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Immunological Basis of Membranous Glomerulonephritis

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1. Introduction

Primary membranous glomerulonephritis (MGN) is a major glomerular disease causing proteinuria in humans (Jones, 1957). It is the prototype of an autoimmune disease (Couser, et al., 1978) characterized by sub-epithelial immune deposits within glomeruli. Its pathogenesis remains still unknown. Immune deposits are formed by IgG₄, their respective antigen and complement. The definition of the immune deposit architecture has been a main focus of the pathology research for years but advances were restricted, until recently, to animal models of the disease, in particular to Heymann nephritis (HN) (Heymann, et al., 1959; Heymann, et al., 1952; Van Damme, et al., 1978). Unfortunately, results from experimental HN cannot be readily exported to human MGN since the major antigen of immune deposits in rat is not present in human glomeruli. Therefore different podocyte antigens are involved in human MGN and their identification is a fundamental step in understanding human pathology. Technology problems, mainly concerning dissection of glomeruli and purification/characterization of glomerular antibodies from human biopsies, have limited the experimental approach in humans for years.

In the last 5 years, human MGN has become the topic of renewed nephrologic research. Debiec et al. (Debiec, et al., 2002, 2004) first showed that neutral endopeptidase (NEP) emerges as podocyte antigen in a rare form of congenital MGN due to maternal NEP deficiency and alloimmunization during pregnancy. More recently, the existence of three new glomerular auto-antigens, i.e. phospholipase A2 receptor (PLA2R), aldose reductase (AR) and superoxide dismutase 2 (SOD2) have been proposed by independent groups (Beck, et al., 2009; Prunotto, et al., 2010).

Technology evolution in the field of laser capture and proteomics allowed a direct experimental approach in humans, a crucial step for a direct analysis '*in vivo*'. It is now clear that IgG₄ eluted from glomeruli of MGN patients recognize a panel of podocyte proteins

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that have been only in part characterized and that represent good candidates for being involved in the pathogenesis of MGN as “auto-antigens”.

The same approach might be extended to different renal auto-immune pathologies. However, before proceeding, the scientific community needs a consensus on criteria and technologies that should be utilized for recognizing and validating auto-antigens.

2. Animal models

Heymann nephritis (Heymann, et al., 1952, 1959) is the animal model most frequently used for studying mechanisms implicated in the process of deposition of antibodies within glomeruli. Passive Heymann nephritis is induced in susceptible rat strains by injection of heterologous antisera from sheep or rabbit immunized with a crude extract of rat proximal tubular antigens known as Fx1A. This model is highly similar to human MGN: renal pathology in HN is constantly characterized by the presence of glomerular sub-epithelial immune deposits. Heymann nephritis is quite simple to be produced and has offered for years the unique chance to study the structure of immune deposits and the mechanisms involved in their formation. This goal has been completed many years ago. Several studies, between 1980 and 1990, demonstrated that megalin is the target antigen of sub-epithelial IgG. Complement factors, mainly C5b-9, and other ancillary proteins such as receptor associated protein (RAP) and anti-RAP IgG complete the structure of immune deposits (Couser, et al., 1978; Kerjaschki, 2004; Kerjaschki & Farquhar, 1982; Kerjaschki, et al., 1987, 1992; Saito, et al., 1994; Salant, et al., 1980a, 1980b; Van Damme, et al., 1978).

The presence of IgG directed against a podocyte antigen triggers the complement cascade that ends with the formation of C5b-9, the key mediator of podocyte damage in MGN. C5b-9 aggregation on the podocyte membrane causes the activation of the epithelial cell. The podocyte starts the production of a cascade of mediators with phosphorylation of PKC and formation of free oxygen radicals (Cybulsky, et al., 2000). The result is a rearrangement of the cytoskeleton and the consequent loss of cell junction that leads to a pathologic alteration of the glomerular filter and to the appearance of proteinuria.

Immune deposits also contain clusterin (Ghiggeri, et al., 2002; Rastaldi, et al., 2006), a natural binder of megalin, that probably represents an endogenous inhibitor of C5b-9.

The definition of pathology features and physiopathology events in Heymann nephritis represented a breakthrough in research of renal autoimmunity. Unfortunately, in spite some of the components above have been detected in human MGN (i.e. C5b-9, clusterin), Heymann nephritis could not be utilized as a direct model of human MGN because megalin is not present in human glomeruli. Moreover, many years later, it was described that megalin structural homolog, the LDL-receptor, is not recognized by circulating IgG₄ in human MGN (Bruschi, et al., 2009).

