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A Disintegrin and Metalloproteinase (ADAM) 10 and 17 in Th2 Mediated Responses

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1. Introduction

Asthma is a chronic airway disease characterized by wheezing, cough, shortness of breath, chest tightness, and “asthma attacks” caused by obstruction in airflow. In the United States, prevalence has increased since 2001 with children and African Americans having the highest incidence [1]. Asthma-related medical costs are \$3,300 per diagnosed individual including missed school and work days and asthma-related deaths totaled 3,404 in 2010 [2;3]. Worldwide, 300 million people are diagnosed with asthma and 70% of those suffer from other allergies as well [4]. Helminth infection, however, is considered a disease of developing countries and is rarely concomitant with allergies [5]. The World Health Organization estimates that 1.5 billion people, or 24% of the world’s population, is infected by soil transmitted helminthes, with the majority of cases occurring in east Asia, China, and Sub-Saharan Africa [6]. Allergy, asthma, and helminth infection are considered classic Th2 diseases with immunoglobulin E (IgE) as the predominant antibody class coordinating the response. IgE levels are tightly regulated, being the antibody with the lowest levels *in vivo* [7]. Interestingly, very small amounts of antigen are detected by IgE, making it a “gatekeeper”, as it is first to detect foreign particles in areas of interface with the environment. When these foreign particles are innocuous, such as pollen, cat dander or peanut proteins, IgE moves from beneficial to potentially life threatening. IgE mediates allergic responses from mild reactions to severe, such as allergic rhinitis, atopic dermatitis, urticaria, asthma, and anaphylactic shock [8].

IgE regulates the immune response in one of three ways. First, antigen specific IgE binds the high affinity IgE receptor, FcεRI, on mast cells (MCs) or basophils where it can persist for up to 21 days waiting to bind to antigen, cross-link the FcεRI and degranulate the cell [9]. Degranulation results in release of vasoactive mediators such as histamine, leukotrienes,

prostaglandins, and other biologically active products, inducing the classic symptoms of allergic diseases (e.g. wheal and flare or urticaria) depending upon the location of the reaction, while additionally activating the MC or basophil to induce late stage cytokine production [8]. Second, circulating IgE can bind to its antigen creating an IgE-immune complex. IgE immune complexes are picked up by circulating follicular (FO) B cells by binding to CD23, the low affinity IgE receptor (FcεRII). These CD23⁺B cells then traffic to the splenic follicles where antigen transfer occurs followed by rapid increases in antigen-specific CD4⁺T cell proliferation and IgG responses [10]. Third, circulating IgE can bind to CD23 on B cells, inducing a negative regulatory response to shut down and control excessive IgE synthesis [11].

Enzymatic regulation of CD23 and downstream IgE synthesis was initially how a disintegrin and metalloproteinase (ADAM) 10 (ADAM10) became an important topic in Th2 mediated disease responses [12]. ADAMs are a family of zinc dependent proteases involved in ectodomain cleavage of transmembrane proteins and regulated intramembrane proteolysis. Of all the ADAMs, ADAM10 and ADAM17, also known as tumor necrosis factor alpha (TNF) converting enzyme (TACE), are most closely related with regards to structure and share many overlapping substrates [13;14]. Structurally, they contain a zinc dependent metalloproteinase domain, disintegrin and cysteine rich ligand binding domain, transmembrane domain, and cytoplasmic domain [15]. ADAM10 is widely expressed in many cells types and is a highly investigated target in disease processes ranging from cancer and Alzheimer's disease to asthma [15]. Since its discovery, many ADAM10 substrates have been identified including CD23, Notch1, TNF, amyloid precursor protein (APP) and epidermal growth factor (EGF), further supporting its ability to participate in an array of pathologic processes [16]. ADAM10 has been of much interest in allergic and other Th2 mediated diseases as it is the principle sheddase of the low affinity IgE receptor, CD23. Through an unknown mechanism, soluble CD23 (sCD23) negatively regulates IgE production, meaning increased ADAM10 and thus sCD23 production leads to enhanced IgE production [12;17]. Furthermore, increased sCD23 is seen in sera of allergic patients in active allergy season, which corresponds with increased circulating IgE [18]. Increased cleavage of CD23 leaves less membrane bound CD23 (mCD23) to negatively regulate IgE production as well as increased sCD23 to interact with other pro-inflammatory receptors such as CD11b-CD18 on monocytes [19;20]. Therefore, blocking cleavage of CD23 could be an important target in regulating IgE synthesis and thus the first step in the allergic cascade.

