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The immunoregulatory roles of lung surfactant collectins SP-A, and SP-D, in allergen-induced airway inflammation

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Abstract

It has become increasingly evident that pulmonary surfactant proteins, SP-A and SP-D, present in the alveolar and bronchial epithelial fluid linings, not only play significant functions in the innate defense mechanism against pathogens, but also are involved in immunomodulatory roles, which result in the protection against, and resolution of, allergen-induced airway inflammation. Studies on allergen-sensitized murine models, and asthmatic patients, show that SP-A and SP-D can: specifically bind to aero-allergens; inhibit mast cell degranulation and histamine release; and modulate the activation of alveolar macrophages and dendritic cells during the acute hypersensitive phase of allergic response. They also can alleviate chronic allergic inflammation by inhibiting T-lymphocyte proliferation as well as increasing phagocytosis of DNA fragments and clearance of apoptotic cell debris. Furthermore, it has emerged, from the studies on SP-D-deficient mice, that, when these mice are challenged with allergen, they develop increased eosinophil infiltration, and abnormal activation of lymphocytes, leading to the production of Th2 cytokines. Intranasal administration of SP-D significantly attenuated the asthmatic-like symptoms seen in allergen-sensitized wild-type, and SP-D-deficient, mice. These important findings provide a new insight of the role that surfactant proteins play in handling environmental stimuli and in their immunoregulation of airway inflammatory disease.

Keywords: Surfactant protein A (SP-A) and D (SP-D); Collectin; Asthma

Introduction

The average person inhales daily about 10,000 l of air, which is laden with bacteria, viruses, oxidants, pollutants and allergens. The lung contains a large array of resident humoral and cellular components of the innate immune system that provide a first-line defense against infectious challenge (Vercelli, 2003). In the allergic patient, inhalation of allergen particles leads to an inflammatory reaction that is initiated by resident airway cells and perpetuated by invasion of inflammatory cells (Holt et al., 1999). Inhaled allergens are initially trapped and degraded in the airway lining fluid, before they come into contact with immune cells. Pulmonary surfactant is a highly surface-active complex of phospholipids and proteins located at the air–liquid interface inside the alveoli. So far, its major role has

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been considered to be the stabilization of alveolar walls and prevention of collapse of the alveoli (Hamm et al., 1992). However, the components of surfactant may also have an important role in the innate immunity of lung. Over the past 10 years, it has been recognized that surfactant proteins A (SP-A) and D (SP-D) – members of the "Collectins" family of proteins of innate immunity, which contain NH_2-terminal collagen-like regions and COOH-terminal C-type lectin domains – play important roles in host defense and immunomodulatory functions in the respiratory tract (Reid et al., 2005; Wright, 2005). Recent advances in this area are summarized in this article, especially with respect to the possible immunoregulatory roles of lung collectins in allergic asthma, and the view that SP-D, in particular, may play an important role in anti-inflammatory processes to bring about alleviation of airway inflammation.

The characteristics of SP-A and SP-D and their roles in innate immunity in the lung

The hydrophilic lung surfactant proteins, SP-A and SP-D, synthesized and secreted primarily by type II alveolar cells, Clara cells, and cells of submucosal glands in the lung, are constitutive mediators of antigen clearance capable of interacting with cellular components of both the innate and adaptive immune system on the mucosal surface (Holmskov et al., 2003). Both SP-A and SP-D show a similar overall structural organization in which each polypeptide chain consists of: a short amino terminal region that is involved in inter-subunit disulfide bond formation; a collagen-like region consisting of Gly–X–Y repeats; an α-helical, coiled-coil, neck region; and a C-type lectin, carbohydrate recognition domain (CRD) (Reid, 1993). Association of three of the polypeptide chains yields a trimeric subunit, by the folding of the collagenous regions into triple helices and coiled-coil bundling of three α-helices in the neck region (Holmskov et al., 2003; Reid, 1993). Six of these triple-helical subunits make up the "bunch of tulips"-like structure of SP-A, while SP-D is composed of a cruciform-like structure with four arms of equal length emanating from a central hub (Kishore et al., 1996; Lim et al., 1994). Both SP-A and SP-D are able to bind, via their multiple CRDs, to arrays of carbohydrates on the surfaces of pathogens, in a calcium-dependent manner, thus bringing about agglutination of the pathogens and enhancement of their recognition by alveolar macrophages (AMs), leading to increased phagocytosis and respiratory burst activity (Crouch and Wright, 2001; Kishore et al., 1996). The antimicrobial activities of SP-A and SP-D, and their roles in host defense mechanisms, have been summarized in recent reviews (Crouch and Wright, 2001; Lawson and Reid, 2000).

There are several reports, regarding the possible roles of SP-A, and SP-D, in the modulation of inflammation, and it appears that they may both enhance, or inhibit, inflammatory change. Gardai et al. (2003) have reported that both SP-A- and SP-D-modulated cellular functions by differentially engaging with either a CD91/calreticulin complex, or signal-inhibitory regulatory protein-α (SIRP-α), on the surface of macrophages, the specific receptor being triggered being dependent upon whether, or not, the CRDs of the collectin were bound to a target pathogen/apoptotic cell. For example, in the absence of binding to a pathogen, SP-A is considered to interact, through its CRD domains, to SIRP-α and mediate an inhibitory signal transduction pathway. In the presence of a foreign microorganism, or cell debris, to which the CRDs of SP-A bind, the free collagen-like regions of the SP-A appear to activate immune cells through the cell surface CD91/calreticulin complex. This interaction enhances p38 MAP kinase activation, NF-κB activity, and the production of proinflammatory cytokines/chemokines in macrophages (Gardai et al., 2003). This intriguing model provides at least a partial explanation for the apparently conflicting reports that both SP-A, and SP-D, enhance and inhibit the production of inflammatory-mediators.

Levels of lung surfactant proteins SP-A and SP-D in lung inflammation induced by allergy

Recent studies have indicated significant changes, sometimes apparently contradictory, in the levels of collectins during allergic inflammation of the lung in animal models (Haley et al., 2002; Kasper et al., 2002; Madan et al., 2001; Wang et al., 2001) as well as in asthmatic patients (Cheng et al., 2000a; Koopmans et al., 2004; van de Graaf et al., 1992). The first study in this area (van de Graaf et al., 1992) reported decreased levels of SP-A in bronchoalveolar lavage (BAL) from patients with asthma, while a more recent study (Cheng et al., 2000a) reported elevated levels of SP-A and SP-D in mild stable asthmatics compared to healthy subjects. In the murine models of allergic lung inflammation, involving sensitization by allergens from dust mites (Wang et al., 2001), fungi (Haley et al., 2002), or ovalbumin (Kasper et al., 2002), it was reported that there are significant changes seen in the levels of collectins, in BAL, during the height of allergen-induced bronchial inflammation. In a recent study (Koopmans et al., 2004) it was observed that asthmatic patients have acute increases in levels of serum SP-D, but not SP-A, 24 h after allergen challenge. A similar selective regulation of SP-D was also previously reported in a murine model of acute allergic lung inflammation (Atochina et al., 2003; Haczku et al., 2001). It has been noted that