Translational Aspects of Primary Membranous Nephropathy

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Summary: Membranous nephropathy (MN) in an autoimmune disease caused by binding of circulating antibodies to podocytic antigens. The search for the responsible target antigens has extended for more than 50 years and led to the identification of the major pathomechanisms leading to MN. The combination of clinical and morphologic observations, experimental work, and technical advancements has enabled us deep insights in the pathophysiology of this disease, simultaneously improving treatment of patients. MN represents a perfect example of how patient care may profit from the convergence of scientific and clinical achievements and the benefits of translational approaches in medicine.

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Translational medicine (TM) is an interdisciplinary part of biomedicine that is supported by three main columns: basic research in the laboratory, treatment of patients, and the collaborative work of basic scientists and clinicians.[1] The "from bench to bedside" aspects of the development and current status of our knowledge regarding primary membranous nephropathy (MN) recently were summarized in an elegant review.[2] Our task is to describe TM aspects of primary MN, which cannot be accomplished without touching some of the considerations made in that review, however, we think that newly published data enhance our knowledge regarding the TM aspects of MN and offer another updated and extended view on the subject.

MN is an autoimmune disease of the kidney clinically characterized by a nephrotic syndrome. The characteristic histomorphologic picture of the disease, first described almost 60 years ago,[3] combined with other findings such as the glomerular IgG deposition in patients with MN,[4] led to the hypothesis of an autoimmune nature of MN. It took more than 5 decades until the search for the pathophysiological mechanisms and the renal targets of the immune system led to the identification of phospholipase A_2 receptor 1 (PLA_2R1) as the major glomerular antigen in MN.[5] Approximately 80% of patients with MN have antibodies directed against PLA_2R1. After this discovery it became clear that, if the pathogenetic concept that the disease is induced by circulating antibodies in the blood binding to endogenous or planted glomerular antigens is accurate, then other antigens also have to be involved in the development of MN. This hypothesis was confirmed by the discovery of thrombospondin type-1 domain-containing 7A (THSD7A) as another target antigen,[6] which accounts for almost 3% of patients with MN. It therefore is likely that additional antigens will be discovered. In this review, we discuss how the combination of clinical investigation, basic research, and experimental work on animal models led to these discoveries and how they already translate into patient care.

PATHOPHYSIOLOGICAL MECHANISMS OF MN: FROM CLINICAL OBSERVATIONS TO ANIMAL MODELS

The initial clinical and pathomorphologic observations in patients with MN have suggested that Igs play a central pathophysiologic role in the development of the disease. The question of how the formation of the subepithelial immune deposits in the glomeruli takes place was answered in three different experimental models. In the rat model of Heymann nephritis, glomerular lesions mimicking those in patients with MN were induced by repeated injection of rat kidney emulsions and Freud's adjuvant.[7] Initially, the disease was presumed to be induced by circulating immune complexes that deposit in the kidney.[8,9] This model was supported by findings in a rabbit model of glomerulonephritis caused by circulating immune complexes.[10] Experiments using isolated perfused rat kidneys, however, showed that formation of the subepithelial immune deposits takes place in the absence of circulating immune complexes, and antibodies bind to an intrinsic glomerular antigen.[11,12] The glomerular antigen later would be identified as megalin.[13] The third model

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predicted that antigens, not found endogenously on the podocytes, might be planted in the glomerular subepithelial space because of their physical and/or chemical properties and thus serve as a target of the immune response.[14] From a clinical point of view the pertinent question was, which of these models would best apply to the processes taking place in patients with MN?