ADAM17, the principal protease of membrane TNF (mTNF), epidermal growth factor receptor (EGFR) ligands, and other vasoactive mediators, has been classically studied in inflammatory syndromes and cancer, with less emphasis on its role in allergy [14]. While ADAM17 is the principle sheddase of mTNF, ADAM10 can cleave TNF albeit to a lesser extent [21]. Dysregulation of TNF is critical for the pathologic characteristics underlying many disease states including cancer, type 2 diabetes, and rheumatoid arthritis [22]. Furthermore, increased TNF production is a key factor implicated in B cell aging, which ultimately curtails class-switched antibody production [23]. B cell TNF is, further, required for maintaining proper secondary lymphoid tissue architecture and antibody production and in its absence severe defects are

seen [24;25]. ADAM17 is potentially a new target for diagnostic and/or therapeutic intervention in Th2 mediated diseases, as it and TNF are reduced in B cells of allergic patients [23;26;27].

Herein, the role of ADAM10 and ADAM17 in B cell responses, maintenance of secondary lymphoid tissue architecture, and Th2 mediated diseases, such as allergic rhinitis, asthma, and helminth infection is explored.

2. ADAM10 in B cell development and function

Through their cleaved substrates, members of the ADAM family regulate a wide range of functions, including cell migration, proliferation, and adhesion [28]. With regards to B cell development and function, ADAM10 and ADAM17 have both been extensively studied with respect to lymphocyte development through initiation of the canonical Notch signaling pathway, germinal center responses, and plasma cell function [17;23;26;29;30]. Four Notch receptors exist in humans and rodents, which can interact with five different ligands [31]. Upon ligand-receptor interaction, ADAM10 initiates S2 cleavage followed by S3 cleavage by γ secretase, effectively releasing the Notch intracellular domain (NICD), which translocates to the nucleus leading to altered gene expression [32;33]. The role of ADAM10 in Notch signaling has been extensively studied as ADAM10 deficient embryos are similar to those of Notch 1-4 deficient embryos [34] and Notch 1 signaling is impaired in ADAM10 deficient thymocytes [30]. Furthermore, ADAM10 but not ADAM17 is required for Notch 1 rate-limiting, S2 cleavage, which has important implications in novel approaches to targeting Notch 1 signaling in cancer [35]. B lymphocytes, however, preferentially express Notch 2 [32] and Notch 2 signaling is noted in pre, pro, immature, follicular and marginal zone (MZ) B cells. MZBs are unique B cells, which behave in a T independent manner and are critical for early antibody production against blood borne pathogens [36]. Interestingly, their development is dependent on ADAM10 as it is critical for initiation of Notch 2 signaling [17]. B cell ADAM10, furthermore, has been shown to be critical for antibody production by follicular B2 cells. While the role of ADAM10 in IgE production is discussed below, *Chaimowitz et al.* described that in the absence of B cell ADAM10, germinal center formation is impaired and antigen specific IgM and IgG1 production is reduced 14 days post immunization with NP-KLH, a T dependent antigen [29]. These mice, additionally, lack a normal number of antigen specific plasma cells and remaining plasma cells are abnormal in function. Specifically, Bcl6, a transcriptional repressor, which must be downregulated during plasma cell differentiation, was increased in plasma cells from which ADAM10 is deleted after class switching to IgG1 [37].

