INTERSTITIAL LUNG DISEASE

Autoimmune Attack Takes Your Breath Away

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Autoimmune targeting of a lung-specific protein can cause interstitial lung disease (Shum et al., this issue).

How to best manage interstitial lung disease (ILD) is a contentious issue, one involving multidisciplinary, and often divisive, discussion between pulmonologists, rheumatologists, and radiologists. This is because the cause of ILD—a diverse group of disorders in which the connective tissue of the lungs becomes inflamed and fibrotic—is often unclear and its different forms ill-defined (1). Some forms of ILD are relatively straightforward, arising from an infection or from exposure to certain drugs or hazardous materials. Other forms are known to develop in association with autoimmune diseases called connective tissue disorders (CTDs), yet their precise etiology remains elusive. Even more perplexing are the forms of ILD deemed idiopathic, although these cases sometimes turn out to be an early manifestation of CTD-associated ILD (CTD-ILD). Because CTD-ILD occurs in the setting of systemic autoimmunity, and even idiopathic ILD may be associated with signs of autoimmunity, there has been much debate about a possible role for autoimmunity in the pathogenesis of ILD (1–7). But no autoimmune mechanism has been evinced—until now. In this issue of Science Translational Medicine, Shum and colleagues (8) show that in a subset of CTD-ILD and idiopathic-ILD cases, autoimmune targeting of a lung-specific protein may be at the root of the disease.

A LUNG-SPECIFIC AUTOANTIGEN

Indirect evidence for an autoimmune etiology of ILD has come from the detection of immune-cell infiltrates in the lungs and autoantibodies in the blood and bronchoalveolar lavage fluid, not only in CTD-ILD but surprisingly also in idiopathic ILD (1–6). Moreover, in idiopathic ILD certain autoantibodies appear to be associated with more severe disease (6) or with acute exacerbation of disease (4). However, none of these autoantibodies targets lung-specific proteins, so it is unclear whether their presence simply reflects the systemic autoimmunity underlying the associated CTD in CTD-ILD and how they could cause disease that is limited to the lungs in idiopathic ILD. Some insight into this conundrum might be gleaned from studies on lung disease that develops in patients with autoimmune polyendocrine syndrome type 1 (APS1), a rare autoimmune disorder. Almohammadi et al. (9) showed that APS1 patients with respiratory symptoms have autoantibodies to KCNRG, a potassium channel–regulating protein preferentially expressed in the bronchiolar epithelium. Finding that loss of immune tolerance to BPIFB9 (also known as vomeromodulin) can cause ILD-like lung pathology in mice, Shum et al. (7) used this information to identify autoantibodies to the related lung-specific protein BPIFB1 (BPIFB9 is a pseudogene in humans) in a patient with APS1-ILD.

In this issue of Science Translational Medicine, Shum et al. (8) broaden their scope, shedding light on the relevance of autoimmunity to the pathogenesis of the more common and inescrutable forms of ILD. They started once more by studying APS1-ILD but then extended their findings to CTD-ILD and idiopathic ILD. Because APS1 involves production of autoantibodies to organ-specific antigens and is a well-characterized monogenic disorder caused by defects in the autoimmune regulator (AIRE) gene, the authors reasoned that studying autoimmune responses in patients with APS1, as well as in mice with an equivalent defect in Aire, would yield mechanistic insights into the pathogenesis of ILD that have so far been lacking—and, importantly, answer the question of whether autoimmunity can cause ILD.

The authors previously detected autoantibodies to BPIFB1 in the blood of a single APS1 patient (7). In the new study (8), they screened a large cohort (n = 104) of APS1 patients with and without ILD and found that BPIFB1 autoantibodies were present in the blood of only a small proportion of the total cohort of APS1 patients but were present in all six of the APS1 patients with ILD. Shum and colleagues then showed that expression of human BPIFB1 is restricted to the lungs and thymus. This expression pattern is telling because the way in which AIRE promotes immune tolerance is by orchestrating the ectopic expression of tissue-specific antigens in the thymus, brokering an encounter between them and maturing T cells; this process—called central tolerance—results in the purging of potentially dangerous T cells that react too strongly with these antigens (10). These new findings (8) suggest that BPIFB1 is a lung-specific protein that normally enjoys AIRE-mediated protection from autoimmune attack, protection that is compromised in APS1. Indeed, in immunofluorescence experiments, antibodies in APS1-ILD serum bound to BPIFB1 present in human bronchiolar epithelium (Fig. 1). Together, these findings identify BPIFB1 as a lung-specific autoantigen in APS1-ILD.

The authors next showed that BPIFB1 autoantibodies were also present in a subset of patients with CTD-associated ILD—and even in a subset of patients with idiopathic ILD (Fig. 1) (8). These autoantibodies were not present in healthy individuals, nor in patients with type I diabetes, an autoimmune disorder that does not feature lung pathology—indicating that the autoantibodies are not simply a general biomarker of systemic autoimmunity but rather an indicator of lung-specific autoimmunity in diverse types of ILD.

