Serum surfactant protein D as a biomarker for diagnosis of ventilator associated pneumonia

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ABSTRACT

Background: Biomarkers could potentially help in early diagnosis of various infections, including VAP. SPD is primarily expressed and secreted by type II alveolar cells (Clara cells) but is also detected in the tracheal and bronchial glands of the lower airways. Firstly SPD was identified in respiratory tract, but current studies demonstrate that the expression of SPD is in almost all mucosal surfaces, including epithelial cells in exocrine ducts, the mucosa of gastrointestinal and genitourinary tract and in tear fluid. SPD has a well demonstrated and important role in pulmonary innate immunity, especially in protection against Gram-negative bacteria.

Keywords:serum surfactant protein-D, ventilator associated pneumonia

Definition of surfactant protein D:

Surfactant protein-D (SP-D) is a member of the collagenous subfamily of calcium-dependent lectins (collectins) that includes pulmonary surfactant protein A (SP-A) and the serum mannose-binding lectin (Eggleton & Reid, 1999). Collectins interact with a wide variety of microorganisms, lipids, and organic particulate antigens, and can modulate the function of immune effector cells and their responses to these ligands.(Crouch, 2000)

Sites of SP-D production:

SP-D is synthesized and secreted into the airspaces of the lung by the respiratory epithelium .At the alveolar level, SP-D is constitutively synthesized and secreted by alveolar type II cells. More proximally in the lung, SP-D is secreted by a subset of bronchiolar epithelial cells, the non-ciliated Clara cells.(Crouch, 2000)

The lung seems to be the major site of SP-D production. However, there is increasing evidence for extrapulmonary sites of expression as assessed with monoclonal or affinity-purified antibodies, reverse-transcriptase-mediated PCR (RT-PCR), and/or hybridization assays of tissues from humans and other large mammals (Madsen et al., 2000)

It is difficult to entirely exclude cross-reactions or amplification of related sequences; however, localization to many of these sites in human tissues was confirmed by using monoclonal antibodies in combination with RT-PCR with sequencing of the amplified products (Madsen et al., 2000). Sites of extrapulmonary expression have also been

described in small mammals. In the rat, SP-D message was identified in RNA extracted from skin and blood vessel (Hartshorn et al., 1996), and both protein and message were identified in gastric mucosa and mesentery. Using RT-PCR, SP-D message has also been identified in mouse stomach, heart, and kidney.(Hartshorn et al., 1996)

Structure:

Its structure is based on a triple-helical collagen region and a C-terminal homotrimeric lectin or carbohydrate recognition domain. Four of the homotrimeric subunits of SP-D are assembled via their N-terminal region into a 520-kDa dodecameric structure that can further oligomerise to form multimers. SP-D is found in the endoplasmic reticulum of type II pneumocytes and the secretory granules of Clara cells.(Mori et al., 2002) Fig (1)

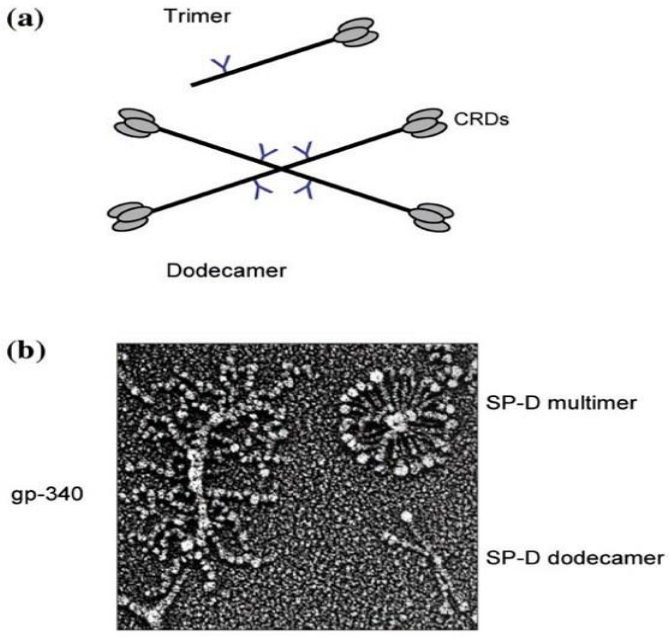

Fig (1) : Molecular structure of SP-D. **(a)** Schematic diagram illustrating the structure of SP-D dodecamers, which consist of four trimeric subunits, and SP-D trimers. **(b)** Quick-freeze deep-etch image of human SP-D dodecamers, SP-D multimers, and the SP-D binding protein gp-340 (kindly provided by John Heuser, Washington University School of Medicine, St Louis, Missouri, USA).(Crouch, 2000)

FUNCTION:

SP-D is a lectin involved in the first line of defense against microorganisms (Leth-Larsen et al., 2003).