Diverse animal models of membranous nephropathy have been developed and different podocyte antigens have been identified such as neutral endopeptidase in rabbit, and dipeptidyl peptidase IV in mouse (Table 1) (Assmann, et al., 1992; Ronco, et al., 1989). These proteins are present in human glomeruli; however they were not identified in immune deposits and their involvement in idiopathic MGN was never proved (Allegri, 1997).

After all, animal models showed the heterogeneity of potential podocyte antigens in MGN and straightened the concept of ‘in situ’ formation of immune deposit. Problems related to the translation of the lesson from animal models to human beings slowed progression in understanding of mechanisms of human MGN. After twenty years, however, new insights

were generated by the observation of familial models of MGN and from the characterization of antigens involved in their pathogenesis.

Animal Models		Ref.
Megalin	<i>rat</i>	Kerjaschki & Farquhar, 1982
Dipeptidyl peptidase IV	<i>rat, mouse, rabbit</i>	Assmann, et al., 1992
Neutral endopeptidase	<i>rabbit</i>	Ronco, et al., 1989
Neonatal MGN		
Neutral endopeptidase	<i>humans</i>	Debiec, et al., 2002
Idiopathic MGN		
Phospholipase A2 receptor	<i>humans</i>	Beck, et al., 2009
Aldose reductase	<i>humans</i>	Prunotto, et al., 2010
Mn-superoxide dismutase	<i>humans</i>	Prunotto, et al., 2010
Alpha enolase	<i>humans</i>	Bruschi, et al., 2011
Others	<i>humans</i>	Bruschi, et al., 2011

Table 1. Glomerular antigens in experimental models and in human MGN

3. Human MGN

3.1 Neonatal MGN

Seminal studies by Debiec and Ronco (Debiec, et al., 2002; Debiec, et al., 2004) represented a fundamental passage on the road of comprehension of human MGN many years after the definition of HN. These authors' contributions led to the definition of neutral endopeptidase as the auto-antigen in rare forms of familial congenital MGN (Table 1). Antibodies against neutral endopeptidase was first recognized in a newborn presenting with congenital nephrotic syndrome. Renal histology demonstrated MGN. The basis of the pathogenesis was the mother, carrying a genetic deficiency of neutral endopeptidase because of an homozygous deletion in *MME*, the corresponding gene. She became alloimmunized against neutral endopeptidase during a prior pregnancy, ended with miscarriage. Anti- neutral endopeptidase antibodies were then transferred to the fetus during the successive pregnancy and congenital MGN developed in the newborn while disappearing thereafter.

This elegant model could therefore demonstrate, for the first time, the pathogenic role of a podocyte antigen in human MGN. Similar mutations of *MME* were found in three further families that had in common at least one case of congenital MGN. Even if the presence and the involvement of antibodies against neutral endopeptidase was clearly demonstrated, the prevalence of this form of MGN is probably very low and these results cannot be translated directly in idiopathic MGN.

There is, in fact, now much debate about considering neutral endopeptidase an auto-antigen in non-familial MGN. In fact, circulating anti- neutral endopeptidase IgG₄ can be detected in a minor part of patients with primary MGN but this antigen is not recognized by IgG₄ eluted from micro-dissected glomeruli (*Ghiggeri, personal observation*). Further studies are required to rule out the involvement of neutral endopeptidase in idiopathic MGN.

3.2 Technology advances for 'in vivo' studies

New technologies in the fields of tissue micro-dissection and protein characterization have recently played an essential role in discovering new auto-antigen in human MGN. They allowed for the first time the analysis of minute amounts of human tissue from a diagnostic renal biopsy. In fact, micro-dissection and proteomics are of fresh development but have been rapidly adapted to renal tissue studies (Murtas, et al., 2011).

The basic approach starts with the laser dissection of glomeruli from cryo-sections of renal tissue. This technique is highly specific and reproducible. It permits to obtain purified glomeruli from which antibodies can be eluted utilizing osmotic gradients and further characterized.

Western blot analysis coupled with mass spectrometry is the second basic technique for characterizing auto-antibodies. In this case, podocyte proteins are first separated with mono-dimensional electrophoresis in both denaturing and non-denaturing conditions (a few proteins are not recognized after mild denaturing treatment) or with two-dimensional gel electrophoresis and they are then incubated with glomerular eluates. The binding of specific IgG₄ with podocyte antigens is detected with anti-IgG₄ antibodies and revealed with chemiluminescence. Finally, podocyte proteins recognized by IgG₄ are characterized by mass spectrometry.

