

Lungs and genetics: RDS and alveolar proteinosis

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There are multiple factors contributing to respiratory failure in the newborn. These include genetic variations, inherent conditions such as gender and prematurity, and environmental conditions including inflammation, glucocorticoid therapy, oxygen and MV. Interactions between these factors are also likely to increase the incidence and/or severity of RDS in infants.

Preterm infants are particularly susceptible to RDS as the final stages of lung maturation do not occur until after 36 weeks gestation. In particular, alveolar lung development occurs during a later stage of gestation than canalicular and saccular development; this correlates with a reduced risk of RDS with increased duration of gestation.

Genetics of neonatal RDS

Molecular and developmental biology can be used to identify candidate genes for neonatal respiratory disease. These genes are likely to be important or critical for at least one of the following processes:

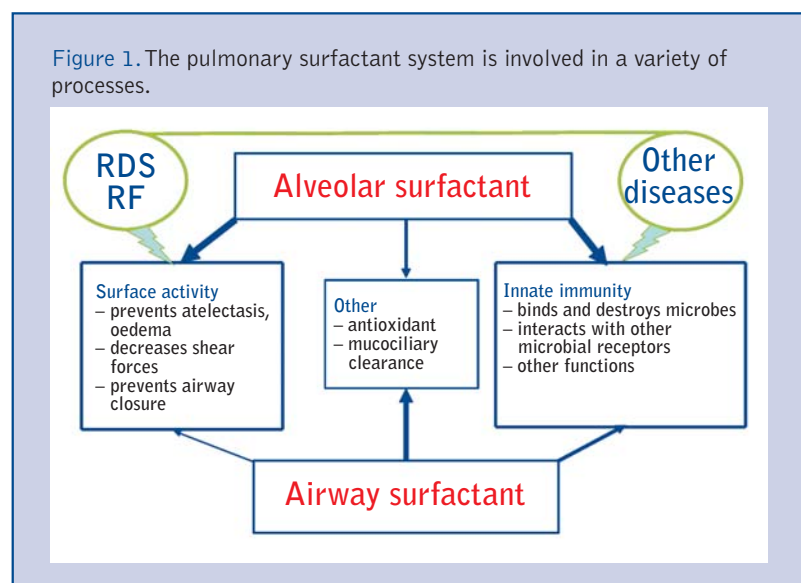
- embryology, lung growth, airway branching, pulmonary angiogenesis;
- surfactant function;
- lung fluid clearance;
- immunity, pro- and anti-inflammatory functions;
- oxygen toxicity, antioxidant function;
- maintenance of water homeostasis;
- vascular reactivity and airway reactivity.

Of these processes, the best studied is pulmonary surfactant function, which is the focus of this presentation. Surfactant genes have a variety of different activities (*Figure 1*).

Mutations in the genes encoding the hydrophobic surfactant proteins SP-B and SP-C and the ABCA3 transporter disrupt alveolar function and cause RDS and/or interstitial lung disease, as discussed earlier. The current presentation focuses on the involvement of the genes for the hydrophilic surfactant proteins SP-A and SP-D, and their interaction with other genes and conditions, in the development of neonatal RDS.

Structure and function of hydrophilic surfactant proteins

SP-A and SP-D are collectins, consisting of collagen plus lectin. Although both are present in pulmonary surfactant, the absence of SP-A or SP-D does not cause neonatal respiratory failure. The SP-A and SP-D genes are located on



chromosome 10. Each has multiple polymorphisms, and it is possible that this may be important during inflammatory stress.

SP-A has a role in both surfactant function and innate immunity. In primates, the SP-A protein is encoded by two genes, SP-A1 and SP-A2, although the reason for this is unknown. SP-A exerts immune activity through the binding and aggregation of microbes, promotion of phagocytosis and generation of cytokines. Its absence is associated with inflammation and infections, particularly group B streptococcal and RSV infection. Despite its involvement in surfactant secretion, the absence of SP-A does not cause respiratory failure after term birth. Like SP-A, the SP-D protein also binds and aggregates microbes and promotes phagocytosis. It also promotes anti-oxidant and anti-inflammatory functions. SP-D can have pro-inflammatory or anti-inflammatory activity, depending on its molecular orientation. The absence of SP-D leads to increased susceptibility to infection, emphysema and alveolar proteinosis. However, SP-D deficiency has not been associated with RDS or TTN.

Interactions between gene mutations and other factors produce lung disease

The major SP-A haplotype that produces susceptibility to RDS is not due to a structural change in protein, but rather an insertion in the 3' untranslated region (UTR) is likely to affect transcription or stability of the mRNA, possibly influencing the induction of SP-A during neonatal development. However, the mechanism for this is unknown. An interaction between SP-A and SP-B genotypes in the development of RDS has been observed, with the association of SP-A1 6A²/6A² to RDS being dependent on the SP-B Ile/Thr genotype (Figure 2).^[1-11] This allelic variation in SP-B affects the processing of the precursor protein and also post-translational processing, sorting and secretion of the SP-B protein, as N-terminal glycosylation occurs with the Thr allele, but not Ile, at Asn129. Mutations in the SP-A1 and SP-A2 genes are associated with increased susceptibility to RDS in preterm infants, but do not appear to have the same effect in near-term infants. This may be due to problems with SP-B processing during the increased perinatal stress associated with preterm birth. In preterm infants, the SP-A1 6A²/6A² variant is associated with a significantly increased risk of RDS only in those homozygous for the Thr/Thr genotype of the SP-B Ile131Thr variation. However, in infants born after >32 weeks gestation, no increased risk of RDS was observed.^[5] Interestingly, the effects of this genetic interaction also differ between singleton and twin births, with an increased RDS risk observed only in singleton births.^[5]

