCF, and numerous stimuli that activate G-proteins, either directly (e.g., basic secretagogues such as the synthetic c48/80) or by binding to GPCRs (e.g., adenosine, complement derived peptides, prostaglandins such as PGE_2, cytokines, and more). Depending on the stimulus type, activated MCs may either release preformed mediators, packaged in secretory granules (class I mediators) as well newly synthesized mediators, including metabolites of arachidonic acid (AA, class II mediators, such as prostaglandins and leukotrienes), cytokines, and chemokines (class III mediators), or may only release a subset of mediators. In some cases, the distinct stimuli interact synergistically resulting in an amplified response.

NON-IMMUNOLOGICAL ACTIVATION OF MCs

Multiple and diverse stimuli can activate MCs independently of IgE (Lagunoff et al., 1983; Bhattacharyya et al., 1998; Theoharides et al., 2007). Already mentioned are neighboring cells and SCF, that by binding to the c-kit receptor, a member of the receptor tyrosine kinase (RTK) family of receptors, transmits signals for MC survival (Iemura et al., 1994), induces direct degranulation of

rat peritoneal MCs (RPMCs; Taylor et al., 1995), and synergizes with the immunological, FcεRI mediated response, in stimulating degranulation, and cytokine release from bone marrow derived MCs (BMMCs) or human MCs (Coleman et al., 1993; Hundley et al., 2004). Toll like receptors (TLRs) serve as pattern-recognition receptors and mediate MCs responses to pathogens (Qiao et al., 2006; Mrabet-Dahbi et al., 2009; Avila and Gonzalez-Espinosa, 2011; Lorentz, 2011; Wesolowski and Paumet, 2011; Chan et al., 2012). Different TLRs are expressed in the different MCs types (reviewed in Novak et al., 2010), that dependently on the ligand/receptor complex type, display distinct modulator functions on the FcεRI mediated responses (Qiao et al., 2006). Finally, and particularly intriguing is the large number of non-immunological pathways that involve activation of G-proteins, either directly (Repke and Bienert, 1987; Aridor and Sagi-Eisenberg, 1990; Aridor et al., 1990, 1993; Mousli et al., 1990), or through binding to G-protein coupled receptors (GPCRs; Okayama et al., 2008; Druey, 2009).

Receptor mimetic activation of G-proteins was demonstrated in RPMCs that seem to display unique membrane characteristics that allow molecules comprising a hydrophobic stretch combined with a positively charged domain, to penetrate the membrane (Ortner and Chingell, 1981) and interact directly with G-proteins (Higashijima et al., 1988; Aridor et al., 1990). This group of molecules, collectively known as the basic secretagogues of MCs, were recognized as early as 1951 as potent IgE-independent activators of MCs that triggered exocytosis in a pertussis toxin (Ptx) sensitive manner, therefore implicating Gi protein(s) as essential mediators of their triggered exocytosis (Nakamura and Ui, 1984, 1985). Indeed, the large repertoire of molecules that constitute this family of stimuli, including neuropeptides, opiates, and the synthetic polyamine compound 48/80 (c48/80; Lagunoff et al., 1983), their common structural features and the fact that micromolar concentrations are required to evoke their biological activity, have suggested that members of this family trigger MC activation in a receptor-independent manner (Repke and Bienert, 1987; Aridor and Sagi-Eisenberg, 1990; Aridor et al., 1990, 1993; Mousli et al., 1990). More recent data demonstrated expression of a low-specificity activation site for basic secretagogues also in human MCs (LAD-2 and CD34-derived) and have identified this site as MrgX2, a member of the Mrg class of GPCRs (Tatemoto et al., 2006; Kashem et al., 2011; Subramanian et al., 2011). Whether or not RPMCs express MrgX2 is presently unknown. However, it is noteworthy that while the basic secretagogues-stimulated signaling networks and outputs, including degranulation, Ca^{2+} rise and activation of the MAP kinases, are Ptx sensitive, Ptx inhibits MrgX2 mediated degranulation in human MCs, but has no effect on Ca^{2+} influx, suggesting that in sharp contrast to the exclusive activation of Gi proteins by basic secretagogues in RPMCs, the MrgX2 couples to both Gi and presumably to Gq in human MCs (Shefler et al., 1999; Shefler and Sagi-Eisenberg, 2002; Subramanian et al., 2011).