Western-blot/mass spectrometry are also utilized for the characterization of circulating antibodies: serum replaces eluted antibodies.

3.3 Glomerular antigens in human MGN

In terms of general discussion it is rational to propose at least three basic characteristics that should be fulfilled by a protein when considered as an auto-antigen in idiopathic MGN. The first one is that the candidate auto-antigen is expressed by podocytes at least in pathological conditions and that it is recognized by IgG₄ eluted from micro-dissected glomeruli. The second criterion is that the candidate antigen co-localizes with IgG₄ (and possibly with C5b-9) in glomerular sub-epithelial immune deposits. The final condition is that IgG₄ against the protein must be detected in MGN patients sera at least during the overt phase of the disease.

A question apart is specificity, that is a major issue of the consensus debate.

Therefore, characterizing an auto-antigen requires a multistep approach: first of all immunoglobulins are eluted from MGN glomeruli. Then their target is evaluated by

western-blot against podocyte proteins. The evaluation of co-localization within the immune deposits, isotype analysis and titration of circulating antibodies are further steps of the same project. Following this scheme three podocyte proteins have been characterized as putative auto-antigens: phospholipase A2 receptor (PLA2r), Mn-superoxide dismutase (SOD2), aldose reductase (AR). Alpha enolase is a recent finding (Table 1 and Figure 1). Few others are still in progress.

PLA2r is a member of the mannose-receptor family that is normally expressed on the podocyte membrane in humans (East & Isacke, 2002; Lambeau & Lazdunski, 1999). It binds circulating phospholipase A2 but its physiological role is still uncertain. In MGN auto-antibodies recognize PLA2r only in its native configuration that is dependent on disulphide bonds and this is the reason why this protein requires stringent conditions of analysis rigorously in non-denaturing environment. It is reasonable that conformation of PLA2r plays a key role in auto-antibodies formation and binding. Studies (Beck, et al., 2009; Hofstra, et al., 2011) in limited groups of patients with idiopathic MGN revealed high circulating levels in a significant portion of patients and their absence in cases of secondary MGN suggesting a direct implication as causative factor.

SOD2 is a key anti-oxidant mitochondrial enzyme implicated in transformation of superoxide ions into hydrogen peroxide and diatomic oxygen (Son, et al., 2008). In the kidney, SOD2 is widely expressed in tubular epithelial cells, especially in the cortex, where it plays a central role in preserving the kidney during ischemia/reperfusion events but it has never been reported in normal glomeruli. In fact, SOD2 is neo-expressed in podocytes and in sub-epithelial immune deposits of patients with MGN. (Figure 1) (Prunotto, et al., 2010). This suggests that conditions associated with hyperexpression and membrane displacement may be implicated in the auto-immune process.

AR belongs to the family of aldo-keto reductases involved in catalysis of NADPH-dependent reduction of aliphatic and aromatic aldehydes and ketones. It is usually a cytoplasmic enzyme. It converts glucose into sorbitol and it is involved in regulation of tissue tonicity and osmolarity (Williamson, et al., 1993). As for SOD2, localization of AR within the normal kidney is limited to tubular epithelial cells of the medulla and it is absent in glomeruli. In MGN patients it become detectable in glomeruli and it co-localizes with deposited IgG₄ (Figure 1) (Barski, et al., 2005; Terubayashi, et al., 1989; Prunotto, et al., 2010).

The fourth antigen, **alpha enolase** (Bruschi, et al., 2011) is one of the most abundant proteins in cytosol where it participates in the glycolysis process as catalyst of the dehydration of 2-phosphoglycerate to phosphoenolpyruvate; it is particularly expressed in tubular kidney cells and in liver epithelia. A plasma membrane localization has also been described. Several autoimmune diseases are associated with circulating anti-alpha enolase antibodies; however a pathogenetic role has never been demonstrated in any pathological entity (Wistow, et al., 1988; Miles, et al., 1991; Aaronson, et al., 1995; Sabbatini, et al., 1997; Gitlits, et al., 2001). The presence of this kind of auto-antibodies in sera of MGN patients is not a new finding (Wakui, et al., 1999). However, alpha enolase neo-expression in MGN glomeruli and its co-localization with IgG₄ straighten the concept that it is another auto antigen implicated in MGN pathogenesis (Figure 1).

Glomerular immunoglobulin eluates interact with other podocyte membrane proteins (Figure 2). They need to be identified and they have to be tested with the approach described above. Probably, the list of MGN antigens will further increase in a few years.

