Published in final edited form as:

J Pediatr. 2010 March ; 156(3): . doi:10.1016/j.jpeds.2009.11.040.

The Pulmonary Collectins and Respiratory Syncytial Virus: Is There a Clinical Link?

Paul S. Kingma, MD, PhD and Jeffrey A Whitsett, MD

Section of Neonatology, Perinatal and Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

More than a decade of basic science research suggests that the pulmonary collectins, surfactant protein A (SP-A) and D (SP-D), are critical components of the lung innate immune system. Mouse models of collectin deficiency indicate that SP-A and SP-D are required for normal clearance of a variety of pulmonary pathogens such as respiratory syncytial virus (RSV) and that if infection occurs in the absence of these proteins, the lungs fill with host immune cells that release excessive amounts of inflammatory cytokines, oxygen radicals, and metalloproteinases. Despite the considerable innate immune defects that are associated with SP-A or SP-D deficiency in animal models, we have yet to find susceptibility to pulmonary infection that is clearly caused by mutations in either of these genes.

Previous studies of genetic modifiers of RSV pathogenesis have focused on candidate genes involved in either viral activities (ie, attachment, fusion, replication, and clearance of the virus) or the response of the host immune system.¹ Because of the role of collectins in both RSV binding/clearance and the regulation of host defense cells, several groups have hypothesized that polymorphisms of the SP-A (*SFTPA*) or SP-D (*SFTPD*) genes would be associated with increased susceptibility or resistance to RSV infection. To this point, the Finnish group led by Mikko Hallman found that the SP-A2 allele 1A³ was present in 5% of infants infected with RSV when compared with 0.5% of healthy control infants.² Specifically, their analysis suggested that substitution of lysine for glutamine at position 223 (part of the SP-A binding domain) was overrepresented in RSV-infected patients, suggesting that this change in SP-A inhibited normal SP-A activity. Analysis of polymorphisms within the SP-D gene found that 72% of infants infected with RSV had methionine at position 11, whereas this allele was found in only 61% of healthy control infants.³ Although these results are intriguing, both of these studies compared hospitalized infants infected with RSV with healthy uninfected control infants. Therefore, even though the authors controlled for RSV exposure variables such as day care, tobacco exposure, and number of siblings, these studies were confounded by the numerous variables that contribute to the exposure and acquisition of RSV infection (eg, hand-washing). In addition, it is difficult to accept that the SP-D methionine 11 allele is abnormal when it is present in 61% of the population. At best, these studies can claim that these polymorphisms are associated with a risk of acquiring RSV infection, but they do not address the severity of the clinical illness resulting from the infection. Considering that most infants are infected with RSV during the first year of life and virtually all infants are infected by their second birthday, predicting which infants are at risk for RSV infection is not useful because all infants are at risk.⁴ The clinically important and biologically relevant question is, once an infant is exposed to RSV and the infectious

process is set in motion, are distinct polymorphisms in SP-A or SP-D associated with a worse clinical outcome?

In this issue of *The Journal*, El Saleeby et al⁵ took a unique approach to examining SP-A polymorphisms. Rather than comparing RSV-infected infants with healthy control infants, their study population included only infants infected with RSV. Within this infected population, they examined the associations between polymorphisms within the surfactant protein A2 gene and clinical markers of disease severity (hospital admission, intensive care unit admission, need for mechanical ventilation, and length of hospital stay greater than 4 days). Although their study design prohibited the analysis of the effect of SP-A on the early stages of RSV infection, it did allow the authors to eliminate the confounding variables of RSV acquisition that severely limited previous studies. Within this population, homozygosity for the 1A⁰ allele was protective against hospitalization (OR = 0.15, CI: 0.05 to 0.47), whereas patients homozygous or heterozygous for asparagine at amino acid position 9 were 2-fold more likely to need intensive care, mechanical ventilation, or hospitalization for longer than 4 days.

From a biological perspective, it is interesting that the authors detected an association between asparagine at position 9 and RSV infection severity but not an association with the previously reported amino acid positions 91 and 223. Because asparagine 9 is within the SP-A signal peptide, it is highly possible that this mutation may affect secretion and/or assembly of the SP-A multimer, which, in turn, may reduce levels of fully assembled SP-A in the lung. Future experiments that measure alveolar levels of SP-A in these patients should test this hypothesis. The discrepancy between the current study and previous reports by the Finnish group may be explained by differences in study design and sample population; however, it may also suggest a biological distinction of SP-A activity in RSV acquisition versus RSV disease severity. It is also important to note that the *SFTPA* and *SFTPD* genes are in close proximity to a chromosomal region known as the collectin locus. Therefore, the changes in RSV disease severity that were associated with SP-A in the current and previous studies may be due to linkage to other genes that regulate the innate immune system that are located in the collectin locus.

From a clinical perspective, the authors argue that identifying patients with asparagine at position 9 “could potentially influence clinical decision-making, as carrier infants may benefit from preventive measures (eg, administration of preventive passive antibodies) or aggressive early antiviral support currently in development.” Although physicians are more likely to consider their clinical assessment rather than the genotype when determining the immediate plan of care of an infected infant, the SP-A genotype may be a useful indicator for determining which infants receive preventive measures. The American Academy of Pediatrics uses RSV risk factors such as prematurity, chronic lung disease, congenital heart disease, child care, age, and siblings to determine which infants receive Palivizumab. Although, the authors’ data do not compare the relative clinical value of SP-A genotype versus these known RSV risk factors, with the support of additional studies, SP-A genotype may be added to the list of indications for Palivizumab in future academy policy statements.⁴

In summary, El Saleeby et al provide the strongest evidence to date to associate the activity of pulmonary collectins and RSV infections in infants. In addition, they have described a potentially useful genetic marker that may help predict which infants are at greatest risk for severe RSV infections. Although their findings support a strong association, studies of larger patient cohorts across diverse populations are still needed. At present, we can only say that we think there is a link.

Glossary

RSV	Respiratory syncytial virus
SP-A	Surfactant protein A
SP-D	Surfactant protein D
HbF	Percent fetal hemoglobin
SCA	Sickle cell anemia

References

1. Miyairi I, DeVincenzo JP. Human genetic factors and respiratory syncytial virus disease severity. *Clin Microbiol Rev.* 2008; 21:686–703. [PubMed: 18854487]
2. Lofgren J, Ramet M, Renko M, Marttila R, Hallman M. Association between surfactant protein A gene locus and severe respiratory syncytial virus infection in infants. *J Infect Dis.* 2002; 185:283–9. [PubMed: 11807709]
3. Lahti M, Lofgren J, Marttila R, Renko M, Klapavuniemi T, Haataja R, et al. Surfactant protein D gene polymorphism associated with severe respiratory syncytial virus infection. *Pediatr Res.* 2002; 51:696–9. [PubMed: 12032263]
4. Policy Statement: Modified recommendations for use of Palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics.* 2009 In press.
5. El Saleeby CME, Li R, Somes GW, Dahmer MK, Quasney MW, DeVincenzo JP. Surfactant protein A2 polymorphisms and disease severity in a respiratory syncytial virus infected population. *J Pediatr.* 2010; 156:409–14. [PubMed: 19914637]