Editorial

Surfactant Protein D Family: Potential for Diagnosis or Monitoring Therapy in Autoimmune Diseases?

In this issue of *The Journal*, Soto-Cárdenas, *et al* examine the frequency of a genetic polymorphism that is associated with elevated surfactant protein D (SP-D) levels and assess levels in a cohort of 210 consecutive patients with primary Sjögren syndrome (pSS)[1]. They find elevated SP-D levels in patients with severe glandular involvement, hypergammaglobulinemia, leukopenia, and extraglandular manifestations including pulmonary and renal.

A key observation of the Soto-Cárdenas, *et al* report is that elevation of SP-D was found in a subset of pSS patients with interstitial pulmonary involvement (1054 vs 700 ng/ml, $p = 0.029$). This raises the possibility that SP-D may be a marker for early pneumonitis or its progression, as has been suggested in both scleroderma lung disease[2,3] and nonspecific interstitial pneumonitis (NSIP)[4].

They also found significant elevation in a subset with renal disease (1880 vs 716 ng/ml, $p = 0.002$). This finding is potentially of interest, because SP-D elevation has not previously been reported, according to a Medline search, in patients with interstitial nephritis.

Their report presents 3 basic observations.

First, patients with pSS exhibit a polymorphism of the gene encoding the SP-D at roughly the same frequency as found in healthy controls. Thus, elevation of SP-D in their patients with pSS could not be attributed simply to genetic polymorphism. An elevated frequency of the T/T genotype was found in patients with pSS and renal involvement, but the significance of this observation remains unclear, because studies in other renal diseases have not been correlated with SP-D levels or genotype.

The second observation was an elevation of SP-D levels in a subset of patients with pSS and that the elevation correlated with serum immunoglobulin levels as well as leukopenia. This suggests that elevations in patients with pSS are due to immune activation rather than genetic polymorphism.

Third, the most intriguing observation was the association of elevation of SP-D with pulmonary manifestations. This extends previous reports of SP-D elevation in patients with acute respiratory distress syndrome and pulmonary involvement in systemic sclerosis.

Elevations of SP-D were also noted by Soto-Cárdenas, *et al* in their pSS patients with renal disease and severe salivary gland disease, as judged by scintigraphy.

For the general rheumatologist, this observation raises several interesting questions:

- Can elevations of SP-D be used for early detection or monitoring therapy of pulmonary disease in pSS?
- Would addition of other markers such as KL-6, surfactant protein A (SP-A), or monocyte chemoattractant protein provide additional prognostic information, as demonstrated in other articles on interstitial pneumonitis[5]?
- Does the activation of pathways leading to SP-D provide a new target for therapy?

Although SP-D has generally been reported in association with pulmonary disease, these authors also found elevation in patients with severe salivary gland disease and renal disease.

To understand the potential specificity for pulmonary disease, it will be important to determine whether the patients with only severe salivary gland disease or renal disease have elevations that would mitigate the use of SP-D as a marker for lung disease.

SP-D is a member of the collectin family — long known to play a key role in the innate immune system and function in recognition and clearance of microorganisms[6]. SP-D is a receptor located on endothelial cells and antigen presenting cells. Its function is to promote opsonization and clearance of microorganisms, or perhaps cell debris from the necrotic or apoptotic process[7].

In the family of surfactants, SP-A and SP-D have been most thoroughly studied, although gene sequencing indicates the likely presence of additional members of this

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family[7]. In this study by Soto-Cárdenas, only data on SP-A levels and polymorphisms are described.

Previous studies have shown that SP-A or other members of the collectin family are elevated in patients with autoimmune pneumonitis, in comparison to healthy subjects, and that patients with usual interstitial pneumonia had higher levels with NSIP[4]. Highly elevated levels of SP-A were a strong predictor of early mortality in idiopathic pulmonary fibrosis[8].

Closer to home in rheumatology, patients with scleroderma and alveolitis had higher SP-D levels than scleroderma patients free of lung involvement, although other markers such as KL-6 were considered more strongly predictive of disease progression[2,9,10].

The second question we posed in this editorial was whether SP-D could represent a new approach to therapy. Mice made genetically deficient in surfactant had increased mortality, predominantly owing to bacterial infections. Replacement of surfactant greatly improves their outcome in pulmonary disease. SP replacement therapy has been successfully used in premature infants and in lung transplants[11]. Recombinant SP-C has been used in respiratory distress syndrome in infants[12].

However, these respiratory conditions were characterized by diminished levels of SP-D, and the observation in patients with pSS was elevated levels of surfactant. It remains unclear whether the elevations of SP-D are part of the pathogenetic process or an appropriate attempt to heal damage from the pSS inflammatory process. Thus, advances in understanding the pathogenetic role of SP-D, as well as the factors regulating SP-D production, will be required before we can feasibly design therapies to alter levels and perhaps, clinical outcome.

In terms of replacement therapy for SP-D in "smaller" areas of patients with pSS, it is worth remembering that vaginal dryness remains an unmet need. SP-D is detected in the vaginal mucosa and is present in vaginal lavage fluid, where it plays an important role in controlling integrity of the mucosal surface[13]. Although not frequently discussed by rheumatologists in our literature, dyspareunia in patients with pSS is likely to result from oxidative damage and inflammation in addition to decreased fluid lubrication.

Surfactants are known to be secreted by the salivary glands[14] and play a role in controlling gingival infection[15]. In patients with chronic sialadenitis, elevated SP-D serum levels have been reported[16], as confirmed by the Soto-Cárdenas report[1], and may represent the inability of the gland to transport the surfactant to the oral cavity. Thus, replacement therapy in limited surfaces such as the mouth may help to control damage to oral mucosa by improved clearance of microorganisms and control of oxidative damage.

The article by Soto-Cárdenas, *et al* brings to rheumatologists' attention the potential of SP family members for diagnosis or monitoring therapy. We will need to determine whether SP-D can be used as a specific marker for occult pulmonary (or renal) disease.

The title hints for an "etiopathogenic" role for SP-D in pSS. Based on available data, it is too early to tell whether SP-D or other members of the collectin family are playing pathogenetic roles. Elevations of SP-D may be appropriate responses to damage initiated by other pathways.

However, the data presented on SP-D in pSS, as well as prior data in scleroderma and NSIP, suggest an important role for SP-D in detection of subtle extraglandular involvement or as a potential marker for monitoring therapy.

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