PROVING CAUSATION

Yet, association does not prove causation. To demonstrate that autoimmune targeting of a BPIFB protein is not only associated with ILD but can actually cause it, Shum et al. (8) performed mechanistic experiments with the Aire−/− mouse model of APS1. They showed that autoantibodies to BPIFB9 [previously identified as a lung-specific autoantigen in mice (7)] served as molecular indicators of the presence and severity of lung disease in Aire−/− mice. In some diseases, autoantibodies can themselves inflict damage, whereas in others, they are an epiphenomenon of pathogenic T cell responses elicited by the same autoantigen. In this case, it was BPIFB9-specific CD4+ T cells, rather than the autoantibodies to BPIFB9, that caused ILD when transferred to immunodeficient mice. Thymic transplantation experiments
showed that BPIFB9-specific autoimmunity
and lung disease developed in mice with
Aire−/− thymi but not in those with Aire+/−
thymi, confirming that defects in central
tolerance to a lung antigen can cause ILD.

However, it is BPIFB1, not BPIFB9, that
is targeted in human ILD, and most cases
of ILD—those not linked to APS1—are not
associated with a known defect in AIRE.
Shum et al. (8) therefore used a different
mouse model to determine whether a break
in tolerance could result in BPIFB1 target-
ing and, hence, ILD. Because Bpifb1−/− mice
have not previously encountered BPIFB1,
they have not developed immune toler-
ance to this protein, so that immunization
of these mice with BPIFB1 induces anti-
BPIFB1 immune responses. Transfer of
BPIFB1-specific lymphocytes from BPIFB1-
immunized Bpifb1−/− mice to lymphocyte-
deficient Bpifb1+/+ mice induced ILD in the
recipient mice, indicating that autoimmune
targeting of BPIFB1—indeed of a de-
fect in Aire—can also cause ILD.

QUESTIONS AND CLINICAL IMPLICATIONS

Thus, by using a well-characterized but rare
disorder as a starting point, Shum et al. (8)
demonstrated that lung-specific autoimmu-
nity may cause ILD associated with more
common diseases, as well as ILD so far
deemed idiopathic. This exciting finding
increases our understanding of ILD and raises
a slew of questions:

How do the autoantibodies to BPIFB1
arise in CTD-ILD and idiopathic ILD? Do
they arise as a result of unknown AIRE de-
fects that are subtler than those in APS1, or
as a result of AIRE-independent defects in
peripheral tolerance (which complements
central tolerance), or both? With this in
mind, do Aire−/− mice with ILD develop au-
toantibodies to BPIFB1, in addition to auto-
antibodies to BPIFB9? Do ILD patients with
autoantibodies to BPIFB1 have BPIFB1-
specific T cells in their lungs? What is the
relationship between autoantibodies to
BPIFB1 and the other ILD-associated au-
toantibodies identified, especially the lung-
specific autoantigen KCNRG (9)? Are they
present in the same or in distinct patient
subsets? What causes CTD-ILD and id-
idiopathic ILD in patients who do not have
autoantibodies to BPIFB1? Is the ILD of
autoimmune origin in these patients as
well, involving targeting of a different lung
autoantigen, or is it not autoimmune but
rather the result of unrecognized exposures
or other factors? Might autoimmunity even
contribute to yet other forms of ILD? For
example, in infection-triggered ILD, protec-
tive immune responses could conceivably
segue to pathogenic autoimmune responses
through cross-reactivity. What other so-
called idiopathic diseases might in fact be
autoimmune in origin?

The findings also have important implica-
tions for disease management. Although it
remains to be tested in an independent pa-
tient cohort, the ability of autoantibodies
to BPIFB1 to identify autoimmune-driven ILD
could prove transformative. A biomarker
enabling identification of individuals whose
ILD is of autoimmune origin would allow
more effective management of their pul-
monary disease, by indicating the need for
immunomodulatory treatment. Indeed, id-
idiopathic ILD has, in general, a worse prog-
agnosis than CTD-ILD, possibly because in-
dividuals with CTD-ILD are more likely to
be treated with immunosuppressive drugs
(aimed at tackling the autoimmunity under-
lying CTDs) (1). Perhaps autoantibodies to
BPIFB1 will also prove useful as biomarkers
that predict the onset or progression of ILD,
which would allow for preventive interven-
tions. Moreover, if BPIFB1 is indeed a critical
lung autoantigen, development of antigen-
specific tolerizing therapies for autoimmune
ILD becomes a possibility. Even if the prom-
ise of biomarker tests and tolerizing therapies
based on BPIFB1 is not borne out, the find-
ings by Shum et al. substantiate the idea that lung-directed autoimmunity can cause ILD. Thus, the stage is set for further dissection of the role of autoimmunity and the benefit of immunomodulatory treatment in ILD, as well as the classification of ILD on the basis of mechanism rather than association.

REFERENCES AND NOTES

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