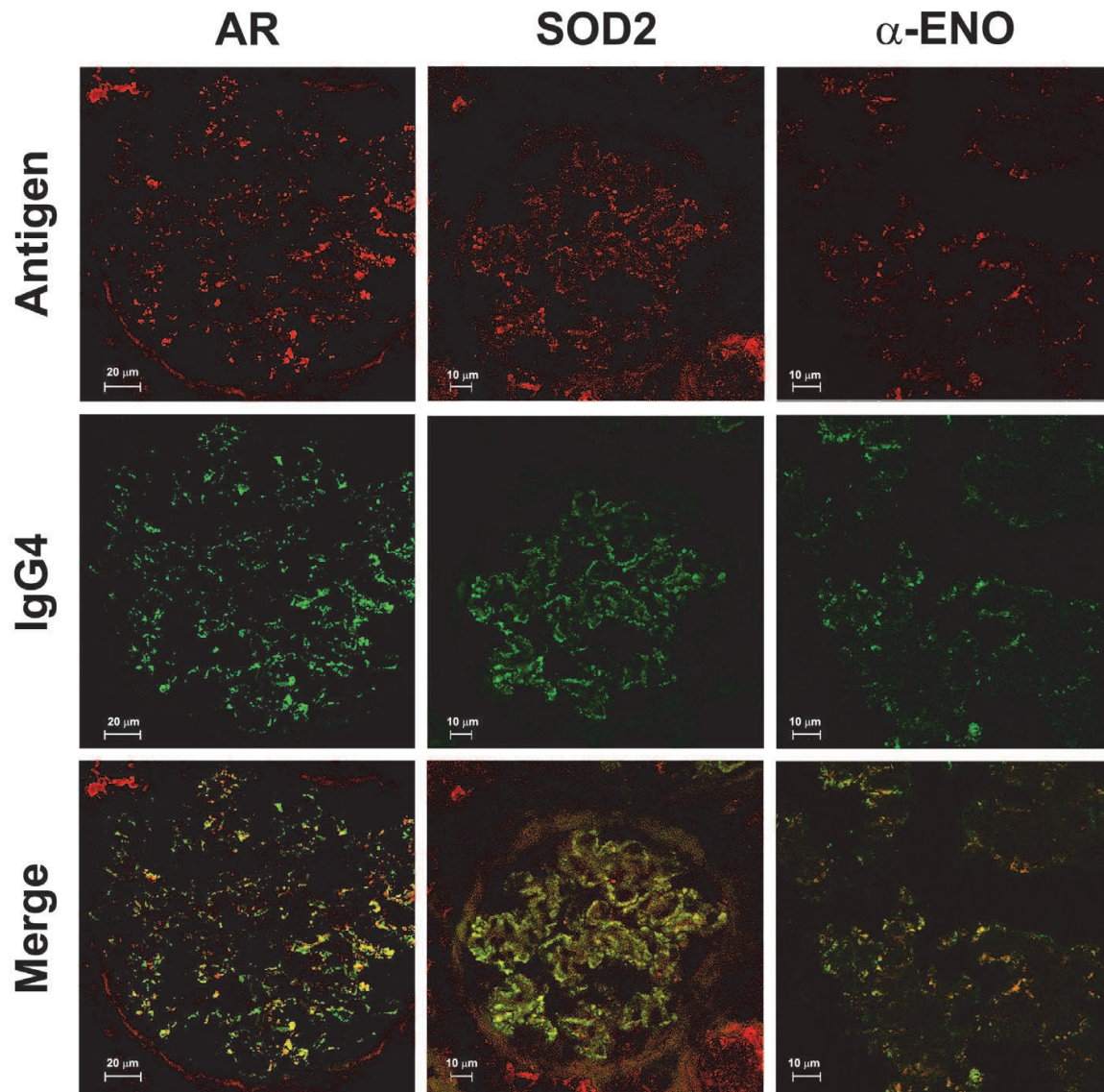


Fig. 1. Glomerular expression of aldose reductase, Mn-superoxide dismutase and alpha enolase in MGN patients. Immunofluorescence on renal cryo-sections analyzed with confocal microscopy. Merged images show co-localization between antigens and IgG₄.

3.4 Antibody isotypes and clinical correlations

IgG₄ typically represents the main body of immune deposits in both Heymann nephritis and human MGN. IgG₁ and IgG₂ are also present.

