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Editorial

Membranous nephropathy - an antigen-specific disease: a paradigm shift in the understanding of this disease

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Abstract: Membranous nephropathy (MN), called Membranous glomerulopathy, is a native kidney disease characterized by sub-epithelial immune complex deposits. Clinically, MN patients present with nephrotic syndrome, especially in the adolescent age group. MN has been traditionally divided into primary and secondary types based on the idiopathic nature and association with secondary causes. The vital breakthrough in understanding the pathogenesis of this disease was the discovery of the M type of phospholipase A2 receptor (PLA2R) antigen. It was found to be associated with 60-70% of primary/idiopathic MN. Thrombospondin type 1 domain-containing 7A (THSD7A) was the second discovered antigen associated with 7-10% of primary MN. PLA2R has become the gold standard for identification of primary MN and is documented as positive both at a tissue level and at a serological level. Later, with the help of laser dissection and mass spectrometry studies, many newer antigens have been discovered, such as NELL-1, Exostosin 1/2, Semaphorin 3B, and Netrin G1, etc., which were found to be associated with both primary and secondary MN. A few of these antigens were found to be specifically related to specific secondary causes, while other antigens had a lot of overlap. Given the substantial overlap associated with the latter, the dichotomy between primary and secondary MN will likely lose its importance. In addition, the need for a renal biopsy for a preliminary diagnosis becomes questionable. Hence, we speculate upon a paradigm shift in the understanding of pathogenesis and nomenclature of this disease since the antigen-based specificity has a potential impact on the therapeutic and prognostic aspects of the disease, which is the crux of this paper.

Keywords: Membranous nephropathy, antigen, disease

Introduction

Membranous Nephropathy (MN), also called Membranous glomerulopathy, is a native kidney disease characterized by diffuse thickening of the glomerular basement membrane (GBM) due to the deposition of sub-epithelial immune complex deposits. MN predominantly affects adults, especially in their 2nd to 4th decade of life, and often manifests as nephrotic syndrome (NS) [1]. Histopathology shows a uniform glomerular basement membrane (GBM) thickened with spike-like projections. Immunofluorescence studies show IgG, C3, Kappa, and lambda deposition in the GBM. Co-dominant IgA deposits are seen in a few cases. Electron Microscopy (EM) shows electron-dense deposits between the podocytes and the GBM. In addition, podocyte foot process effacement can be visualized [2].

The understanding of the pathogenesis of MN has evolved over the past six decades. MN was traditionally considered to be an autoimmune disease mounted against an unknown antigen. Earlier animal studies that were conducted suggested an autoimmune pathogenesis in experimental rats; however, the human target antigen was first discovered in the year 2009 [3, 4]. This discovery led to the identification of numerous other antigenic targets. At present, more than 20 antigenic targets have been identified in MN [5]. This editorial focuses on the journey of antigen discovery in MN, detailing the characteristics of such newly identified antigenic targets. It also emphasizes the potential impact

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of these discoveries on the diagnosis, treatment, and prognosis of patients with MN.

Classification of MN

Traditionally, MN has been divided into primary (~70%) and secondary types (~30%). Primary MN denotes an idiopathic group having a renal-limited autoimmune disease. In contrast, the secondary type revolves around MN associated with systemic diseases such as malignancies, infections, hematopoietic stem cell transplants, drugs, and toxins. Primary and secondary MN have similar clinical manifestations; however, the prognosis differs due to underlying pathogenesis and secondary disease association differences. The distinction between primary and secondary MN is of paramount importance in the treatment aspect as well, since primary MN requires symptomatic and/or immunosuppressive therapy. In contrast, secondary MN requires additional treatment of the underlying disease for a definitive cure [6].

Discovery of antigenic targets in MN

The earliest evidence for the pathogenesis of MN came from the Heymann nephritis rat model [3]. The presence of antibodies against the 'Megalin' antigen expressed on the podocytes of experimental rats had been implicated in the pathogenesis of MN [7]. The formation of the antigen-antibody complex against the podocyte antigen in situ culminates in the activation of the complement proteins, leading to membrane attack complex formation and subsequent damage to glomeruli. However, in humans, the target antigen of MN was unknown since the Megalin glycoprotein was not expressed in human' podocytes [7-9]. Later, neutral endopeptidase was demonstrated as a target antigen in a subset of infants with antenatal MN who were born to mothers with neutral endopeptidase deficiency. This further supported the role of podocyte antigens in eliciting immune-mediated injury in MN [10, 11].

