Is Reynolds syndrome a genetic laminopathy?

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Summary  Reynolds syndrome is a rare disease associating primary biliary cirrhosis (PBC) and systemic scleroderma (SSc). Although generally considered as an autoimmune disease owing to the presence of typical autoantibodies and to microscopical abnormalities suggesting autoimmunity (lymphoid infiltrate around the biliary ducts and the cutaneous vessels, pericarditis, pleurisy), other causes have been searched for, especially genetic. The discovery of a new mutation in the Lamin receptor B in a French patient suffering from Reynolds syndrome [1] revives this controversy. Laminopathies have a great variety of manifestations, but some are quite comparable with either SSc or PBC, and the new mutation has been found neither in a group of 27 other patients with SSc, nor in 400 normal subjects. After bioinformatics searching, the authors claim that it is plausible that the new mutation is pathogenic. It remains to be shown, however, that this is really the case by testing directly the liver and skin fibroblasts of the patient. Moreover, looking at a series of CBP patients and at a larger SSc sample will be enlightening to appreciate the real value of that discovery.

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Inflammatory attack of small vessels is the hallmark of some rare diseases, especially vasculitis (blood vessels) and biliary tree (biliary vessels) disorders whose causes remain largely unknown. The association of primary biliary cirrhosis (PBC) and systemic scleroderma (SSc) is called “Reynolds syndrome” since 1970 and is considered by the majority of clinicians as an example of multisystemic disease involving the liver and the skin. It is typically classified as an autoimmune disorder since there are specific autoantibodies associated with both facets of the disease (antimitochondrial antibodies for PBC and anticientromere/antitopoiso merase for SSc), and suggestive microscopical abnormalities in the skin and liver. However, those antibodies are more biomarkers than pathogenic agents, there is no maternofetal transmission of the disease and immunosuppressive drugs are not dramatically efficacious. Moreover, there are data pointing towards a genetic predisposition to SSc and similarities with progeria spectrum of disorders are stimulating alternative explanations for the etiology of SSc.

It is thus timely that researchers in Marseille (France) publish a case [1] where a new mutation in the Lamin B receptor gene has been discovered in the white blood cells, suggesting that nuclear signalling defects could be a cause, at least in some patients, in Reynolds syndrome. This mutation has been found neither in 27 SSc patients nor in 400 control healthy subjects. Other PBC patients have not been tested. Various refined bioinformatic tools have been used by the Marseille research team to suggest that the
mutation could be pathogenic by interfering with the normal nucleic traffic of communication molecules. So a new research area has been opened to look for laminopathies as a possible cause for Reynolds syndrome.

Indeed, laminopathies have a wide spectrum of manifestations but they very often modify the connective tissue functioning and the wound healing process, the typical examples being the progeria syndromes. Moreover, autoantibodies to the Lamin B receptor have been discovered in some patients with either PBC, or scleroderma.

However, further studies remain to be done to prove that fibroblasts and biliary duct cells of the patient share the abnormality, to enhance the plausibility of the pathogenic claims by testing greater numbers of patients and animal models of SSc and PBC, and the family of the index case.

We live in a time where genetic tools are rapidly expanding and (at least for SSc) new genes associated with the occurrence of the disease or of different facets of it are discovered each month. On the other hand, environmental influences revealing genetic tendency to those rare diseases are recognized, and many researchers feel that finally a plausible explanation could be an interplay between agents like virus, silica, chemicals or radiations, on one hand, and genetic background on the other hand, to yield orphan diseases like Reynolds syndrome. One can speculate whether in some time (if the aforementioned data are confirmed) bioarrays of orphan disease-associated genes like LaminB could be developed to help clinicians dealing with patients such as SSc or PBC.

Conflict of interest

None.

Reference