PRIMARY AND SECONDARY MN

Most patients with MN have an otherwise unremarkable medical history, therefore, MN is designated as idiopathic or primary. However, there are medical conditions that exist unusually often in patients with MN, who therefore are considered to have a secondary form of the disease. The prevalence of malignant diseases has been described to be up to 10 times higher in patients with MN, compared with the normal population, leading to the hypothesis that the renal lesion might reflect an immune response, originally initiated by the tumor.[15,16] This hypothesis originated from clinical observations and later was supported by experimental findings showing that the tumor and glomeruli might share common antigens in patients with MN.[17] MN also was associated with use of different medications (such as gold and penicillamine),[18,19] infectious diseases (such as hepatitis B),[20] autoimmune diseases (such as lupus erythematosus),[21] or other conditions.[22] As was the case in primary MN, the exact pathomechanisms linking the supposed secondary cases of MN to the associated diseases could not be clarified. To achieve the clinical goal of a more specific diagnosis and safer treatment, it was important to differentiate whether the same immunologic processes led to the renal lesions found in primary and secondary MN, or that primary and secondary MN represent similar histomorphologic pictures of very different diseases. Adding to the confusion was the clinical observation that in up to one third of patients with MN the disease spontaneously disappears, whereas a considerable portion of patients progress to end-stage renal disease.[23] Because no clinical or morphologic characteristics could predict the prognosis of patients at the time of diagnosis reliably, the identification of a marker that would depict disease activity, risk of progression, and reflect the pathophysiology of disease would be extremely useful for the clinical management of patients with MN.

THE WAY TO THE PLA_2R1

The identification of PLA_2R1 as the major target antigen in MN is a good example of how translational medicine stimulates advancement in patient care. Clinical–morphologic observations led to the hypothesis that MN develops as an autoimmune disease upon formation of immune complexes in situ by binding of circulating antibodies to an endogenous glomerular antigen. The identification of megalin as the target antigen in the rat model of Heymann nephritis[13] supported this hypothesis. This was an important step on the road to elucidate the pathophysiologic mechanisms responsible for MN and led to extensive basic research efforts to identify the target antigens in human beings, because it turned out that megalin is not expressed in glomerular podocytes. It took until 2002, when the first evidence for the in situ formation of immune complexes in human MN was discovered. In the very rare antenatal form of MN, neutral endopeptidase, which is expressed on podocytes, was found to be the target antigen.[24] Transplacental transfer of antibodies against neutral endopeptidase from the mother to an unborn child led to the development of MN in the infant. The mother, who was genetically deficient for neutral endopeptidase, was immunized during a prior pregnancy. Although neutral endopeptidase does not play a role in adult MN, this finding was an important confirmation of the hypothesis that immune deposits can form in situ.

PLA_2R1 IS THE MAJOR ANTIGEN IN MN

In a landmark study in 2009, Beck et al[5] discovered that PLA_2R1 is the target antigen in approximately 80% of patients with MN. This finding would prove pivotal for the evolution of scientific and clinical research in recent years.

PLA_2R1 is expressed on podocytes, the antigenic epitopes are conformational, and can be bound by PLA_2R1 antibodies (PLA_2R1-Ab) only in nonreducing conditions. PLA_2R1-Ab were found only in patients with MN, and were not detectable in healthy donors, patients with proteinuric diseases other than MN, or patients with secondary MN. IgG eluted from the glomeruli of patients with MN was shown to be reactive to PLA_2R1. No circulating immune complexes of PLA_2R1 and PLA_2R1-Ab were detectable in the blood. The initial analyses also showed an association of PLA_2R1-Ab levels with disease activity because patients with proteinuria had high PLA_2R1-Ab levels whereas patients in remission had was a decrease or disappearance of PLA_2R1-Ab before proteinuria resolved. The identification of PLA_2R1 provided the opportunity to transfer the knowledge of the immunologic processes taking place during the development of MN, largely acquired in the MN model of passive Heymann nephritis, to clinical practice.

CLINICAL IMPLICATIONS OF THE IDENTIFICATION OF PLA_2R1 AS TARGET ANTIGEN IN MN

The basic pathophysiologic mechanisms involved in MN have been investigated for years and convincingly have shown that MN is an autoimmune disease. Until