C3a Receptors Signaling in Mast Cells

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1 Introduction

Mast cells are multifunctional immune cells that play a sentinel role in innate immunity (Echtenacher, Mannel, and Hultner 1996; Marshall and Jawda, 2004; Supajatura, Ushio, Nakao, Okumura, and Ogawa 2001) but also mediate a variety of inflammatory diseases including cardiac anaphylaxis (Bani, Nistri, Mannaioni, and Masini 2006; Marone, de Crescenzo, Adt, Patella, Arbustini, and Genovese 1995) asthma (Williams and Galli 2000; Yu, Tsai, Tam, Jones, Zehnder, and Galli 2006) and rheumatoid arthritis (Maruotti, Crivellato, Cantatore, Vacca, and Ribatti 2006). Of the inflammatory diseases in which mast cells participate, their role in asthma has been studied in most detail. Asthma is a complex inflammatory disease characterized by bronchoconstriction, airway hyperresponsiveness (AHR) and inflammation. Approximately 35 million Americans suffer from asthma, and in recent years, its prevalence and severity have been increasing dramatically world-wide. It is generally accepted that the disease arises because of inappropriate immunologic responses to common environmental antigens in genetically susceptible individuals. Following antigen presentation, CD4⁺ T cells produce T_H2 cytokines which induce B cells to synthesize IgE molecules. These IgE molecules then bind to their high affinity receptors (FceRI) on the surface of mast cells. Subsequent cross-linking of FceRI on mast cells by allergen results in degranulation, leukotriene generation and cytokine synthesis (Choi, Kim, Combs, Frohman, and Beaven 2002; Gonzalez-Espinosa, Odom, Olivera, Hobson, Martinez, Oliveira-Dos-Santos, Barra, Spiegel, Penninger, and Rivera 2003; Hundley, Prasad, and Beaven 2001; Sayama, Diehn, Matsuda, Lunderius, Tsai, Tam, Botstein, Brown and Galli 2002; Tkaczuk, Beaven, Brachman, Metcalfe, and Giffiían 2003), which cause increased vascular permeability, recruit inflammatory cells to the airway and promote smooth muscle contraction (Brightling,
The complement system forms an important part of innate immunity against bacteria and other pathogens. As a system of ‘pattern recognition molecules’, foreign surface antigens and immune complexes initiate a proteolytic pathway leading to the formation of a lytic membrane attack complex. The anaphylatoxins C3a and C5a are generated as byproducts of complement activation, and interact with cell surface G protein coupled receptors (GPCRs) in target cells to mediate a variety of inflammatory responses (Bao, Osawe, Haas, and Quigg 2005; Boos, Szalai, and Barnum 2005; Kildsgaard, Hollmann, Matthews, Bian, Murad, and Wetsel 2000). Recent studies have shown that C3a levels are elevated in bronchoalveolar lavage (BAL) fluid after segmental allergen challenge in asthmatic but not healthy subjects (Castro, Schmitz-Schumann, Rother, and Kirschfink 1991; Humbles, Lu, Nilsson, Lilly, Israel, Fujiwara, Gerard, and Gerard 2000; Nakano, Morita, Kawamoto, Suda, Chida, and Nakamura 2003). Furthermore, plasma C3a level is elevated in acute exacerbations of asthma (Nakano et al. 2003) and C3a receptors are upregulated in subjects who died with asthma compared with subjects who died from other causes (Fregonese, Swan, Van Schadewijk, Dolhnikoff, Santos, Daha, Stolk, Tschernig, Sterk, Hiemstra, Rabe, and Mauad 2005). Additionally, single nucleotide polymorphism in C3 or C3a receptor (C3aR) gene increases susceptibility to asthma (Hasegawa, Tamari, Shao, Shimizu, Takahashi, Mao, Yamasaki, Kamada, Doi, Fujiwara, Miyatake, Fujita, Tamura, Matsubara, Shirakawa, and Suzuki 2004). In animal models, complement activation modulates both AHR and airway inflammation (Drouin, Corry, Kildsgaard, and Wetsel 2001; Taube, Rha, Takeda, Park, Joetham, Balhorn, Dakhama, Giclas, Holers, and Gelfand 2003). Furthermore, deletion of C3aR gene or administration of C3aR inhibitors attenuates both AHR and lung inflammation (Baelder, Fuchs, Bautsch, Zwirner, Kohl, Hoymann, Glaab, Erpenbeck, Krug, and Braun 2005; Bautsch, Hoymann, Zhang, Meier-Wiedenbach, Raschke, Ames, Sohns, Flemme, Meyer Zu Vilsendorf, Grove, Klos, and Kohl 2000; Drouin, Corry, Hollman, Kildsgaard, and Wetsel 2002; Humbles et al. 2000; Wills-Karp and Koehl 2005). Collectively, these findings demonstrate an important role for C3aR in the pathogenesis of asthma.

2 C3a Generation and Its Effect on Allergen Sensitization

There is evidence to suggest that a combination of different pathways generates C3a in the airway of individuals with asthma (Ali and Panettieri 2005). It is likely that antibody generated during sensitization interacts with allergen to activate the classical complement pathway. Additionally, airway epithelial cells and pulmonary macrophages secrete both C3 and several components of the alternate pathway of complement (factors B, H, and I and properdin) (Strunk, Eidlen, and Mason 1988; Vandermeer, Sha, Lane, and Schleimer 2004; Varsano, Kaminsky, Kaiser, and Rashkovsky 2000). Thus, activation of alternative or the lectin pathway by allergen may also lead to the generation of C3a. It is noteworthy that house dust mite protease