3. ADAM10 and ADAM17 in germinal center formation and secondary lymphoid tissue architecture

TNF and its closely related family members have been extensively studied in the development and maintenance of secondary lymphoid tissue architecture. Because ADAM10 and ADAM17

are closely related ADAMs, many questions have been raised about their functional redundancy under physiologic as well as in various genetically manipulated animal models. While ADAM17 is the principle sheddase of TNF, ADAM10 is known to cleave TNF, especially in the absence of ADAM17 [38]. In addition to TNF, *Le Gall et al.* described that in the absence of ADAM17, ADAM10 cleaves epidermal growth factor receptor (EGFR) ligands, which are classically considered ADAM17 substrates. However, under physiologic conditions, ADAM17 dominates as the principal sheddase [38]. *Mezyk-Kopec et al.* further demonstrated that in ADAM17 deficient mouse embryonic fibroblasts, ADAM10 increases and ADAM10 dependent cleavage of TNF is seen [39]. *Folgosa et al.* described a compensatory relationship between ADAM10 and ADAM17 in B cells. In C57Bl/6 B cell specific ADAM10 deficient mice, B cell ADAM17 expression and activity increased resulting in excessive cleavage of TNF [26]. Excessive B cell TNF production has been implicated in B cell aging and reduced antibody production, which may help to explain the reduction in antibody production by B cell specific ADAM10 deficient mice [23]. Furthermore, the direct contribution of *B cell* TNF to maintenance of secondary lymphoid tissue architecture has been widely studied. Specifically, failure to produce B cell sTNF, as seen in mutated B cells with an un-cleavable form of mTNF, and excessive B cell sTNF production, as in ADAM10 deficient B cells, both result in dramatic alterations in secondary lymphoid tissue architecture [25;26]. Both aberrant B cell TNF conditions result in abnormal B cell/T cell localization with loss of a proper cortico-medullary junction, reduced germinal center formation, and impaired follicular dendritic cell (FDC) network development. Furthermore, naïve and draining lymph nodes (post-immunization) of B cell ADAM10 deficient mice, which exhibit excessive B cell TNF production, have increased angiogenesis and collagen deposition [26]. Therefore, secondary lymphoid architecture is highly sensitive to B cell TNF levels, which is maintained by a proper ratio of ADAM10 to ADAM17 expression and function. Interestingly, however, these differences are not noted in ADAM10^{B-/-} mice on a Th2-biased background, Balb/c [27]. Th2 prone strains were shown to have enhanced ADAM10 but reduced ADAM17 and TNF relative to Th1 prone strains and are less adept at increasing ADAM17 expression in the absence of B cell ADAM10 [27]. These findings suggest that the B cell and its ADAM10/ADAM17 profile plays a role in the classic Th1/Th2 paradigm rendering the B cell more than a passive participant waiting for a T cell signal.

4. ADAM10 and ADAM17 in murine and human allergic airway disease

4.1. ADAM10 is the principle sheddase of CD23

CD23 is a unique Fc receptor as it is a type 2 transmembrane protein and a member of the calcium dependent (C type) lectin family. It exists in two isoforms, CD23a and CD23b, and has three domains: (1) IgE interacting carboxy terminal domain, (2) stalk regions, and (3) a short cytoplasmic tail [11]. Surface CD23 levels can be increased in an IL-4 or IL-13 dependent manner [11]. In humans, peripheral blood mononuclear cells stimulated with IL-4 exhibit increased CD23 shedding and IgE production whereas treatment with anti-CD23, which prevents its cleavage, inhibits IgE production [40]. Several enzymes have been implicated in

the cleavage of CD23 including ADAM8 [41] and other hydroxymate sensitive metalloproteinases [42], but ADAM10 was determined by *Weskamp et al.* in a series of loss and gain of ADAM protease function experiments to be the principle sheddase of CD23 in B cells [12]. Once cleaved from the surface, sCD23 negatively regulates IgE production by an unknown mechanism. Several models exist that attempt to explain this relationship including: (1) High levels of IgE stabilize mCD23 and reduce further IgE production while allergen proteases and anti-CD23 stalk monoclonal antibodies destabilize CD23, increase its proteolysis, and increase IgE production [11]; and, (2) sCD23 crosslinks membrane IgE and CD21 resulting in increased IgE production [43]. This relationship between ADAM10, CD23, and IgE has since ignited much interest in the asthma and allergy fields regarding the use of ADAM10 or CD23 cleavage inhibitors as a mechanism to prevent IgE synthesis.