In sera IgG₄ against the described glomerular antigens are prevalent. However, also IgG₁ can be detected in case of auto-antibodies against alpha enolase. Circulating auto-antibodies are made up of the same he same IgG₄/IgG₁ isotypes indicating a good homology between the circulating and the renal counterparts (Figure 2). How the IgG isotype can influence pathogenesis of MGN is still matter of debate since a few issues are not clear. The first one is related to the described inability of IgG₄ to activate complement, that might suggests an independence between IgG₄ deposition and C5b-9 formation. Another concern is about IgG₁: their role in MGN need to be re-evaluated.

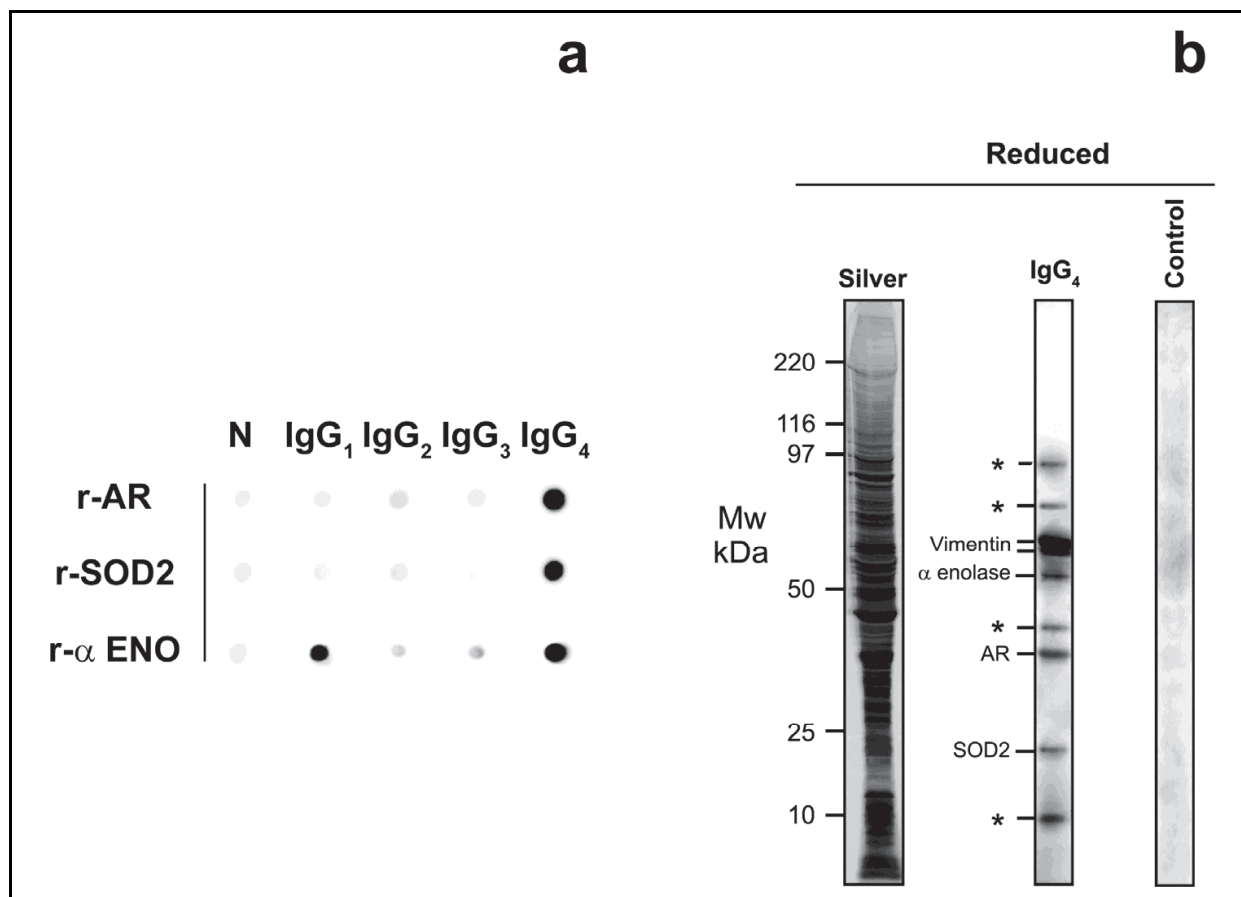


Fig. 2. (a) Circulating immunoglobulin isotypes referred to autoantibodies againsts AR, SOD2 and alpha enolase. In the former two cases the predominant isotype is IgG₄, in the case of alpha enolase both IgG₁ and IgG₄ are detectable. (b) Western-blot with IgG₄ eluted from glomeruli of patients with MGN. A few podocyte proteins are recognized. Three of them have been characterized as aldose reductase (AR), Mn-superoxide dismutase (SOD2) and alpha enolase.

