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Surfactant protein A and surfactant protein D variation in pulmonary disease

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Abstract

Surfactant proteins A (SP-A) and D (SP-D) have been implicated in pulmonary innate immunity. The proteins are host defense lectins, belonging to the collectin family which also includes mannan-binding lectin (MBL). SP-A and SP-D are pattern-recognition molecules with the lectin domains binding preferentially to sugars on a broad spectrum of pathogen surfaces and thereby facilitating immune functions including viral neutralization, clearance of bacteria, fungi and apoptotic and necrotic cells, modulation of allergic reactions, and resolution of inflammation. SP-A and SP-D can interact with receptor molecules present on immune cells leading to enhanced microbial clearance and modulation of inflammation. SP-A and SP-D also modulate the functions of cells of the adaptive immune system including dendritic cells and T cells.

Studies on SP-A and SP-D polymorphisms and protein levels in bronchoalveolar lavage and blood have indicated associations with a multitude of pulmonary inflammatory diseases. In addition, accumulating evidence in mouse models of infection and inflammation indicates that recombinant forms of the surfactant proteins are biologically active in vivo and may have therapeutic potential in controlling pulmonary inflammatory disease. The presence of the surfactant collectins, especially SP-D, in non-pulmonary tissues, such as the gastrointestinal tract and genital organs, suggest additional actions located to other mucosal surfaces. The aim of this review is to summarize studies on genetic polymorphisms, structural variants, and serum levels of human SP-A and SP-D and their associations with human pulmonary disease.

Keywords: Surfactant proteins A and D; Pulmonary diseases; Innate immunity; Inflammation; Phospholipid homoeostasis

Introduction

The epithelial lining of the alveoli and airways of the lung are continuously exposed to inhaled pollutants, microbes, and allergens. The alveoli are lined with a thin layer of aqueous film comprising the pulmonary surfactant secreted by pulmonary epithelial cells. About 90% of surfactant is lipids or phospholipids that are essential for reducing surface tension at the air–liquid

Abbreviations: ALI, acute lung injury; BPD, bronchopulmonary dysplasia; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CTLD, C-type lectin domain; CVD, collagen vascular disease; IPF, idiopathic pulmonary fibrosis; MBL, mannan-binding lectin; PAP, pulmonary alveolar proteinosis; PRR, pathogen recognition receptors; PRM, pathogen recognition molecules; RDS, respiratory-distress syndrome; SNP, single nucleotide polymorphisms; SP-A and D, surfactant proteins A and D

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interface of the lung. Maintenance of surface tension is essential for the diffusion of oxygen and carbon dioxide between inspired air and the circulation. The last 10% of surfactant is protein. Four surfactant proteins are known: SP-A, SP-B, SP-C, and SP-D. SP-B and SP-C are small hydrophobic molecules integrated in the phospholipids and important for the ability of surfactant to reduce surface tension. SP-A and SP-D are large hydrophilic proteins that are members of the collectin family of proteins (Holmskov et al., 2003; Wright, 2005). The collectins are characterized by collagen-like regions that trimerize the peptides through repeating Gly–Xaa–Yaa triplets flanked by short N-terminal regions with cysteine residues involved in higher oligomerization of the molecules and C-terminal located C-type lectin domains (CTLDs) that bind calcium-dependently to lipid and carbohydrate-derived microbial substances. Their main function is related to host defence and regulation of inflammation, but SP-A also organizes the structure and affects function of surfactant lipids (Haagsman et al., 1991; Voorhout et al., 1991; Ochs et al., 2002). Some SP-A immunoregulatory functions are reported to be modulated by surfactant lipids (Kremlev et al., 1994; Tino and Wright, 1996; Stamme and Wright, 1999; Chiba et al., 2006). SP-D binds to phosphatidylinositol and glycosylceramide, and phospholipids accumulate in the lungs of SP-D deficient mice along with inflammatory cells (Kuroki et al., 1991).