We identified the G-protein Gi3 as the principal mediator of basic secretagogues-induced exocytosis in RPMCs by demonstrating that a peptide comprising the 10 C-terminal amino acids of Gαi3 (KNNLKECGLY), introduced into permeabilized cells, could inhibit c48/80-induced histamine release (Aridor et al., 1993). We then engineered a cell permeable version of this peptide, in which an importation sequence derived from the signal sequence of the Kaposi fibroblast growth factor (AAVALLPAVLLALLAP) was fused to Gαi3 C-terminal sequence, giving rise to a 16 amino acids peptide, we termed ALL1. We could show that ALL1 efficiently penetrates into intact RPMCs and blocks c48/80-induced histamine secretion, protein tyrosine phosphorylation, and release of Prostaglandin D2 (PGD_2) in a dose dependent fashion (Shefler et al., 2008).

Mast cells can also be activated by ligands that bind to classical, high-affinity, GPCRs. Included are some basic secretagogues, such as the neuropeptide substance P, that activates human or MMCs by binding to a tachykinin class receptor (Asadi et al., 2012), as well as prostaglandins, sphingosine-1-phosphate, histamine, cytokines, adenine nucleotides, complement, and adenosine (reviewed in Okayama et al., 2008; Druey, 2009; Gilfillan et al., 2009). This list includes mediators that are also released by activated MCs, or whose concentrations are elevated consequently to tryptase release (e.g., C3a, generated upon complement processing; Ali, 2009). These ligands may thus act in a paracrine or autocrine fashion to amplify or modulate the MC cellular inflammatory responses (reviewed in Okayama et al., 2008; Druey, 2009; Gilfillan et al., 2009).

ADENOSINE AND MC-MEDIATED INFLAMMATION

Non-immunological activation of MCs is primarily linked with chronic inflammation and accounts for MC involvement in autoimmune and degenerative diseases and cancer (Theoharides and Kalogeromitros, 2006; Theoharides et al., 2007; Ribatti and Crivellato, 2009; Ribatti, 2011). In most cases, the underlying mechanism involves stimulation of selective release of a subset of mediators, with no massive degranulation by PMD, described above. For example, such is the case of corticotropin-releasing hormone (CRH) or prostaglandin E2 (PGE_2), that stimulate release of VEGF without degranulation from the human mast cell line (HMC-1) or human umbilical cord blood derived MCs (HUCBMCs; Cao et al., 2006). Adenosine, the focus of this review, is produced both intracellularly and extracellularly under conditions of increased energy consumption such as stress or hypoxia that develop at sites of inflammation and injury (Linden, 2001; Bours et al., 2006). Hence, during systemic inflammation, the circulating adenosine concentration increases rapidly (Ramakers et al., 2011). Adenosine then functions in an autocrine or paracrine fashion through binding to four GPCRs: the A1, A2a, A2b, and A3 receptors that display distinct pharmacological characteristics. The A1R and A2a subtypes have the highest affinity for adenosine, whereas the affinity for adenosine of the A2b and A3 receptors is significantly lower (Linden, 2001). Individual receptors can be specifically activated or blocked by type specific agonists or antagonists (**Table 1**). Adenosine receptors also couple to different G-proteins, whereby the A1 and A3 receptors couple to Ptx sensitive Gi proteins, while the A2aR couples to Gs and the A2bR to Gs and Gq/G11 (reviewed in Brown et al., 2008). Accordingly, engagement of the adenosine receptor subtypes evokes distinct cellular responses (**Table 1**).

Adenosine has been long implicated in a variety of inflammatory processes, including allergy and especially asthma (Bours

Table 1 | Adenosine receptor subtypes and their cellular distribution and functions in MCs.