4.2. ADAM10, ADAM17, and their substrates in murine and human airway hypersensitivity

Mouse models of airway hypersensitivity are classically used to model asthma in humans. The role of ADAM10 and ADAM17 and their substrates has been widely studied in lung inflammation models used to simulate upper and lower airway disease. First, as described herein, ADAM10 is critical in the regulation of IgE production through its substrate, CD23. Transgenic mice overexpressing CD23 (CD23Tg) had been shown previously to have reduced IgE and lung inflammation [44;45]. In a OVA-induced lung inflammation model, *Mathews et al.*, using C57Bl/6 CD23Tg and B cell specific ADAM10 deficient (ADAM10^{B-/-}) mice, demonstrated that when mCD23 is increased, symptoms and features of IgE-dependent experimental asthma are reduced (17). Specifically, airway cellular infiltration, eosinophilia, airway resistance, and OVA-specific IgE production were reduced in mice lacking B cell-ADAM10 [46]. Furthermore, treatment with an ADAM10 inhibitor decreased antigen-specific IgE, Th2 cytokines in the lung, AHR, lung inflammation, and infiltration of eosinophils. Additionally, ADAM10 inhibitor therapy resulted in reduction of the Th2 transcription factor, GATA3, expression but had no effect on Th1 transcription factor, Tbet [46]. Interestingly, recent evidence has shown that ADAM10 and ADAM17 regulation in B cells is highly strain dependent. Classic Th1 (including C57Bl/6, SJL/J) and Th2-prone strains (including Balb/c, A/J) strains were characterized as high (SJL/J), intermediate (C57Bl/6), and low (Balb/c, A/J) IgE responders based on *in vivo* IgE production post immunization [47]. Furthermore, B cells from Th2 prone mouse strains (Balb/c, A/J), which are more susceptible to allergic airway disease induction and exhibit increased IgE synthesis have increased ADAM10 and reduced ADAM17 and TNF compared to those from Th1 prone mouse strains (C57Bl/6, SJL/J). In a house-dust mite (HDM) airway hypersensitivity model, Balb/c WT, which exhibit increased B cell ADAM10, experience more severe disease induction than C57Bl/6 WT including HDM specific IgE production, goblet cell metaplasia, mucus production, and airway cellular infiltration. Furthermore, Balb/c B cell specific ADAM10 deficient mice fail to reduce antigen specific IgE, cellular infiltration, mucus production, or goblet cell metaplasia to the extent of C57Bl/6 B cell specific ADAM10 deficient mice [27]. This evidence is further substantiated by B cell ADAM10, ADAM17, and TNF differences in Th2 prone allergic patients compared to non-allergic controls (Th1-prone). In human patients with allergic disease or asthma, increased circulating IgE is a diagnostic criteria, and has been correlated with increased circulating sCD23[18], implicating ADAM10

in the disease cascade. Recent evidence has shown that patients with actively symptomatic allergic rhinitis exhibit increased B cell ADAM10 supporting these findings. Furthermore, allergic patient B cells were described as having reduced ADAM17 and TNF, suggesting that these are protective against an allergic phenotype [27]. However, there is also evidence suggesting TNF inhibition would be beneficial in reducing asthma symptoms and disease manifestations. TNF can amplify inflammation by recruiting neutrophils, eosinophils, and monocytes as well as aiding in T cell activation. Furthermore, TNF can enhance airway remodeling by causing fibroblast proliferation and also contributes to enhanced airway resistance [48]. Therefore, while reduced B cell TNF may be more indicative of Th2-prone B cells, TNF produced by other cells can cause detrimental airway symptoms. Overall, Figure 1 demonstrates the novel model synthesizing evidence for ADAM10 and ADAM17 regulation in B cells from Th1 and Th2 prone mouse strains and humans. Th2 prone mouse strains and humans exhibit reduced ADAM10 and increased ADAM17 relative to Th1 counterparts resulting in increased sCD23 and IgE and decreased TNF and cell proliferation, as suggested by *Folgosa Cooley et al.* [27] and *Frasca et al.* [23;49]

