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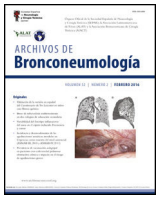

Editorial

Serum Biomarkers in Diffuse Interstitial Lung Diseases☆

Biomarcadores séricos en las enfermedades pulmonares intersticiales difusas

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Biomarkers or biological markers are defined as molecules, substances or clinical parameters that reflect the underlying biological processes involved in a disease.[1] Biomarkers can be classified in 4 ways: as indicative of risk or predisposition, or as diagnostic, prognostic, or therapeutic, depending on their function.[1] The clinical utility of biomarkers in diffuse interstitial lung diseases (ILD) has been evaluated primarily in idiopathic pulmonary fibrosis (IPF), although in recent years some promising biomarkers have also been identified in other ILDs.[1–5] The complexity of diagnosing and predicting the outcome of fibrosing ILDs has been challenging in the search for valid biomarkers, and, although many have been identified, very few have been easily obtainable or reproducible, or representative of the pulmonary process in the long term.[1–7] However, a few biomarkers with these characteristics are currently being validated with the collaboration of international networks, thanks to technological advances and the availability of registries and biobanks.[5,8,9] Pulmonary fibrosis biomarkers in serum that have been studied in most depth are divided into 3 categories: those associated with alveolar epithelial dysfunction, those associated with extracellular matrix remodeling and fibroproliferation, and those associated with the immune system regulation and host defense mechanisms.[1,6,7]

The most important genetic markers associated with epithelial-mesenchymal reparative changes are variants that encode proteins that synthesize or regulate the telomerase enzyme (TERT, TERC, DKC1, PARN, RTEL1, TINF1, OBFC1, NAF1), those that encode surfactant proteins (SFTPC, SFTPA2, ABCA3), and in the case of markers associated with ciliary changes and cellular defense alterations, the genetic mutation that encodes MUC5B.[5,10–12] A recent study that included thousands of patients with sporadic and familial IPF confirms that the common variant of the MUC5B gene, rs35705950, increases the risk of developing the disease, with an odds ratio (OR) of 5.45, 95% CI: 4.91–6.06 in the presence of a mutant allele, and an OR 18.68, 95% CI: 13.34–26.17 in 2 mutant alleles.[5] Rare TERT and RTEL1 telomerase variants and telomere shortening are also associated with a greater risk of developing the disease.[5,10] Moreover, the presence of telomere shortening and telomerase mutations confer a worse prognosis in patients with IPF, especially in younger subjects, and warrant special considerations from a management and therapeutic perspective.[10,11] The presence of MUC5B polymorphism and telomere shortening has been associated with the pulmonary fibrosing component of other ILDs, such as rheumatoid arthritis or hypersensitivity pneumonitis, in which they have prognostic implications.[12] Gene expression has been shown to improve the multi-dimensional Gender, Age, and Physiology (GAP) predictive model that includes gender, age and forced vital capacity and lung diffusing capacity of CO.[8] As such, the study of genetic biomarkers involved in lung fibrogenesis could be useful in ILDs with limited survival associated with the fibrosing pulmonary component.

Protein biomarkers have also been evaluated for decades, but progress has only been achieved in recent years, thanks to research networks and group collaborations. Examples of these collaborative efforts are the PROFILE study and the EurIPFRegistry, which include hundreds of samples from IPF patients from different regions, while the PROFILE study also collected longitudinal serological determinations.[4,9] The most widely tested serum biomarkers are the following: (a) cytokines such as KL-6 (a marker of alveolar damage), which was particularly high in subjects with increased risk of exacerbations, and CCL-18, which was associated with poorer survival[1]; (b) metalloproteinases (MMP), mainly MMP-7 and MMP-1, associated with lung function decline and mortality[2,3]; (c) pulmonary surfactant products SPA, SPD, associated with increased alveolar damage[2,3]; (d) neoepitopes and collagen degradation substances as predictors of worse prognosis[4]; and (e) cell and tissue aging products such as the AGE/RAGE ratio or heat shock proteins (HSP) including HSP45, which show higher serum concentration in cases with more rapid progression.[13] Although these biomarkers have been validated in terms of prognostic capacity, most series include a limited number of cases and none has been a decisive factor in the differential diagnosis of the different fibrosing ILDs. Finally, some clinical trials, such as FLORA and INMARK, include serum biomarkers to monitor progression and pharmacological

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effect. Of particular interest in the FLORA clinical trial was the effect of the drug GLPG1690 on lysophosphatidic acid levels in blood, which decreased when the compound was being administered and rose again after it was discontinued.[14]

In spite of the usefulness that some of these biomarkers have demonstrated in different studies, their use in daily clinical practice is limited and the international guidelines are slow to recommend their use.[15] As such, there is a gap between scientific advances and the information obtained through biomarkers and their use in clinical practice. Several reasons for this gap have been proposed, primarily: the general unavailability of the techniques specifically required for determining some biomarkers; the lack of efficiency studies that demonstrate cost-benefit compared to clinical parameters already in use; the absence of consensus on the most useful measurements; and the limited, though growing, scientific evidence from large, validated clinical trials. Just as international genetic studies have identified genetic variants that increase the risk of developing the disease, it is possible that in the near future international collaborative studies and clinical trials will identify a combination of serum biomarkers that, united in a single platform, can be evaluated correctly in different countries.

In conclusion, the progress of knowledge on serum biomarkers in interstitial diseases, and ILD in particular, may be one of the keys to optimizing the diagnosis, prognosis, and treatment of these patients. National and international collaboration among the various biobanks and registries is essential if we are to achieve these aims in minority diseases such as these.

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