SP-A, SP-D gene polymorphisms affect infection risk

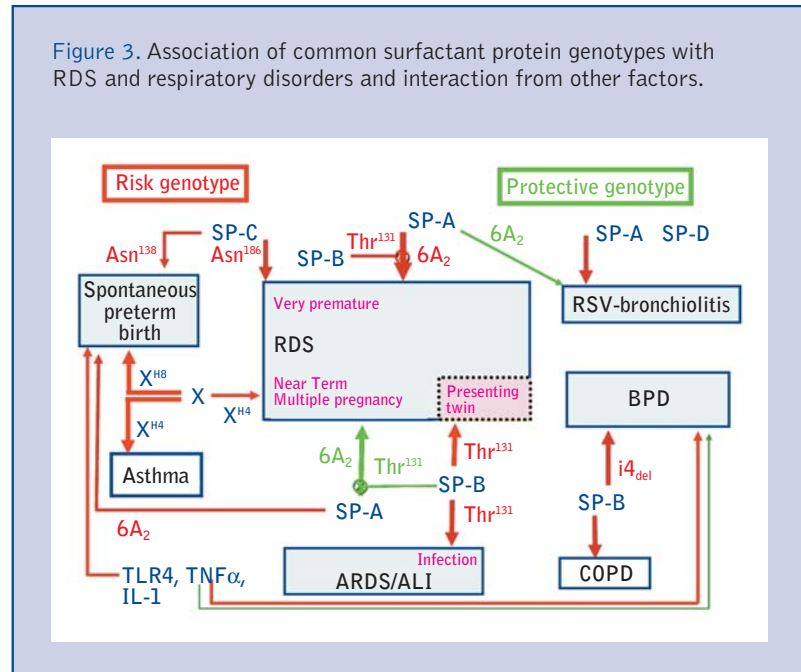
In addition to effects of interaction between SP-A and SP-B on the risk of RDS, exonic SP-A alleles influence susceptibility to severe RSV infection in early infancy. Individuals with the Lys223 SP-A2 allele may be predisposed to severe RSV bronchiolitis, and this allele may also be less effective than Gln223 in binding and aggregating RSV. Similarly, the Pro91 allele of SP-A2 protects from severe RSV infection. In the case of SP-D, the Thr11 allele and the Met11Thr genotype are protective against severe RSV bronchiolitis in early infancy.^[12] However, the Met11 allele protects against tuberculosis in a different population.^[13] It appears that certain forms of the SP-D protein are more or less effective in the binding and aggregation of different pathogens.^[14]

Figure 2. Genetic susceptibility to RDS and TTN varies according to surfactant protein haplotype.

Gene	Allele/Haplotype	Disease No risk	Gene/environment/Constitution: test	Reference
SP-A1	Hplt 6A2	RDS+	<ul style="list-style-type: none"> • SP-B 131 Thr • TDT • Near term twin 	Ramet 2000, Floros 2001 Haataja 2000 Haataja 2001 Marttila 2003
	Hplt 6A2	RDS+		
	Hplt 6A2	RDS+		
	Hplt 6A2	RDS-		
		protection		
SP-A2	Hplt 1A0	RDS+	<ul style="list-style-type: none"> • SP-B 131 Thr • Near term twin 	Kala 1998, Ramet 2000 Haatoja 2000 Marttila 2003
	Hplt 1A0	RDS+		
	Hplt 1A0	RDS-		
		protection		
SP-B	ΔI4del/ins	RDS+?	Race?	Floros 2001
	ΔI4del/ins	S-RDS+		Makri 2002
	131 Thr	RDS+	Presenting twin	Marttila 2003
	131 Thr	RDS+	Small preterm	Rova 2004
	Heteroz 121ins2	TTN-		Tutdibi 2003
SP-C	186 Asn, 138 Asn Mutations	RDS+	<ul style="list-style-type: none"> • Very preterm, ♀ • Term ♀ 	Lahti 2004, Rova 2004 Bullard 2005
		RDS+		

Impact of genotype on respiratory disease risk

As discussed previously, the absence of the critical surfactant proteins SP-B and SP-C or ABCA3 causes respiratory disease in newborns. However, it has also been shown that allelic variation in other genes expressed in the distal lung epithelium is associated with susceptibility to common, multifactorial lung diseases in early infancy. Moreover, interactions between these genotypes and additional constitutional, environmental or genetic factors may also contribute to the development of lung disease in infants (Figure 3).



Interactions complicate lung disease genetics

Determination of the genetic basis of lung disease is complicated by the interaction between multiple genes, and the fact that RDS is a syndrome but not, strictly speaking, a single disease. Multiple factors affect the development of neonatal respiratory disease, including the degree of prematurity, multiple birth, birth order and gender. In addition, the placenta and the foetal lung interact closely during the antenatal and intranatal periods. Better understanding of the molecular genetics of rare pulmonary diseases and improved use of bioinformatics may enable such diseases to be prevented through genetic counseling and/or foetal medicine, and may also facilitate the development of rapid diagnostics and new treatments. This research is also likely to be applicable to more common respiratory diseases.

References

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