In 2009, a paradigm shift in the understanding of MN occurred with the discovery of the M-type Phospholipase A2 receptor as the target antigen in primary MN, using Western blot analysis and mass spectrometry. Patient serum, normal, and recombinant glomerular extracts were used in this experiment, which resulted in the identification of PLA2R as a target antigen [4]. PLA2R has been implicated in 60-70% of primary MN. It served both as a tissue marker and a serum marker for the diagnosis, prognosis, and monitoring of the disease [12]. PLA2R is an 185-kD transmembrane glycoprotein that is expressed in the process of podocyte foot. It acts as a receptor for the secreted phospholipase A2 enzyme that crosses the GBM [13]. In PLA2R-associated MN, the antibodies are formed against the extracellular N-terminal cysteine-rich domain. In most patients, epitope spreading and the formation of antibodies against distal regions of the extracellular domains of PLA2R have been documented [14, 15]. The anti-PLA2R antibodies are predominantly of the IgG4 subclass; however, IgG1 and IgG3 have also been documented in a subset of patients [4, 16]. The overall quantification of serum anti-PLA2R antibody levels can be performed by enzyme-linked immunosorbent assay (ELISA) or chemiluminescence immunoassay (CLIA) and serves as a useful tool to monitor the response to therapy [17]. The immunological remission marked by the decline of anti-PLA2R antibodies precedes clinical remission [18]. Additionally, the PLA2R antigen can also be demonstrated on a renal biopsy sample by direct immunofluorescence testing or immunohistochemistry. This also serves as a useful tool for the detection of PLA2R-associated MN.

In 2014, Thrombospondin type-1 domain-containing 7A (THSD7A) was discovered as the second target antigen using a similar approach [19]. Antibodies against THSD7A were detected in 2-3% of primary MN [20]. THSD7A is a 250 kD transmembrane glycoprotein expressed on the slit diaphragm of podocytes and the GBM [21]. Apart from primary MN, THSD7A-associated MN has also been observed in malignancies overexpressing THSD7A [22, 23]. Antibodies against THSD7A have been demonstrated in the serum and can be used to monitor the treatment response. The serum antibody levels decline with response to therapy, similar to anti-PLA2R antibodies, and such a decline is found to precede clinical remission [1]. The antibodies against PLA2R and THSD7A are mutually exclusive. In the remaining cases of MN, it was thought that other endogenous podocyte antigens might be involved in the pathogenesis [24].

What's new?

The exploration of novel target antigens in MN gained momentum with the application of laser microdissection and tandem mass spectrometry. This approach unveiled several new target antigens in both primary and secondary MN which include Neural epidermal growth factor-like protein 1 (NELL1), Exostosin 1/Exostosin 2 (EXT1/EXT2), Semaphorin 3B (SEMA3B), Protocadherin 7 (PCDH7), Neural cell adhesion molecule 1 (NCAM1), Protocadherin FAT1, Neuron derived neurotrophic factor (NDNF), Contactin 1 (CNTN1), Proprotein convertase subtilisin/kexin 6 (PCSK6), Transforming growth factor beta receptor 3 (TGFBR3), Netrin G1 (NTNG), and serine protease High-temperature requirement protein A1 (HTRA1) [25-36]. Recently, Caza TN et al. [37] identified seven new putative antigenic targets in MN which include Ficolin 3 (FCN3), CD206, Early endosome antigen 1 (EEA1), Seizure-related six homolog like 2 (SEZ6L2), Natriuretic peptide receptor 3 (NPR3), Macrophage stimulating 1 (MST1), and Vasorin (VASN). Despite these discoveries, the target antigen is yet to be determined in nearly 10% of MN [37]. The newer markers were implicated in specific subsets of secondary causes of MN. However, these associations have been discredited because there were no specific associations between these antigens and MN. There was a lot of overlap between the antigens and particular conditions, and some of these markers have been found to be associated with primary MN. Although, the corresponding serum antibodies are yet to be determined for some of the antigenic targets, and therefore they are listed as putative antigens.