Receptor subtype	A2a	A2b	A3
Synthetic agonists	CGS21680 HE-NECA CV-1808 CV-1674 ATL146e (Fredholm, 2007)	LUF 5853 (Fredholm, 2007) C0036E08 (Buceta et al., 2008) BAY 60-6583 (Michael et al., 2010)	Cl-IB-MECA (Jacobson, 1998) IB-MECA (Jacobson, 1998) 2-Cl-IB-MECA (Fredholm, 2007) AB-MECA (Olah et al., 1994) DBXRM (Jacobson, 1998)
Synthetic antagonists	SCH58261 ZM241385 KF 17387 (Fredholm, 2007)	MRS1754 (Fredholm, 2007) Enprofylline (Linden et al., 1999) IPDX (Feoktistov et al., 2001) CVT-5440 (Zablocki et al., 2005) MRS1706 (Li et al., 2007) PSB-1115 (Michael et al., 2010)	MRS 1220 MRE 3008-F20 MRS 1191 MRS1523 (rat) VUF 8504 (Fredholm, 2007)
EXPRESSION PROFILE			
Mouse	Cardiac MCs (Rork et al., 2008) BMMCs (Marquardt et al., 1994)	BMMCs (Hua et al., 2007)	Lung MCs (Zhong et al., 2003) BMMCs (Salvatore et al., 2000)
Rat			RBL-2H3 (Jin et al., 1997) Pleural MCs (Reeves et al., 1997)
Human	Lung MCs (Sereda et al., 2011) Cultured MCs (Suzuki et al., 1998; Kulka et al., 2009) HMC-1 (Ryzhov et al., 2006) LAD-2 (Kulka et al., 2009)	HMC-1 (Ryzhov et al., 2006) Primary human cultured MCs (Kulka et al., 2009; Yip et al., 2011) MCs isolated from bronchoalveolar fluid (Buceta et al., 2008) LAD-2 (Kulka et al., 2009)	Lung MCs (Gomez et al., 2011) LAD-2 (Kulka et al., 2009) Primary human cultured MCs (Kulka et al., 2009)
CELLULAR RESPONSES			
Mouse			
Anti-inflammatory	Inhibition of cardiac MC degranulation (Rork et al., 2008) Inhibition of airway reactivity and inflammation (Bonneau et al., 2006; Nadeem et al., 2007; Haskó and Pacher, 2008)	Inhibition of β-hexosaminidase release (Hua et al., 2007)	
Pro-inflammatory		Inhibition of airway reactivity and inflammation by A2b antagonism (Mustafa et al., 2007) Pro-inflammatory effects in BMMCs (Ryzhov et al., 2008)	Induction of murine lung MC degranulation (Zhong et al., 2003) Increase in circulating histamine levels (Smith et al., 2002) AHR (Hua et al., 2008) Potentiation of BMMCs degranulation (Salvatore et al., 2000) Chemotaxis (Endo et al., 2005; Kitaura et al., 2005; Kuehn et al., 2010)

Table 1 | Adenosine receptor subtypes and their cellular distribution and functions in MCs.

Receptor subtype	A2a	A2b	A3
RAT			
Anti-inflammatory			
Pro-inflammatory			Enhancement of MC degranulation *in vitro* and direct induction of degranulation *in vivo* (Fozard et al., 1996) Inosine stimulates RBL-2H3 cells degranulation (Jin et al., 1997) Enhancement of RBL-2H3 cells degranulation and signaling (Ali et al., 1996)
HUMAN			
Anti-inflammatory	Inhibition of Fc epsilon RI mediated mediator release from human MCs (Suzuki et al., 1998) Closure of KCa3.1 channels in human lung MCs (Duffy et al., 2007) Inhibition of complement-mediated activation of human MCs (Kulka et al., 2009)	Inhibition of MC activation (Feoktistov et al., 2001)	
Pro-inflammatory	Stimulation of tPA activity in human lung MCs (Sereda et al., 2011)	Up-regulation of IL-4 (Ryzhov et al., 2006) Up-regulation and release of angiopoietin (Feoktistov et al., 2003) Mediate histamine release (Buceta et al., 2008) Stimulation of IL-8 secretion (Feoktistov and Biaggioni, 1995) Influencing pathways critical for pulmonary inflammation and injury *in vivo* (Sun et al., 2006) Potentiation of anti-IgE-induced degranulation (Hua et al., 2011)	Induction of IL-8 release in HMC-1 cells (Meade et al., 2002) Gene up-regulation in HMC-1 cells (Feoktistov et al., 2003; Baram et al., 2010) Induction of primary human lung MC degranulation (Gomez et al., 2011)