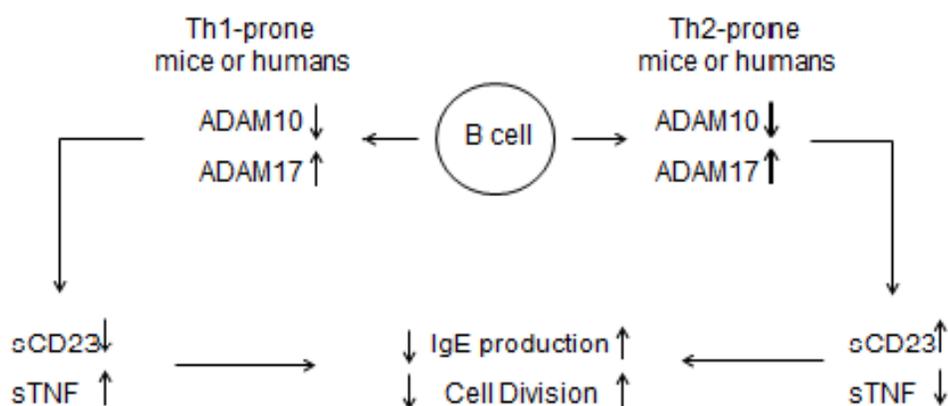


Figure 1. Novel model for regulation of ADAM10 and ADAM17 in B cells of Th1-prone compared to Th2-prone mice or humans.

Lastly, while glutamate is classically known for its role as an excitatory neurotransmitter, glutamate receptors have been found on T cells [50], macrophages [51], and human B cells [52]. The kainate receptor is a multi-subunit, ionotropic glutamate receptor. *Sturgill et al.* was first to describe the presence of the kainate receptor on B cells and demonstrated that kainate receptor activation increases ADAM10 expression, CD23 cleavage, and B cell proliferation [52]. Therefore, localized kainate receptor inhibition could be a unique approach to treating allergic airway disease as it could reduce CD23 cleavage, rounds of B cell proliferation, and thus IgE synthesis. Overall, there is substantial evidence advocating for the therapeutic benefit of ADAM10 or CD23 cleavage inhibitors in the treatment of allergic airway disease.

In addition to B cells, neutrophils or leukocytes and their respective ADAM10 and ADAM17 levels have also been described in lung inflammation models. Neutrophils recruitment occurs early during inflammation and their mediators affect the activity and recruitment of many other immune cells. The number of neutrophils in sputum was seen to be elevated in patients

with both acute and chronic asthma and especially those with lower eosinophil numbers and those unresponsive to corticosteroid treatment [53-55]. Both ADAM10 and ADAM17, with some conflicting reports, have been described to be important for leukocyte migration to the airway in lung inflammation models. In leukocyte specific ADAM17 deficient mice, *Arndt et al.* described a decrease in alveolar leukocyte recruitment following aerosolized LPS induction of acute airway inflammation. Furthermore, there was reduction in alveolar levels of CXCL1 and CXCL5, both neutrophil chemokines [56]. *Pruessmeyer et al.*, however, in leukocytes isolated from either hematopoietic cell specific ADAM10 or ADAM17 deficient mice showed that ADAM10 and not ADAM17 is required for leukocyte migration to the alveoli following LPS induced acute lung inflammation [57]. Therefore, ADAM10 inhibition could lead to reduced neutrophil infiltration.

Epidermal growth factor receptor (EGFR) signaling is reported to be integral in tissue repair, airway remodeling in asthma, and MUC5AC mucin production in lung inflammation models [58-60]. ADAM17 is responsible for the processing of epidermal growth factor receptor ligands including transforming growth factor alpha (TGF α) [14]. In normal human bronchial epithelial (NHBE) cells, *Booth et al.* demonstrated that ADAM17 induced TGF α cleavage as well as IL13 mediated proliferation. Furthermore, IL13, a key Th2 cytokine, was noted to redistribute TGF α to apical regions of NHBE for ADAM17 cleavage resulting in epithelial hypertrophy [61]. Therefore, further exploration of the IL13/ADAM17/TGF α axis is integral in better understanding methods to curb airway remodeling in chronic asthma. *Shiomi et al.* additionally described the importance of the ADAM17 on compressive stress to airway epithelial cells or bronchoconstriction, which is mediated through ERK and AKT phosphorylation. In this study, conditional deletion of ADAM17 from murine tracheal epithelial cells reduced ERK and AKT phosphorylation and thus attenuated compressive stress gene regulation [62]. Furthermore, ADAM17 is known to regulate transforming growth factor beta (TGF β) through cleavage of vadorin, a TGF β trap. Therefore, when ADAM17 is inhibited, less vadorin is cleaved, and TGF β signaling is increased [63]. In asthma patients, TGF β 1 is increased in bronchoalveolar lavage samples as well as in lung biopsy samples. Furthermore, TGF β 1 was found predominantly in inflammatory cells beneath the basement membrane in bronchial biopsy samples and may be important for collagen deposition and thus airway remodeling [64]. Taken together, this evidence suggests that reduced ADAM17 levels as seen in human patients' B cells (discussed above) could lend to increased TGF β 1 and thus enhanced asthma symptoms compared to control patients, who exhibited higher ADAM17 levels.