NELL1 is the second most common antigenic target in primary MN [5, 26]. It has also been implicated initially with drug and toxin-induced MN, like mercury-containing indigenous medications; however, it was later observed in association with lipoic acid use, malignancy, autoimmune disease, and the intake of non-steroidal anti-inflammatory drugs (NSAIDs) [26, 38]. The use of indigenously derived medications and skin fairness creams that were found to have mercuric compounds has also been linked to NELL1-associated MN [39]. Similarly, lipoic acid is often used as an over-the-counter dietary supplement and is implicated in NELL1-associated MN for neuropathic conditions [38].

The IgG antibodies are predominantly of the IgG1 subtype. Important to note is the staining for NELL1 in renal biopsy, which has a segmental distribution in some of the glomeruli [26, 40].

EXT1/2 antigenic targets are often detected in MN secondary to autoimmune diseases, such as lupus nephritis and mixed connective tissue disease. EXT1/2 staining often co-exists and is predominantly seen in young females [24, 25]. EXT1/2 staining is seen in 30-40% of lupus MN. The corresponding serum antibodies are yet to be determined. A possible reason could be due to antibody response against the truncated EXT protein, or the level could be low, such that the glomeruli act as a sink. The presence of EXT 1/2 is associated with fewer chronicity features in renal histopathology, reduced risk of progression to end-stage kidney disease, and it carries a better prognosis [41, 42].

Sema3B-associated MN is predominantly seen in the pediatric population. Semaphorins are a group of secreted and transmembrane proteins that have varied functions. There are eight subclasses of semaphorins, which are expressed as transmembrane or secreted proteins. Semaphorin 3 family is a secreted protein that is detected in the endothelial cells, podocytes, and tubular epithelial cells [43, 44]. Interestingly, IgG staining in renal biopsy samples is seen in the GBM as well as the tubular basement membrane (TBM), particularly in children <2 years. However, immunostaining for Sem3B is observed only in the GBM and is absent in the TBM. EM shows electron-dense deposits in GBM and TBM in such cases. The IgG antibodies are of the IgG1 subtype [24].

PCDH7-associated MN is predominantly seen in elderly males [29]. PCDH7 is a 116-kD glycosylated protein expressed on the cell membrane that has seven extracellular cadherin domains.

The exact role of PCDH7 is unknown; however, it is likely to play a role in cell signalling [45]. The antibodies against PCDH7 are predominantly of the IgG1 subtype. Kidney biopsy shows absent or minimal complement deposits. PCDH7-associated MN often has a good outcome [29].

NCAM1-associated MN is seen in a subset of patients with SLE. NCAM1 is a transmembrane

Table 1. Characteristics of the target antigens in MN

	Molecular weight (kD)	Overall frequency in MN	Location/Compartment	Circulating antibodies	Disease Association
Target antigens					
PLA2R [5]	185	55%	Transmembrane	Yes	None
NELL1 [26, 38]	90	10%	Secreted	Yes	Lipoic acid, malignancy, mercury, drugs, autoimmune disease
THSD7A [5, 19]	250	2%	Transmembrane	Yes	Malignancy
Sema3B [28]	83	2%	Secreted	Yes	None
PCDH7 [24, 29]	116	2%	Transmembrane	Yes	None
NCAM1 [33]	95	2%	Transmembrane	Yes	SLE
PCSK6 [36]	37	2%	Secreted	Yes	Prolonged NSAID use
HTRA1 [27]	51	1.4%	Secreted	Yes	None
FAT1 [30]	500	1%	Transmembrane	Yes	HSCT
NDNF1 [35]	56	1%	Secreted	Yes	Syphilis
CNTN1 [32]	125	1%	GPI-linked	Yes	CIDP
NTNG1 [31]	50	0.2%	GPI-linked	Yes	None
Putative Antigens					
EXT1/2 [5, 25]	86/82	7%	Transmembrane, Secreted, Golgi protein	No	Autoimmune disease, SLE
TGFBR3 [34]	93	3.6%	Transmembrane	No	SLE
FCN3 [37]	33	0.6%	Transmembrane	No	SLE
CD206 [37]	166	0.6%	Transmembrane	No	None
EEA1 [37]	162	0.2%	Transmembrane	No	SLE
SEZ6L2 [37]	98	0.2%	Transmembrane	No	None
NPR3 [37]	60	0.2%	Transmembrane	No	None
MST1 [37]	60	0.2%	Secreted	No	SLE
VASN [37]	72	0.2%	Transmembrane	No	SLE