This table lists synthetic compounds that display agonistic or antagonistic activity toward adenosine receptor subtypes, their expression profile in MCs and the anti versus pro-inflammatory responses observed upon their activation in rodent or human MCs.

et al., 2006; Spicuzza et al., 2006; Matera and Polosa, 2007; Brown et al., 2008; Polosa and Blackburn, 2009). That MCs mediate adenosine responses in allergic inflammation was first indicated by the ability of adenosine to potentiate IgE-induced mediator release from rodent MCs (Holgate et al., 1980). The physiological relevance to human was then advocated by observations documenting the ability of adenosine to provoke bronchoconstriction in atopic and asthmatic individuals, but not in normal subjects, a phenomenon referred to as adenosine hyper responsiveness (AHR; Cushley and Holgate, 1985). Furthermore, elevated levels of adenosine are found in bronchoalveolar lavage fluid and exhaled breath condensates of allergic inflammation patients (Driver et al., 1993; Huszar et al., 2002; Vass et al., 2006) and inhalation of adenosine by asthmatics leads to increased levels of MC mediators such as histamine and tryptase in bronchoalveolar fluid. Finally, blockers of mediators released by activated MCs inhibit the bronchoconstrictor response to adenosine in asthma (Meade et al., 2001; Spicuzza et al., 2006). This notion was supported further by the findings that MCs express the two ecto-enzymes, CD73, a nucleoside triphosphate phosphohydrolase, and CD39, an ecto-5′-nucleotidase, that by concerted conversion of adenine nucleotides to adenosine increase its extracellular concentrations (Linden, 2001); prominent secretion of adenosine is observed in activated MCs (Marquardt et al., 1984) as well as the rat derived mast cell line, RBL-2H3 (Lloyd et al., 1998); and that MCs express adenosine receptors (Carruthers and Fozard, 1993). However, the identity of the specific adenosine receptor(s) that mediate(s) adenosine triggered MCs responses remained elusive.

THE A3R AS MEDIATOR OF MCs-DEPENDENT INFLAMMATION

Animal models have substantiated the central role played by activated MCs in mediating AHR and have identified the A3R as the major contributor. Specifically, airway responses elicited by adenosine are significantly attenuated in A3R- or MC-deficient mice (Tilley et al., 2003). Furthermore, aerosolized adenosine-5′*N*-ethylcarboxamide (NECA; a non-selective ligand) induces hyper responsiveness in *wt* or A1R-deficient mice, but not in A3R knockout mice (Hua et al., 2008) and AHR develops in MC-deficient mice that are reconstituted with *wt*, but not with $A3R^{-/-}$ MCs (Hua et al., 2008). *In vitro* studies employing isolated MCs and selective receptor agonists have substantiated this notion further by demonstrating that adenosine directly stimulates murine lung MCs degranulation by activating the A3R (Zhong et al., 2003). In a similar fashion, intravenous application of *N*6-2-(4-aminophenyl)ethyladenosine (APNEA; Fozard et al., 1996) or intradermal introduction of the A3R agonist 2-(1-Hexynyl)-*N*-methyladenosine (IB-MECA; Reeves et al., 1997) to rats, respectively induced MC degranulation or plasma protein extravasation (PPE), confirming a key role for the A3R in mediating MCs responses. However, exposure of rat isolated pleural MCs, RBL-2H3 cells, or BMMCs to IB-MECA, enhanced FcεRI-induced secretion, but failed to induce directly such degranulation (Ramkumar et al., 1993; Reeves et al., 1997; Yamano et al., 2005, 2006). Therefore, collectively these studies have firmly established the involvement of the A3R in MC degranulation. Yet, they have also indicated that whether or not engagement of the A3R suffices to promote MCs degranulation, or whether additional signals, stemming from the FcεRI or the other adenosine receptors (i.e., A2bR, see below), are required, depends on the MC type, the tissue it resides in, and perhaps even the species or the mouse strain (Meade et al., 2001).

