CRITICAL CARE

COMMENTARY

Surfactant protein genetics in community-acquired pneumonia: balancing the host inflammatory state

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See related research by García-Laorden *et al.*, http://ccforum.com/content/15/1/R57

Abstract

Community-acquired pneumonia is a common disease. Abnormalities in the first step of host defense may severely compromise subsequent steps of successfully combating infections. In the previous issue of *Critical Care*, García-Laorden and colleagues reported genetic associations between single-nucleotide polymorphisms and haplotypes of the surfactant proteins with susceptibility, severity, and outcome of community-acquired pneumonia. Although the limited information shows regulatory differences among variants, it is currently unknown how the difference in surfactant protein A genotypes in this and other studies affects the individual's phenotype. The lung is continually exposed to a host of irritants yet maintains health. It is plausible that, under physiologic conditions, surfactant protein A, in addition to having a dominant effect on anti-inflammatory processes, mediates a low level of proinflammatory processes that are essential for the health of the lung. Understanding the maintenance of the balance of the inflammatory state may be one of the keys to understanding pulmonary disease progression.

Community-acquired pneumonia (CAP) is a common cause of intensive care unit admission and can lead to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS), major causes of mortality after CAP. At present, treatment is supportive, and determining which patients will have a higher likelihood of disease severity is not possible. In the previous issue of *Critical Care*, García-Laorden and colleagues [1] attempted to begin to unravel the complex gene-environment interactions in a syndrome whose progression is felt to be multifactorial. The authors should be commended for this work. Determining who is more likely or less likely to develop CAP, develop ARDS and MODS after CAP, or die from this infection is an important endeavor. Innate immunity clearly plays an important role. Abnormalities in the first step of host defense may severely compromise subsequent steps of successfully combating infections. The hope is that novel therapies can target these most susceptible patients, even before the downstream clinical events fully develop. However, before this next step may be taken, certain limitations of the present study require further work. Of paramount importance is whether the results of this study are generalizable to populations other than a relatively homogeneous Spanish Caucasoid group. Before studies such as the present one can be universally accepted, they require validation in a distinct group of individuals.

The authors reported genetic associations between single-nucleotide polymorphisms of the surfactant proteins, as well as haplotypes encompassing these genes, with susceptibility, severity, and outcome of CAP. Several associations remain significant even after stringent multiple comparison corrections. These findings are not surprising, given the important role of innate immunity in host defense. There are a significant number of studies in which associations of genetic variants of surfactant protein A (SFTPA) 1, SFTPA2, and SFPD with disease susceptibility have been identified and these cover the entire life span, from birth and childhood through adulthood [2]. Owing to their extensive complexity, the SFTPA genes, in particular, provide a good model with which to study disease susceptibility and severity. The extensive complexity makes it a challenge to fully understand and interpret any associations made (including those in the present study) but at the same time provides an opportunity to learn about disease pathogenesis. At present, although some insight into mechanisms underlining differential regulation of the different variants in response to various insults such as bacteria or oxidative stress (or both) has been gained [3-7], this knowledge is still in the early stages and is insufficient for assessing how the difference in SFTPA

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genotypes in this and other studies affects the individual's phenotype or for contemplating therapeutic points of interventions based on SFTPA genotype.

The authors clearly appreciate the dual role of SP-A, its ability to promote proinflammatory processes in response to pathogens or other insults, and its ability, under 'basal' conditions, to suppress nuclear factor-kappa-B (NF-κB) activation and inflammation. However, we would like to raise the point that even under 'basal' physiologic conditions (that is, in the absence of an overbearing pathogen load), the lung is exposed daily to hundreds of thousands of irritants (for example, bacteria, viruses, pollen, and toxins) yet the lung maintains a healthy status. We would like to put forward the idea that, under physiologic conditions, SP-A, in addition to having a dominant effect on anti-inflammatory processes, mediates a low level of proinflammatory processes that are essential for the health of the lung. Several *in vitro* studies have shown the ability of SP-A, in the absence of pathogens, to generate a low-level proinflammatory response [8-16]. It is possible that the SP-A-mediated proinflammatory activity (high or low levels) is 'context-dependent' and reflects the magnitude of the threat. Whether the mechanisms of this proinflammatory activity at low physiologic level overlap with or are completely different from those of the high-level activity generated in the presence of high-load pathogens or other irritants remains to be determined.

The collective data, including the data from this study of the association of surfactant proteins with disease risk, beg for a better understanding of the functional and regulatory differences among common and rare SPFTA variants. Understanding the underlining regulatory control differences among SPFTA variants could identify points amenable to therapeutic intervention, which could lead to treatment options that are truly individualized to the patient's genotype. The ultimate goals, once the mechanisms by which these genetic differences influence outcome have been determined, would most likely be to develop novel technologies that will allow the addition of SP-A (or even a specific SP-A variant) and SP-D into exogenous surfactant preparations (similar to SP-B and SP-C formulations that are presently being tested) and to target a group of individuals based on both their etiology of lung disease (that is, infection) and their individual genotype.

Abbreviations

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; MODS, multiple organ dysfunction syndrome; SFTPA, surfactant protein A.

Competing interests

NJT serves as a consultant and is a member of the Advisory Board for Discovery Laboratories, Warrington, PA. JF has no competing interests.

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