Commentary: Surfactant protein A and D polymorphisms: Personalized medicine or a day at the SP-A

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In this issue of the *Journal*, Aramini and colleagues¹ report that human donor lung slices carrying the surfactant protein A2 (SP-A2) gene allele 1A0 (*SP-A2*1A0*) have greater expression of SP-A than do those with other alleles when treated with methylprednisolone. They previously found that SP-A and SP-D levels in bronchoalveolar lavage were associated with lung allograft dysfunction. They propose that SP-A polymorphisms could be used to personalize immunosuppressive regimens after lung transplant.

Although previous work on steroid regulation of SP-A expression has been performed in NIH-441 cells, the use of an immortal papillary adenocarcinoma cell line may not recapitulate findings in normal type II alveolar cells in donor lungs. In addition, the genotype 6A46A4/1A51A5 found in NIH-441 cells is uncommon and is not represented in the donor lung slices evaluated in this study by Aramini and colleagues¹ or in 42 lung allografts evaluated in another study by their group.² Why not focus on the 16 human donor lung slices that more accurately represent the available genotypes in the lung donor population? Kumar and associates³ also found that SP-A genes were regulated differently in H441 cells than in fetal lung explants. In the current study, Aramini and colleagues¹ found that while SP-A levels were dose responsive to methylprednisolone in NIH-441 cells, SP-A levels were not dose responsive in human donor lung slices.

Although Aramini and colleagues¹ state that SP-A2 messenger RNA (mRNA) expression is stimulated by methylprednisolone, others have found a decrease in SP-A mRNA expression with steroids.³ Wang and colleagues⁴ found a decrease with all polymorphisms, including a significant decrease with *SP-A2*1A0*, in response to dexamethasone. Hoover and Floros⁵ found that dexamethasone had an inhibitory effect on surfactant SP-A1 and SP-A2 expression, but the inhibitory response was less for the 6A2 and 1A0 alleles. Although the current study by Aramini and colleagues¹ found increased differential expression of SP-A and SP-D proteins with *SP-A2*1A0* after methylprednisolone,

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Central Message

Although it is interesting to suggest that donor pharmacogenetics should be considered, further research is needed to determine whether SP-A polymorphisms can be used to tailor immunosuppression.

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one of the coauthors previously reported that *SP-A2*1A0* was associated with low SP-A mRNA levels with a higher frequency in respiratory distress syndrome.⁶ Kala and co-workers⁷ also found that the 6A26A2/1A01A0 genotype was associated with low to moderate levels of SP-A mRNA.

Further research will be needed to clarify the mechanism behind how these polymorphisms affect SP-A and SP-D expression in the donor lungs. It is also unclear how an allele of the gene for SP-A2 affects mRNA expression of the genes for SP-A1 and SP-D. A recent study found that the gene for SP-A2 influences the expression of multiple micro-RNAs, which may then regulate SP-A and SP-D expression.⁸ Other studies have also speculated that normal lung function may depend on the ratio of SP-A1 to SP-A2 and not on the total levels of SP-A.⁹

Whether immunosuppression can be titrated based on the basis of SP-A polymorphisms remains unclear. Although surfactant may have an important role, steroids have multiple other effects that are not reflected by SP-A levels, including inhibiting transcription of interleukins and tumor necrosis factor α and interferon γ and cytokine production. It is interesting to suggest that donor pharmacogenetics should be considered; however, further research is needed to determine whether these results can be used as the basis of tailored immunosuppression or personalized medicine remains a dream, a day at the SP-A.

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