In addition to direct or synergistic effects on MC degranulation, occupied A3R mediates the stimulatory impacts of adenosine and the FcεRI on MCs migration (Endo et al., 2005; Kitaura et al., 2005; Kuehn et al., 2010). Since MC migration is an important mechanism toward their accumulation at allergic inflammatory sites, this activity of the A3R further adds to its pro-inflammatory functions.

Genetic and pharmacological approaches have assigned the A2aR anti-inflammatory properties (Bonneau et al., 2006; Nadeem et al., 2007; Haskó and Pacher, 2008), and have revealed a complex function of the A2bR (**Table 1**). Hence, BMMCs derived from A2bR knockout mice demonstrated increased sensitivity to IgE-mediated anaphylaxis (Hua et al., 2007), but work in the adenosine deaminase (ADA)-deficient model, pharmacological studies employing the A2bR antagonist CVT-6883 in a mouse model of ragweed sensitization and challenge, and *in vitro* studies on BMMCs derived from A2bR knockout mice, supported a pro-inflammatory role of this receptor in mediating MC functions, and have particularly placed this receptor in playing a role in late-stages or chronic features of airway diseases such as asthma (Sun et al., 2006; Mustafa et al., 2007; Ryzhov et al., 2008; Polosa and Blackburn, 2009).

STUDIES IN HUMAN MCs

Studies employing human lung MCs demonstrated that at low concentrations, adenosine potentiated degranulation of immunologically activated MCs, whereas at higher concentrations a counteractive inhibitory process took place (Peachell et al., 1988, 1991). These responses were interpreted as being mediated by the A2 type receptors. Consistent with these results, studies with HMC-1, a human mast cell line, confirmed the expression of both the A2a and A2b receptors, where A2bR mRNA was eightfold more abundant than A2a mRNA (Meade et al., 2002). A2bR stimulation resulted in the release of IL-4, IL-8, and IL-13, cytokines linked with allergic inflammation and asthma (Feoktistov and Biaggioni, 1995; Ryzhov et al., 2004, 2006). Taken together with the demonstration that enprofylline and theophylline, two anti asthmatic drugs, block adenosine-induced release of IL-8 from HMC-1 cells, these results implicated the A2bR as the principal mediator of AHR in humans (Hasků et al., 2009). Thus, while the studies in rodent MCs have provided unequivocal evidence for the involvement of the A3R in mediating the adenosine bronchoconstrictor response, this role was questioned in human MCs and was rather assigned to the A2bR. Moreover, studies in humans demonstrating A3R-mediated inhibition of neutrophils degranulation (Bouma et al., 1997) and eosinophils chemotaxis (Knight et al., 1997; Walker et al., 1997), have suggested that the A3R may play an anti-inflammatory role. However, against this dogma are results obtained in HMC-1 cells, where the data clearly indicate that IL-8 release can also be stimulated by IB-MECA (Meade et al., 2002). The latter was approximately fivefold less potent than the A2bR agonist, but this lower potency was consistent with A3R being

eightfold less abundant than the A2bR in this cell line (Meade et al., 2002). Further analyses revealed that activation of A3R in HMC-1 cells induces the expression, though not secretion, of angiopoietin-2, by a mechanism, which did not involve inhibition of adenylyl cyclase or activation of PLC (Feoktistov et al., 2003). Activation of A2b could enhance secretion of the angiogenic factor, but a maximal response depended on the simultaneous activation of both the A2b and A3 receptors (Feoktistov et al., 2003).