CD206, Cluster of differentiation 206 (mannose receptor); CIDP, Chronic inflammatory demyelinating polyneuropathy; CNTN1, Contactin 1; EEA1, Early endosome antigen 1; EXT1/2, Exostosin 1 and Exostosin 2; FAT1, Protocadherin FAT1; FCN3, Ficolin 3; HTRA1, Serine protease High-temperature requirement protein A1; THSD7A, Thrombospondin type-1 domain-containing 7A; MST1, Macrophage stimulating 1; NCAM1, Neural cell adhesion molecule 1; NELL1, Neural epidermal growth factor-like protein 1; NPR3, Natriuretic peptide receptor 3; NSAID, Non-steroidal anti-inflammatory drugs; NTNG1, Netrin G1; PCDH7, Protocadherin 7; PCSK6, Proprotein convertase subtilisin/kexin 6; PLA2R, Phospholipase A2 receptor; Sema3B, Semaphorin 3B; SLE, Systemic lupus erythematosus; SEZ6L2, Seizure-related 6 homolog like 2; TGFBR3, Transforming growth factor beta receptor 3; VASN, Vasorin.

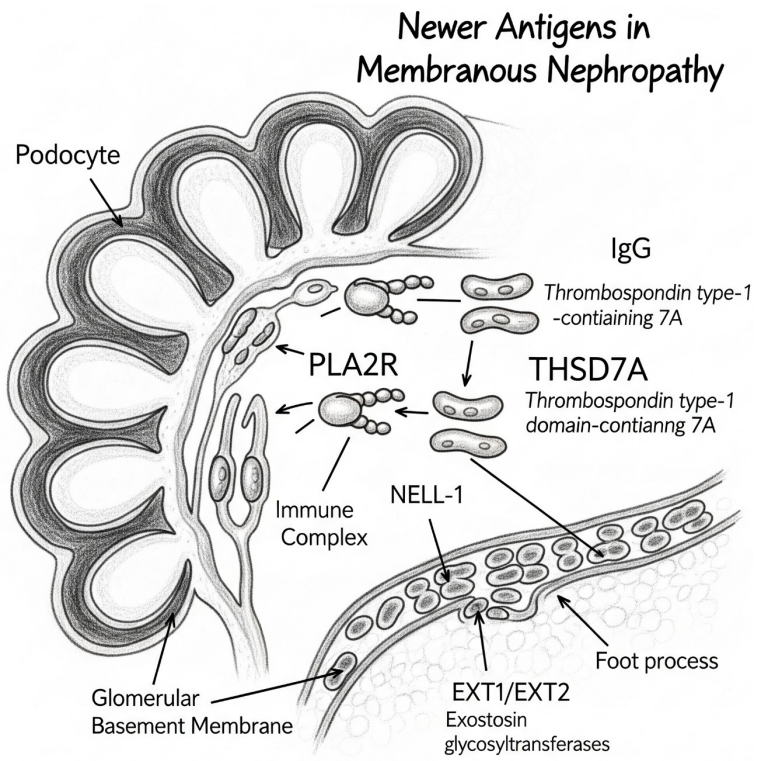

Figure 1. Depicts the newer antigens and their localisation in Membranous Nephropathy.

protein that belongs to the Immunoglobulin (Ig) superfamily. They are expressed in the central nervous system, peripheral nerves, thyroid, adrenals, heart, stomach, immune cells, podocytes, and interstitial cells of the kidney. The NCAM1 association is seen in approximately 6% of membranous lupus nephritis. The IgG antibody subclass is variable [33].

PCSK6-associated MN is often seen in patients with prolonged non-steroidal anti-inflammatory drug use (NSAID). The antibodies belong to the IgG1 and IgG4 subclasses. The majority of patients respond to conservative management and discontinuation of NSAID use. PCSK6 is a serine protease that is secreted into the extracellular matrix and cleaves many proteins. It also helps in the maturation of transforming growth factor beta and plays a role in the activation of the lectin and alternative complement pathway. The exact role of NSAIDs in triggering PCSK6 and subsequent immune response in MN is yet to be determined [36]. The salient features of other target antigens in MN are provided in **Table 1** and **Figure 1**.

The future?