5. ADAM10, CD23 and MDSCs in helminth infection

In industrialized countries, incidence of helminth infection is greatly reduced and when observed it is commonly associated with a reduced parasite burden [65]. Worldwide, over one billion individuals are heavily infected with helminth and are rarely affected by allergic disease [5], a correlation demonstrated by many epidemiological studies [65;66]. Allergic diseases share many factors with helminth infections, including a similar cytokine milieu (e.g. IL-13, IL-4, IL-5) and most importantly up-regulation of IgE [65;66]. These factors contribute to the

symptomology of allergic disease, yet in helminth infected individuals, are protective [65;66]. This is despite helminth being the strongest natural promoter of IgE synthesis [67]. It is well established that parasite-specific IgE is important for anti-helminth immunity, but helminthes are also known to elicit large amounts of polyclonal or non-specific IgE in the sera of infected individuals. This finding has been thought to be a protective response by the parasite [67]. Helminth evolution has selected for this trait that benefits parasite life and reproduction, assisting the helminth in immune evasion [67].

In both allergy and helminth infection, IgE responses have been associated with CD23 expression and thus ADAM10 enzymatic activity [68-70]. The product, sCD23, has been a diagnostic indicator in many different diseases [69;71]. In an epidemiological study of individuals infected with the helminth *Schistosoma haematobium*, increased sCD23 levels correlated with infection intensity, but were inversely correlated with helminth-specific IgE [69]. Though ADAM10 activity was not measured in this study, increased ADAM10 mediated CD23 cleavage during helminth infection may be inducing this correlation.

Mast cells (MCs), which are important in mediating response to helminth infection, have been shown to express ADAM10 [72]. ADAM10 deletion results in reduced proliferation and migration of bone marrow derived mast cells *in vitro* (BMMC) [72]. Furthermore, loss of ADAM10 has been shown to regulate the MC response to stem cell factor (SCF), which binds to c-kit on MCs to induce proper migration and distribution of tissue mast cells in mice [72]. Currently, the substrate ADAM10 cleaves in this scenario is unknown. It has been hypothesized that Notch 1 may be involved, as Notch 1 promotes IgE-mediated cytokine production in mast cells, but other substrates such as Notch 2 and CD44 have also been considered [73-75].

ADAM10Tg mice, generated by injection of ADAM10 cDNA under control of the H-2Kb promoter and the IgH enhancer, overexpress murine ADAM10 and were initially made to study the role of ADAM10 in lymphocyte development [76-78]. Inclusion of the IgH enhancer results in preferential expression on B lineage cells. This overexpression of ADAM10 was observed on bone marrow (BM) cells and markedly reduced the numbers of pro, pre, and immature B cells in the BM resulting in an almost complete loss of peripheral B2 B cells due to improper Notch cleavage and signaling [17]. The only B cell population unaltered by ADAM10 overexpression was B1a and B1b cells, which typically reside in the peritoneal and pleural cavities [17]. ADAM10Tg animals also exhibit significant myeloid accumulation. In the BM of these mice, CD11b⁺Gr-1⁺ cells constitute over 90% of total BM cells. These cells leave the BM and migrate to all secondary lymphoid organs, where they are defined as myeloid derived suppressor cells (MDSCs). Recent work has shown a similar scenario exists in human disease, with defects in Notch signaling driving MDSC accumulation [79].