Employing the HMC-1 cell line, we found no evidence for A3R stimulated degranulation or cytokine release (Baram et al., 2010). However, a wide-genome screen demonstrated up-regulation of genes that play important roles in allergic inflammation and asthma upon A3R activation (Baram et al., 2010). The latter included cytokines such as IL-8, chemokines, growth factors, and angiogenic factors (Baram et al., 2010). Therefore, these studies supported a pro-inflammatory, modulator role of this receptor in human MCs. Consistent with this premise we also obtained evidence for the activation of the A3R, in an autocrine manner, in cells activated through contact with T cell derived membranes (Baram et al., 2010).

Because HMC-1 cells do not express the FcεRI, the modulator action of adenosine on immunologically stimulated MCs could not be investigated in this model. However, this question was addressed using HUCBMCs, in which only an inhibitory A2aR-mediated function could be detected (Suzuki et al., 1998). Specifically, exposure of HUCBMCs to 4-[2-[[6-Amino-9-(*N*-ethyl-β-D-ribofuranuronamidosyl)-9*H*-purin-2-yl]amino]ethyl]benzene propanoic acid hydrochloride (CGS21680), a specific agonist of the A2aR, resulted in the inhibition of tryptase release (Suzuki et al., 1998). Accordingly, RT-PCR analysis indicated the dominant expression of A2aR mRNA, though A3R mRNA was detected as well (Suzuki et al., 1998). Using the same model of HUCBMCs, a biphasic effect of adenosine was noted on anti-IgE-induced degranulation, where potentiation was assigned to the A1R and inhibition of the anti-IgE-induced responses to the A2bR (Yip et al., 2009). Finally, in a recent study, where HUCBMCs were treated for 3 days with IL-4 and IgE, addition of adenosine potentiated anti-IgE-induced degranulation and this enhancement was reduced or abolished by A2bR antagonists or A2b specific siRNA implicating the A2bR in mediating the adenosine synergistic response (Hua et al., 2011). In same study, neither selective A3R agonist, nor an A3R antagonist displayed any activity. In fact, in human MC cultures derived from CD34+ peripheral blood progenitor cells (HuMCs) or the LAD-2 cells, adenosine failed to effect degranulation (Kuehn et al., 2011). But then contradictory to these observations, a recent study employing human lung derived MCs demonstrated potentiation of IgE-induced degranulation by adenosine in a Ptx sensitive fashion. Furthermore, an A3R-specific agonist recapitulated this potentiation (Gomez et al., 2011). Notably, these lung derived MCs were shown to express threefold more A3R mRNA than do skin MCs (Gomez et al., 2011).

Taken together, these studies illustrate the difficulties faced studying human MC A3R, whose properties might be altered by physiological/environment specific responses not recapitulated in cell lines or even primary MCs (Gessi et al., 2008).

A3R SIGNALING IN RODENT AND HUMAN MCs

To gain insights into the molecular mechanisms behind the A3R function, the signaling pathways elicited by this receptor were explored. These studies demonstrated that histamine release induced by the engagement of the A3R in isolated murine lung MCs is associated with a Ptx-and LY294002-sensitive rise in cytosolic Ca^{2+} (Zhong et al., 2003). These results therefore implicated Gi protein(s), phosphatidylinositol 3 kinase (PI3K) and presumably phospholipase Cβ (PLCβ) as principal mediators of A3R stimulated degranulation in murine lung MCs. Ca^{2+} rise, PI3K as well as ERK activation were also noted in BMMCs, whose FcεRI-induced release of mediators was potentiated by the A3R (Yamano et al., 2005, 2006). Finally, studies in RBL-2H3 cells demonstrated A3R stimulated and Ptx sensitive activation of PLC (Ramkumar et al., 1993) and PLD (Ali et al., 1996), rise in Ca^{2+}, and activation of PI3K/Akt (Gao et al., 2001). Microinjection of an antibody to either Gαi3 or Gαq inhibited the Ca^{2+} signal suggesting the involvement of both G-proteins in Ca^{2+} mobilization (Hoffman et al., 1997). However, since an antibody to Gαi2 was not tested, the involvement of Gi2, that is co-expressed in MCs, cannot be excluded. Consistent with this notion, rat A3R (rA3R), expressed in CHO cells could interact primarily with Gi2 and Gi3 and to a significantly lesser extent with Gq and G11 (Palmer et al., 1995).