The determination of circulating levels of antibodies against auto-antigens and their clinical correlation is now in progress. Only small cohorts of patients have been evaluated. Moreover, in each population only one antigen have been tested (Beck, et al., 2009; Prunotto, et al., 2010; Debiec & Ronco, 2011; Hofstra, et al. 2011). A correlation of autoantibodies level with proteinuria has been proposed, suggesting that high circulating titers are in relationship with phases of immunological activity of the disease. A strong association with clinical outcome is still lacking. It is also an important issue to establish a correlation among antibodies against different antigens; such studies are on the way. Probably they will help in establishing a hierarchy between antigens, if it exists.

Another key aspect would be to find out a correlation between glomerular deposits and serum levels or clinical outcome. Surrogate biomarkers are needed for guiding treatment and long-term follow-up in MGN patients.

3.5 Predisposing factors

Many immunological or infectious diseases, neoplasms and toxic or pharmacological agents have been associated with MGN. In these situations MGN is considered "secondary" to the

respective pathological entity, even if the presumptive antigen has never been isolated from the affected glomeruli. A classical pathogenetic theory affirms that the causative agent can initiate the pathological process in genetically susceptible individuals.

In primary MGN some association has been proved with HLA alleles: in particular HLA-B8, HLA-B18 and HLA-DR3. The latter has been described probably conferring a threefold increased risk of the disease (Dyer, et al., 1992; Klouda, et al., 1979)

More recently a genomewide association study conducted in three white European population reported an evident association of MGN with single nucleotide polymorphism (SNP) in PLA2R gene and, more strongly, in HLA-DQ alpha chain 1 (HLA-DQA1). The authors do not report any association in AR and SOD2 genes. The MGN risk in relation with SNPs in PLA2R gene is proposed also in two other Asian studies (Stanescu, et al., 2011).

Even these data are not conclusive, they might suggest a “two hits” model also for the pathogenesis of MN. In fact, a variation in some component of the immune system (HLA-DQ variation) might confer an autoimmunity predisposition. Successively, an alteration, congenital or acquired, of the localization or of the structure of an antigen (PLA2R or others), can make the antigen itself became the target of the disregulated immune system.

4. Conclusions

Research on MGN pathogenesis restarted recently, after many years of frustrating findings. Technology evolution was the major incentive to new studies.

The finding of at least four auto-antigens implicated in the pathogenesis of MGN, needs an explanation in a complex pathogenetic theory. Nowadays, it seems reasonable that mechanisms related to the formation of auto-antibodies against membrane proteins, such as PLA2r, are different from auto-antibodies against antigens typically localized inside the cell, such as SOD2 (mitochondrial), and AR or alpha enolase (cytosolic). Antibody promiscuity can be in some way justified by mimicry in case of membrane proteins whereas, for molecules such as SOD2, AR or alpha enolase, mechanisms of de-localization should play a role.

Anyway, before a complete elucidation of MGN pathogenesis several studies have to be performed: more clinical data, new insights on cellular localization of antigens and , maybe, new animal models are needed.

There is a some kind of hierarchy between different targets of autoimmunity? The production of a first autoantibody stimulates podocyte expression of other auto-antigens and a new wave of immunization? There are types of autoantibody not correlated with clinical evolution that are only some kind of “epiphenomenon”? There are different clusters of MGN patients with different autoantibody profile?

Many questions raise when considering recent discoveries on MGN. They will be correctly answered only if scientific community proceeds with shared approach in discovering and testing candidate antigens. Exciting times are coming for the researches involved in studies on MGN and other renal auto-immune diseases.

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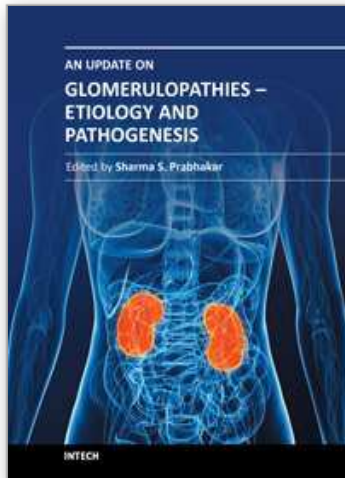
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