MDSCs accumulate in a spectrum of disease states including cancer, the natural aging process, solid organ transplantation, parasitic infections, sepsis, autoimmune disease, trauma, and burns [80-83]. MDSCs are classified as either monocytic (CD11b⁺Ly6C⁺Ly6G⁻) or granulocytic (CD11b⁺Ly6C^{int}Ly6G⁺) subsets [84]. This heterogeneous population was observed within the MDSCs in the ADAM10Tg [17]. Although MDSC accumulation is a byproduct of ADAM10 overexpression in early hematopoietic progenitors, ADAM10 expression is not altered in these

cells. ADAM10Tg mice, therefore, could be exploited to study MDSC-mediated immune regulation in an environment devoid of confounding factors.

While MDSCs are most well-defined for their immunosuppressive role in cancer, a new role for accumulation of MDSCs in Th2-driven parasitic infection, such as *Nippostrongylus brasiliensis*, shows they play an immunosupportive role [80;85;86]. ADAM10Tg mice infected with *N. brasiliensis* have significantly reduced L4 lung worms, L5 adult worms and fecal egg burden [87]. These findings directly correlated with MDSC levels, as depletion of MDSCs reversed these findings.

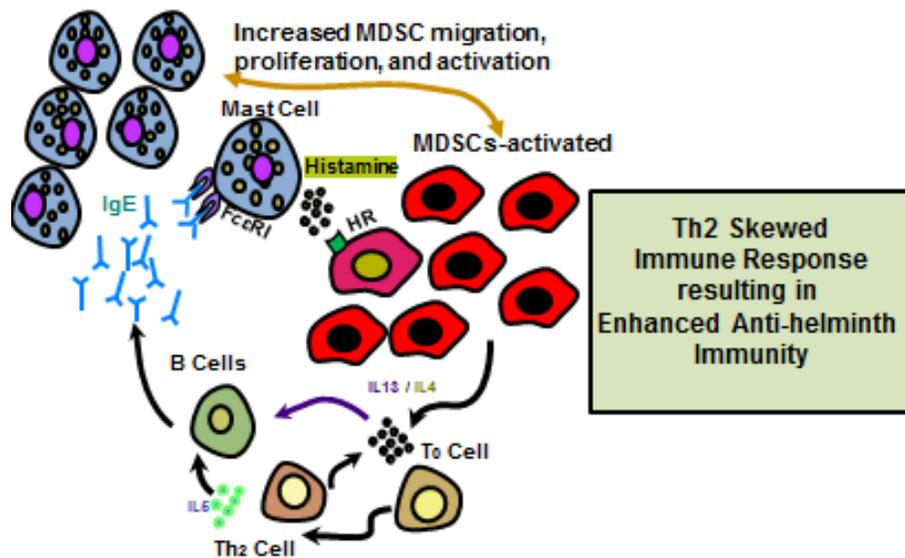


Figure 2. Model of MDSC/MC interaction. MCs are required for MDSC activity. MCs in the liver release mediators, which create a chemokine gradient that increases migration of MDSCs, resulting in accumulation in the liver. MCs release mediators, such as histamine, that induce MDSC activation, proliferation and Th2-skewed immune responses that promote allergy and parasitic clearance and diminish antitumor responses.

Recent evidence is beginning to suggest that mast cells (MCs) contribute to the recruitment and activity of these MDSCs [86;88;89]. While MCs have been well documented to mediate allergic inflammation, new evidence is emerging to define the novel interaction between the MDSC and the MC. In MC-deficient mice, MDSC enhanced parasitic clearance is completely reversed. Additionally, co-culture of MCs and MDSCs results in enhanced IgE-mediated cytokine production by the MC [90]. Without MCs, MDSCs fail to migrate to the liver. This is thought to be through MC mediators such as histamine and IL-13 [86;87]. Histamine has been shown to induce MDSC proliferation, migration and activation (Figure 2) [87]. This is reflected in humans as reported by *Martin et al.* that patients with symptomatic allergic inflammation and increased ADAM10 have increased circulating MDSCs [27;87]. Figure 2 demonstrates the proposed model for MDSC/Mast Cell interaction, with MCs in the liver releasing histamine, which induces MDSC activation, proliferation, and release of Th2 cytokines such as IL13 and IL4, which in turn skews the immune response Th2. Therefore, while this model is favorable for elimination of helminth infection, it would diminish antitumor responses.