The pharmacological evidence for the involvement of PI3K in mediating A3R function was further supported by genetic studies that indicated that adenosine, acting through the A3R, transiently increases $PI(3,4,5)P_3$ exclusively via PI3Kγ (Laffargue et al., 2002). Moreover, PI3Kγ deficient mice did not form edema after intradermal injection of adenosine or when challenged by passive systemic anaphylaxis (Laffargue et al., 2002). Further analyses of the mechanisms by which PI3Kγ relays inflammatory signals revealed that the p84:p110γ complex was specifically required for synergistic adenosine-promoted degranulation and chemotaxis (Bohnacker et al., 2009). Taken together these results are compatible with a model (**Figure 2**), where by coupling to Gi2/Gi3 and Gq, the rodent A3R transmits signals that effect the activation of PLCβ and PLD, which in turn function to mediate MC degranulation (i.e., in lung MCs) or synergize with the FcεRI-elicited signals (Kuehn et al., 2008). In addition, activation of PI3Kγ promotes the activation of the ERK pathway that mediates gene up-regulation and presumably also the generation of arachidonic acid metabolites (Zhang et al., 1997a,b; Shefler et al., 1999) and mediates cell migration (Bohnacker et al., 2009).

We have analyzed the signaling patterns associated with gene up-regulation in the A3R-activated HMC-1 cells. By taking advantage of ALL1, the cell permeable Gi3 inhibitory peptide, we also assessed the role of Gi3 in mediating A3R elicited responses. These studies revealed that Cl-IB-MECA enhances phosphorylation of MAP kinases, including ERK1/2, RSK1, p38α,β,γ, JNK, and GSK3α, in an ALL1-sensitive fashion, confirming the involvement of Gi3 (Baram et al., 2010). Though not tested, it is tempting to speculate that the lack of activation of PLCβ by the A3R in the HMC-1 cells prevents them from degranulation and restricts this receptor function to the induction of gene up-regulation and possibly the generation of arachidonic acid metabolites (**Figure 2**). Interestingly, exploring the signaling patterns of the A3R in

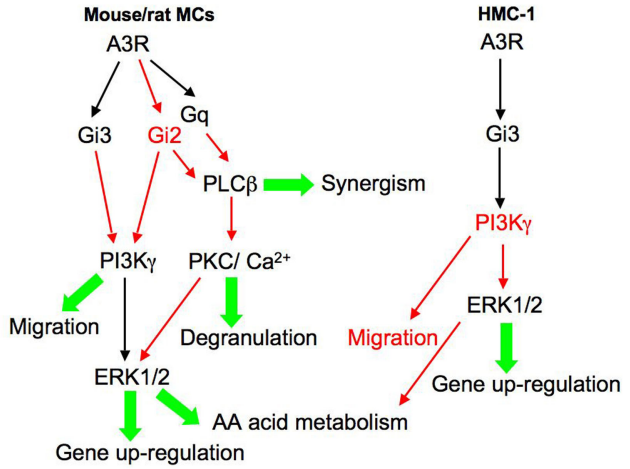

FIGURE 2 | Signaling pathways elicited by the human and rodent A3 adenosine receptor in MCs. This model aims to integrate the signaling pathways reported in the literature, where marked in red are proposed, not yet proven, pathways. According to this model, the rodent A3R couples to Gi2, Gi3, and Gq, leading to the activation of PLD, PLCβ, and PI3Kγ. As a result, the cytosolic concentration of Ca^{2+} rises and protein kinase C (PKC) and the ERK MAP kinases are activated. According to this model, activation of PLCβ mediates MC degranulation or synergizes with the FcεRI-elicited signals to potentiate degranulation. PI3Kγ and ERK1/2 mediate respectively MC migration and class II and class III mediator formation. In contrast, the human A3R couples mainly to Gi3 leading to activation of ERK1/2 and gene up-regulation.

