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Immuno-pathogenesis and precision medicine in membranous nephropathy

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Primary membranous nephropathy has undergone a quiet revolution over the last 15 years in terms of the understanding of disease immunopathogenesis and how this information can be leveraged to better manage these patients, so that effective treatment can be provided in a timely and safe manner.

The new knowledge is taking us to an era of personalised treatment of this condition where there would be less reliance on application of the same approach for all patients. Rather, the treating team can develop bespoke approaches to suit the unique clinical and immunological characteristics. Such approach also provides increased opportunity for the patient to participate in the decision-making process, bringing shared decision making to the treatment of glomerular diseases.

The breakthrough started with the identification of phospholipase A2 receptor (PLA2R) as the target antigen of the disease in 60-70% of patients, followed by the discovery of thrombospondin like domain-7 (THSD7A) in about 10% cases. The finding that antibodies to these molecules were present in patients who had membranous nephropathy alongside other conditions such as hepatitis B and C on cancer, challenged the existing notion of primary and secondary membranous nephropathy. It became more useful to identify whether the disease was associated with antibody to a specific target antigen.

Of even more practical value is the fact that the titers of the PLA 2R antibodies to can be used to follow a patient's progress, predict the treatment response since there is good data to suggest that immunological response preceded and reliably predicts clinical response.

Even more interesting one the recent findings that it might be possible to further personalize the therapies using in particular the epitope specificity of the antibody. The discovery of epitope spreading of the anti-PLA2R antibody and its relationship with response to therapy is particularly exciting and offers the possibility of skipping the traditional wait period before deciding to start immunosuppressive therapies.

Knowledge of what are the roles of genetic variations, in particular the HLA-DQ and PLA2R and how does it interact with antibody dynamics and treatment response needs more investigation. The role of various arms of the immune system - such as the B and T cells and their various subgroups is an evolving field.