The discovery of target antigens in MN has opened the way to newer Monoclonal antibodies. It has also created a significant impact on patient diagnosis, prognosis, treatment, and monitoring of the disease. A new nomenclature of the disease has been proposed based on antigen-specificity due to its impact on the therapeutic and prognostic aspects of the disease. The detection of serum antibodies provides a viable non-invasive tool to assess the disease activity and response to therapy. Immunoassays like ELISA and CLIA are used to characterize serum antibodies in MN [17]. However, given the vast spectrum of antigenic targets in MN, a proteomics-based approach using laser microdissection of glomeruli and subsequent mass spectrometry may also be employed to detect the target antigens [5]. In the future, the use of mass spectrometry-based antigen characterization may evolve as an invaluable adjunctive test in renal pathology laboratories for the evaluation of MN patients in addition to standard renal biopsy testing.

The diagnostic work-up may be formulated as follows:

Initial work-up can include performing an Immunohistochemistry [IHC] for PLA2R and NELL-1 antigen, which will cover 60-70% of cases. In case of negativity, the IHC for other commonly discovered antigens is performed, which may be used as a 'panel' as per the institutional preference. Ten per cent of the cases may not be positive for any of the possible antigens. In such cases, a mass-spectrometry-based antigen characterization may add to the existing literature and help us understand more about the disease per se, as well as the progress of the disease.

Such a protocol may not be possible in low-volume/resource-poor settings. It may be pro-

posed that at least a basic workup with the two common antigens [PLA2R and NELL-1] be put into use in such a scenario, which may cover at least a handful of cases.

A Kidney biopsy report may contain the following for a wholesome report to the clinician:

(1) The pattern of injury to look for other forms of injury, like a segmental lesion, mesangial lesions, subendothelial or extraglomerular deposits, full-house Ig, etc., which may serve as morphological indicators to rule out the secondary forms of the disease.

(2) The details of the target antigens [panel-based] that were performed with both positive and negative results.

(3) The Direct Immunofluorescence report contains the subtype of IgG antibody detected [IgG1/IgG4].

(4) The clinical relevance, the prognostic & the therapeutic implications of the target antigens.

(5) The Electron microscopic stage of the disease, based on Ehrenreich and Churg staging.

Management

Renin-angiotensin-aldosterone system (RAAS) blockers form the first line of treatment for proteinuria in all patients with MN, irrespective of aetiology [46]. Recent trials have shown that adding sodium glucose co-transporter-2 (SGLT2) inhibitors further reduces proteinuria and the risk of kidney disease progression [47, 48].

Hyperlipidaemia is managed with statins, and prophylactic anticoagulation with warfarin is to be considered for patients with severe nephrotic syndrome (serum albumin <2.5 g/dl) who have a high risk for developing thromboembolic complications.

All patients with MN should be evaluated to rule out associated conditions like lupus, malignancy, infections, and inciting drug use. Staining the kidney biopsy tissue for novel antigens may give a clue to the underlying aetiology. If an underlying condition is diagnosed, MN therapy is directed towards that. In the absence of an underlying condition, immunosuppressive (IS) therapy is needed, at least in a subset of MN patients, who are at moderate to high risk for progression to end-stage kidney disease (ESKD) [46]. Around one-third of the primary MN patients can go into spontaneous remission without IS treatment [49]. Treatment of PLA2R-positive and negative MN is not different if associated conditions are ruled out.

Like the understanding of the disease, the immunosuppressive treatment of primary MN has evolved over the years. Ponticelli et al. described the success of 6-month alternating courses of steroids and chlorambucil in attaining remission of proteinuria [50]. Subsequently, chlorambucil was modified to cyclophosphamide with similar results but fewer adverse effects [51]. Being a proteinuric disease, calcineurin inhibitors (CNIs) with low-dose steroids had some success, but the relapse rates were high after discontinuation of CNIs [52, 53]. After discovering the PLA2R antigen, MN was recognized as an antibody-mediated disease, and the anti-CD20 agent rituximab transformed its treatment [54, 55]. Rituximab is now considered the first option in the initial treatment of primary MN [56]. With the response rate of rituximab around 60-70 percent, newer anti-CD20 antibodies like ofatumumab and Obinutuzumab have also been tried in resistant cases [56, 57]. These anti-CD20 antibody therapies are used regardless of the novel antigen subtypes.

Conclusion

MN is an autoimmune disease targeting podocyte antigens. The recent advent of laser microdissection and tandem mass spectrometry has dramatically enhanced the understanding of MN by revealing a vast spectrum of antigenic repertoire. This progress necessitates a new classification system for MN based on the underlying antigenic target to align it with the pathogenesis of the disease. This new system is essential to improve the diagnosis, treatment, and patient monitoring.

Disclosure of conflict of interest

None.

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