BMMCs derived from a humanized mouse, in which the mouse A3R gene was replaced by its human counterpart, revealed that A3R activation evoked a Ptx sensitive rise in Ca^{2+}, but failed to enhance ERK1/2 or Akt phosphorylation, which are stimulated by the murine A3R (Yamano et al., 2005). These results led the authors to conclude that the hA3R couples to different G-proteins for Ca^{2+} mobilization and PI3K/ERK1/2 activation (Yamano et al., 2005). In contrast, a chimeric receptor, in which the whole intracellular region of the hA3R was substituted by the corresponding mouse A3R, did display identical activity to the murine A3R (Yamano et al., 2006). Yet, the full hA3R was able to activate ERK1/2, via PI3K, when transfected into CHO cells (Graham et al., 2001; Schulte and Fredholm, 2002). Therefore the rodent and human A3 adenosine receptors clearly elicit distinct signaling patterns that are dictated by the G-protein combinations they couple to in a specific cellular setting. Indeed, unlike most GPCRs, the rodent, and human A3Rs share only 72% homology (Linden, 1994). Moreover, these receptors also differ in their down-regulation patterns, reflecting again their variance in partner interactions (Yamano et al., 2005).

CONCLUSION AND FUTURE PERSPECTIVES

While the role of the rodent A3R-activated MCs in mediating AHR is firmly established, the role of the hA3R in inflammation and particularly in mediating MC responses remains elusive. Two reasons are likely to account for the difficulties encountered when studying this receptor in human samples. First, it is quite challenging to obtain and culture human MCs, thus enforcing the use of model systems (i.e., HUCBMCs, lung derived MCs, HMC-1, and LAD-2 cell lines), each of which having its own limitations (Hua et al., 2011). Second, it is quite plausible that the human receptor is regulated differently than the rodent counterpart, including by more complex physiological and environmental factors. Consistent with this perception is the up-regulation of the A3R in MCs of chronic obstructive pulmonary disease (COPD) patients (Varani et al., 2006). Indeed, unlike most GPCRs, the rodent and human A3R share only 72% homology, while the Gi proteins are highly conserved. Therefore, these A3Rs may couple to different Gi proteins, thereby yielding differential signaling. In fact, the Gi protein they couple to may vary depending on receptor occupancy or strength of signal, resulting in differential outputs. The variance in their amino acid sequences may also drive distinct interactions with accessory proteins, giving rise to distinct spatio-temporal regulations. The human and rodent A3Rs may also display distinct crosstalk with their co-expressed adenosine receptors. ATP and ADP also activate the MCs by binding to P2 receptors. The P2 receptors are subdivided to P2X and P2Y receptors that are GPCRs whose activation may impact MC responses. Moreover, since various combinations of P2 receptor subtypes are expressed in MCs derived from different sources (e.g., human CBMCs, HMC-1, or BMMCs and RBL-2H3), their contributions to the overall signaling and cellular responses elicited by purinergic receptors may vary accordingly (Bulanova and Bulfone-Paus, 2010). Finally, three isoforms of the A3R have been cloned in human and two in mouse. Whether or not these isoforms play a role in fine-tuning of the receptor is presently unknown. It is noteworthy that the majority of GPCR genes are intronless. However, for GPCRs that are subjected to alternative splicing, the variants have proven to be of physiological relevance (Markovic and Challiss, 2009). Hence, an important lesson from the studies on the adenosine receptors, at least from a therapeutic standpoint, is that the mouse studies do not necessarily predict what is happening in the human. Thus, the question of whether an A3R agonist or rather an A3R antagonist should be considered in asthma treatment still remains unresolved.

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