The binding of SP-A and SP-D to microbial surfaces leads to several well-characterized anti-microbial functions including aggregation and neutralization (Jounblat et al., 2004), opsonization for phagocytosis (van Iwaarden et al., 1990, 1991), direct gram-negative bacterial cell-membrane lysis (Wu et al., 2003; Kuzmenko et al., 2006), and also result in the inhibition of bacterial and fungal growth in a macrophage and aggregation-independent manner (McCormack et al., 2003). At the same time SP-A and SP-D adjusted the inflammatory response to the incoming threat in a way so that free and bound collectin may act as anti- and proinflammatory molecules, respectively (Gardai et al., 2003; Holmskov et al., 2003; Wright, 2005).

SP-A and SP-D are mainly found in the lung where they are localized to Clara cells, pulmonary type II pneumocytes, serous cells of tracheobronchial glands, and goblet cells (Saitoh et al., 1998; Madsen et al., 2000, 2003a; Kasper et al., 2002), but both molecules are also reported to be produced at extra-pulmonary sites and they are found in the circulation.

In this review, the associations of SP-A and SP-D with pulmonary diseases are discussed. In this context it is important to note that both proteins may have multiple functions in surfactant metabolism and in innate immunity.

Structure of SP-A and SP-D and their genes

Inducible responses of the innate immune system are initiated by recognition of pathogens or host debris by a set of so-called pathogen recognition receptors (PRRs) and soluble pathogen recognition molecules (PRMs). The PRRs and PRMs classification is based on whether the proteins are anchored in cellular membranes or exist in soluble form. The overall function of the PRRs and PRMs is to provide resistance to microbes and scavenging of cellular debris. The resistance is obtained through broad-spectrum recognition of conserved molecular patterns rather than specific recognition of ligands and results in the facilitated clearance of microorganisms. PRRs and PRMs comprise a heterogeneous group of proteins with several types of protein domains involved in pathogen recognition. Prominent domains include the CTLD (Drickamer, 1988; Zelensky and Gready, 2005), the scavenger receptor cysteine-rich domain (e.g., scavenger receptor A1) (Sarrias et al., 2004), the leucine-rich repeat domain (e.g., toll-like receptors) (Matsushima et al., 2005), the pentraxin domain (e.g., serum amyloid A) (Garlanda et al., 2005), and the fibrinogen-related domain (Matsushita and Fujita, 2002).

SP-A and SP-D are both PRMs and belong to the family of collectins, which is a subgroup of C-type lectins. The human collectins also comprise the serum protein mannan-binding lectin (MBL) (Holmskov et al., 2003; Takahashi et al., 2006c), and the classification is now extended to include the endothelial protein membrane-type collectin, collectin placenta 1 (CL-P1) (Ohtani et al., 2001), and the liver collectin (CL-L1) (Ohtani et al., 1999).

Genomic organization

The genes for SP-A, SP-D, and MBL have been mapped to a cluster on the long arm of chromosome 10, with the loci for the pulmonary collectins being linked to each other (Floros and Hoover, 1998) and located in a region spanning from 10q22 to q23.1 (Fig. 1). The human SP-A locus consists of two functional genes (*SFTPA1* (White et al., 1985) and *SFTPA2* (Katyal et al., 1992)) corresponding to two different SP-A polypeptides (SP-A1 and SP-A2). Furthermore, a truncated *SFTPA* pseudogene has been characterized with sequences highly homologous to the 3rd and 4th protein coding exon (Korfhagen et al., 1991). The human SP-D locus consists of one gene (*SFTPD*) (Crouch et al., 1993a; Kolble et al., 1993).

The SP-A and SP-D loci were demonstrated by Hoover and Floros (1998) to be oriented, with the overall order being: centomere-*SFTPD*-*SFTPA2*-pseudogene-*SFTPA1* and it was found that the two SP-A