6. ADAM10, CD23 and IgE immune complexes

Antibody, in complex with its antigen, provides the immune system with a feedback response against the complexed antigen. This feedback mechanism results in immune stimulation or suppression depending upon the antibody class [91]. IgE, complexed with antigen, has long been shown to induce a significantly increased immune response over antigen alone. This response results in increased antigen specific T cell proliferation and antigen specific IgG *in vivo* [92]. ADAM10 may additionally play a role in this up regulation as ADAM10 B^{-/-} mice show significantly increased T cell proliferation over WT mice [93]. This may be due to the increased CD23 found on the surface of ADAM10 B^{-/-} mice, but may additionally be related to a not previously described ADAM10 effect. The low affinity receptor for IgE, CD23 has been known to internalize IgE antigen complexes and promote antigen presentation. Extensive studies using CD23^{-/-} animals proved CD23 to be essential to the immunostimulatory properties of IgE antigen complexes [92]. Recent findings show that CD23⁺B cells rapidly transfer the antigen to the spleen [94] and were dispensable after 4 hours post IgE antigen complex injection. After that period, DCs were required [95]. These findings suggested that IgE antigen complexes or fragments thereof were being carried to the secondary lymphoid system, in this case the spleen, by CD23⁺B cells and then were being transferred to DCs.

Exosomes are defined as tiny membrane bound particles ranging from 30-150nm. Although originally discovered in the 1980s and thought to be primarily for cellular waste [96], exosomal research has undergone a resurgence given the protein and micro-RNA cargo that is packed into these particles [97]. In a previous publication, *Mathews et al.* demonstrated that CD23 and its protease, ADAM10 were found in B cell derived exosomes (bexosomes) from both mouse and human B cells [98]. Additionally, β -adrenergic stimulation of B cells further increased both CD23 and ADAM10 levels in bexosomes [99]. *Martin et al.* showed that B cells stimulated with anti-CD40 and IL-4, in the presence of IgE antigen complexes, release bexosomes that contain both CD23 and IgE. In agreement with earlier studies [100], these bexosomes were capable of directly stimulating antigen specific T cells *in vitro*, presumably via the MHC peptide complexes found on these bexosomes [93]. Culture of these bexosomes with bone marrow derived DCs (BMDC), followed by isolation and injection of DCs additionally enhanced *in vivo* antigen specific T cell proliferation. Overall, *Martin et al.* shows that bexosomes are responsible for antigen transfer from B cells to DCs, thus, providing a mechanism and suggesting a model to explain the importance of DCs in the immunostimulatory activity of IgE complexes [93].

7. Conclusion

ADAM 10 and 17 proteases have been widely studied in Th2 mediated disease responses including allergic rhinitis, asthma, and helminth infection. Enzymatic regulation of ADAM10 and 17 substrates as well as the relative amount of ADAM10 and 17 on immune cells is critical for preventing Th2 mediated disease as well as maintenance of normal antibody production,

germinal center formation, and secondary lymphoid tissue architecture. While the role of ADAM10 in Th2 diseases is classically recognized for its regulation of IgE synthesis by CD23 cleavage, predisposition to asthma as well as severity of disease appears to be in part controlled by a tight regulation of ADAM10 and ADAM17 proteolytic activity, which in turn controls the cleavage of key substrates such as CD23, TNF, TGF α , and TGF β 1. These substrates ultimately effect IgE production, airway remodeling, inflammatory cell infiltration, and airway responsiveness.

Attenuation of MC degranulation and neutralization of MC mediators such as histamine and leukotrienes are common targets of therapeutic interventions used in asthma and allergic airway disease. MC histamine release is critical, however, for function, migration, and activation of MDSCs, which have been shown to alleviate helminth infection by decreasing parasite burden. This finding was studied using a unique model of MDSC accumulation in a mouse model that overexpresses ADAM10. Therefore, while MDSCs could be considered harmful in severe allergy, they may also be essential for protection against helminth infection.

This review has demonstrated the essential role of ADAM10 and 17 and their substrates in Th2 mediated disease and provided a review of evidence supporting the continued exploration of ADAM10 and ADAM17 as potential therapeutic and diagnostic targets.

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