SP-D interacts specifically with a wide variety of respiratory pathogens, modulates the leukocyte response to these organisms, and participates in aspects of pulmonary immune and inflammatory regulation(Crouch, 2000) (Table (1)

SP-D binds to and aggregates both gram-negative and gram-positive bacteria, such as Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Streptococcus

pneumoniae, as well as Mycoplasma pneumoniae and influenza A virus (Crouch, 2000) . These interactions can result in aggregation of the microorganisms and altered interaction with host cells. Without microbial ligands, SP-D binds directly to alveolar macrophages (Miyamura et al., 1994) and blood leukocytes and exerts a potent chemotactic effect on neutrophils and monocytes(Cai et al., 1999)

SP-D can influence the activity of phagocytes through CRD-dependent and CRD-independent interactions. At least some of the effects of SP-D result from aggregation with enhanced binding of the agglutinated ligand to their natural 'receptors'. Although the lung is the major site of SP-D expression, it is likely that the protein has more generalized roles in host defense and the acute response to infection and tissue injury (Crouch, 2000).

The infections are associated with increased cytokine and oxidant production and decreased macrophage phagocytosis. However, when the SP-D (/) mice are challenged with influenza A virus a reduced clearance is observed(LeVine et al., 2001). The viral clearance and the cytokine response are normalized by the coadministration of SP-D.

Finally, SP-D is a potent endogenous inhibitor of lipid peroxidation and oxidative cell damage (Bridges et al., 2000), and it has been suggested that it contributes to protecting the lungs from oxidative stress due to atmospheric or supplementary oxygen, air pollution, and inflammatory processes (Leth-Larsen et al., 2003)

Table (1):

Potential functional roles suggested by published studies in vitro and in vivo

Anti-inflammatory	
	Regulation of inflammatory response to microorganisms and microbial products
	' Neutralization' of LPS/altered presentation of LPS to host cells
	Regulation of pulmonary oxidant metabolism
Antimicrobial	
	Enhanced opsonization and killing of some organisms
	Decreased internalization of some intracellular pathogens
	Enhanced microbial agglutination with enhanced physical or cellular clearance
	Enhanced inflammatory response to SP-D/microbial complexes

Altered microbial growth

Immunomodulatory

Decreased proliferative response of lymphocytes to various mitogens

Altered presentation of antigens to specifically sensitized cells

Proinflammatory/repair

Enhanced directed migration or airspace retention of phagocytes

Altered macrophage production of metalloproteinases

Surfactant homeostasis

Altered spatial organization of PI-enriched sub-fractions of surfactant lipid

Normal cellular uptake and metabolism of surfactant lipid

Table (1): (Crouch, 2000)

Pulmonary SPD as a Serum biomarker :

The main site of synthesis of SP-D is the type II cells of the lung, but epithelial cells of an array of different organs also produce SP-D (Madsen et al., 2000). The source of SP-D constitutively found in the circulation is unknown, but it has been speculated that SP-D enter the circulation primarily from the lung. Several pathways have been suggested and different mechanisms may prevail in different disease states(Honda et al., 1995) . Increased permeability of lung vessels is probably a major determinant for increased vascular leakage, particularly in infections. Since SP-D is derived from epithelial cells, it is considered that SP-D levels are reflecting damage to or release of SP-D from epithelial cells due to the inflammatory response.(Leth-Larsen et al., 2003)

Measurement of surfactant protein D in serum :

The concentration of SP-D in serum was assessed with an established enzyme-linked-immunosorbent-assay validated for measurements in serum (Yamasa Corporation, Choshicity, Japan)(Nagae et al., 1997).

SPD and diagnosis for ventilator associated pneumonia:

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection among critical patients and is associated with increased mortality, morbidity and duration of mechanical ventilation (MV) and ICU stay, with an obvious impact on patient management costs. There is still no definitive validated diagnostic gold-standard procedure and early diagnosis of VAP remains a challenge to the intensivist. (Mongodi et al., 2016)

Tekerek et al in their study to detect the most effective biomarker to confirm ventilator associated pneumonia (VAP) , they concluded that serum SPD is the most sensitive biomarker in diagnose of VAP which can be used as an early and organism specific marker for Acinetobacter baumannii and Pseudomonas aeruginosa.(Tekerek et al., 2018)

Also, Said et al. mentioned that analysis of SPD in Broncho alveolar lavage fluid (BAL) would serve as an early biomarker for VAP.(Said et al., 2012)

And according to Saleh et al SP-D seems to be a good predictor for the detection of CAP severity in hospitalized children(Saleh et al., 2022)

Conclusion:

Thus, to conclude that serum SPD can be used as an early diagnostic tool and sensitive biomarker for diagnosis of ventilator associated pneumonia.

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