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REVIEW

Complement components as potential therapeutic targets for asthma treatment

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Summary
Asthma is the most common respiratory disorder, and is characterized by distal airway inflammation and hyperresponsiveness. This disease challenges human health because of its increasing prevalence, severity, morbidity, and the lack of a proper and complete cure. Asthma is characterized by T_H2–skewed inflammation with elevated pulmonary levels of IL-4, IL-5, and IL-13 levels. Although there are early forays into targeting T_H2 immunity, less-specific corticosteroid therapy remains the immunomodulator of choice. Innate immune injury mediated by complement components also act as potent mediators of the allergic inflammatory responses and offer a new and exciting possibility for asthma immunotherapy. The complement cascade consists of a number of plasma- and membrane-bound proteins, and the cleavage products of these proteins (C3 and C5) regulate the magnitude of adaptive immune responses. Complement protein are responsible for many pathophysiological features of asthma, including inflammatory cell infiltration, mucus secretion, increases in vascular permeability, and smooth muscle cell contraction. This review highlights the complement-mediated injury during asthma inflammation, and how blockade of active complement mediators may have therapeutic application.

Abbreviations: AHR, airway hyperresponsiveness; BAL, bronchoalveolar lavage; ASM, airway smooth muscle; MAC, membrane attack complex; Treg, regulatory T cells.

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Contents

Introduction

Asthma is a chronic inflammatory disease of the bronchi arising because of inappropriate immunological responses to common environmental antigens in genetically susceptible individuals [1]. It is thought to be mediated by $CD4^+$ T lymphocytes that produce T_H2 cytokines linked with elevated specific IgE, eosinophilia, and airway hyperresponsiveness (AHR) [2–4]. This perspective will explore how an important component of the innate immunity, the complement system, normally a key defense against mucosal bacteria, viruses, fungi, helminthes, and other pathogens, may also play an important role in the pathogenesis of asthma. Although complement factors have been associated with development of pathophysiology of asthma [5,6], the role of individual complement components in the pathogenesis of allergic asthma is not clear. Biologically active fragments (C3a, C5a), generated through the classical, alternative, lectin pathways, and by the direct action of certain proteolytic enzymes on C3 or C5 [7] (Fig. 1), participate in AHR induction. Infections, and allergens of respiratory tract activate local complement activation participate in AHR [8–10] because of their ability to recruit, activate leukocytes, increase vascular permeability, stimulate contraction of smooth muscle, and trigger degranulation of mast cells [9,11–13]. In addition to allergens, other triggers of asthma have been shown to activate complement cascade in human, and in animal models [13]. It has been demonstrated that bronchoalveolar lavage (BAL) of asthma individuals contain quantitatively higher levels of C3a and C5a as compared to healthy control subjects at baseline [14].

In asthma, overproduction of activated complement fragments may promote asthma susceptibility [13]. This imbalance results in up regulation of biologically active fragments, C3a and C5a, which may act on cells of the

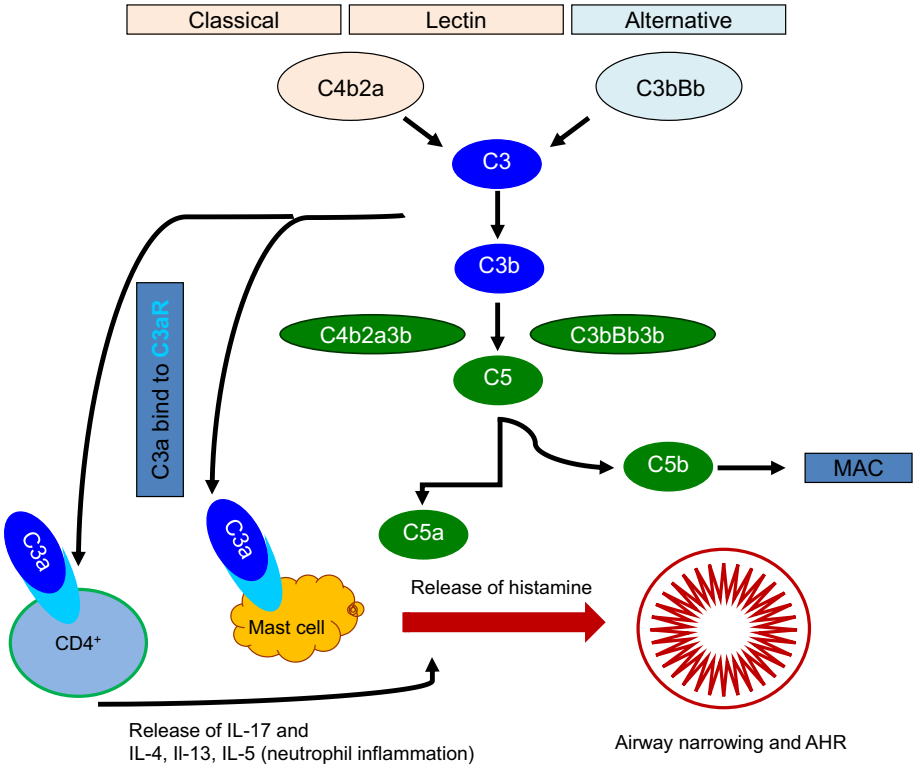

Figure 1 Model explains the generation of C3a and C5a through classical, lectin and alternative pathway during airway inflammation. Further, C3a binds to C4aR on $CD4^+$ T cells and promotes recruitment of IL-17^+CD4^+ cells, neutrophil inflammation and activation of Mast cells that leads to histamine mediated AHR.