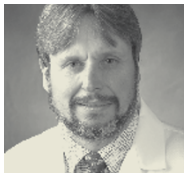
PERSPECTIVE



Clues, not conclusions

Scientists have some way to go before they can prove that COPD should be treated as an autoimmune disease, says **Steven R. Duncan**.

Chronic obstructive pulmonary disease (COPD) has many enigmatic traits. A progressive respiratory disorder that causes severe breathing difficulties, it can worsen even after patients stop smoking, may flare up unpredictably without apparent cause, and is often associated with other medical conditions such as atherosclerosis, osteoporosis, renal dysfunction and cancer. Many characteristics of COPD could be attributable to pathologic autoimmune processes[1]. And there are increasing numbers of reports that autoantibodies against many different lung proteins are often present in COPD patients[2,3].If the underlying cause of COPD were indeed autoimmunity, new treatments might improve quality of life for patients.

Nonetheless, scepticism about the role of autoimmunity in COPD still abounds and is probably justified, albeit with several qualifications.

Some of the uncertainty may be explained by the nuanced and complex biology of autoimmunity[4]. Low-level reactivity to most (or maybe even all) of the body's own proteins is common, and is probably critical in preventing the immune system from mistakenly launching an injurious inflammatory response against our own cells and tissues. But in several studies, patients diagnosed with certain diseases, including COPD, have shown significantly higher levels of one or more antibodies that bind to the body's own proteins, compared to demographically matched healthy people. These findings are generally considered evidence of autoimmunity.

Several investigators have used variations of this approach to identify a "COPD autoimmune response." The increasing availability of high-throughput antigen array chips that can detect the presence of autoantibodies against thousands of proteins simultaneously, and the ease by which antigen-specific autoantibodies can be discovered, may soon spur a profusion of similar studies.

However, not all of these autoantibodies should be considered pathogenic, even if their presence is abnormal. The problem lies in understanding whether a particular one causes or contributes to disease.

Autoimmunity often develops as a consequence of chronic inflammation caused by distinct disease processes[4]. In all but a few cases, it is unknown how or why initial, narrowly targeted, and appropriate immune responses become misdirected to attack normal tissues and cause disease. One plausible explanation goes that in COPD patients, host defences triggered by microbial infection of the airways promote the development of autoimmune responses[1,2]. The tobacco smoke that is the number-one risk factor for COPD in industrialized societies is a complex mix of highly reactive chemicals that can modify native proteins. These modified proteins may no longer be recognized as 'self' by the immune system, and can be targeted by an immune response[3].

Most autoantibodies have no apparent pathogenicity. A few, however, are profoundly pathogenic and cause severe tissue damage[4]. The trick for researchers is to determine whether observed autoimmune responses are actually pathogenic, or simply abnormal and harmless. Many studies have found links between autoantibodies and the severity of COPD. That's a good start. But because underlying inflammation could be proportionally driving harmless (epiphenomenal) autoimmune responses, it is a less than wholly compelling explanation. Some researchers maintain that particular COPD autoantibodies can be meaningful only if they are not associated with other diseases. In reality, however, fundamental immunologic processes are often shared among very different clinical syndromes. Hence, the presence of a superficially similar autoantibody in two or more clinical syndromes says little about the pathogenicity in any one of those diseases. Someday someone might discover the autoantibody that is the exclusive cause of COPD, and then the respective assay will be absolutely sensitive and specific for this disease. For now, though, this seems unlikely.

In the meantime, establishing the contribution of any given autoimmune response to COPD requires, at the least, a demonstration of pathogenicity. Autoantibodies can be isolated from patients and tested for their effects on human cell targets *in vitro*[2]. If auto-immune responses are truly pathogenic, there should also be clear evidence of characteristic injuries within the target organ[2,3]. T cells have exquisite specificity for antigens and considerable potential pathogenicity, and are inert to self-antigens in healthy patients. Accordingly, the presence of autoreactive T-cells is highly abnormal and is strong evidence for the presence of a pathogenic autoimmune process.

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So far, however, few mechanistic studies show specific COPD autoimmune responses that cause injury. Proof that a particular autoimmune response contributes to COPD will probably require recreating the disease in an animal model through adoptive transfers of patient-derived pathogenic autoantibodies or lymphocytes — a task that may prove difficult because of key differences between the immune systems of mice and humans.

When, as many of us working on COPD anticipate, autoimmune mechanisms are more convincingly demonstrated to be factors in COPD pathogenesis, clinical trials will have the potential to yield unprecedented medical advances. Currently available treatments for COPD primarily ameliorate symptoms. Some treatments do attack the underlying inflammation, but not very effectively, and they do not dramatically alter the overall progression of the disease. But modalities to remove autoantibodies or minimize their subsequent production are already available, and several more agents are now being developed that could also work[5]. We may soon have the rationale and tools to implement novel, and potentially better, therapies for this extremely morbid and otherwise unremitting syndrome. ■

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