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The LAMP Story and what It Means for ANCA Positive Vasculitis in Nephrology

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1. Introduction

From the nephrological point of view, the last couple of years have brought some major advances both in our understanding of ANCA positive vasculitis pathogenesis mechanisms and in treatment options. Recent discoveries of completely new antigens such as LAMP-2 meant a huge step forward, and the fact that this antigen is homologous to proteins of bacterial fimbria caused a shift in the focus regarding underlying pathomechanisms of ANCA vasculitis towards bacterial infections, mainly with *Klebsiella* or *Escherichia* species, playing a major role in triggering the disease. So nephrology has seen real progress in our understanding of glomerulonephritis disease mechanisms – not only regarding primary membranous glomerulonephritis (with the recent identification of the phospholipase A2 receptor being the underlying antigen) but also regarding secondary pauci-immune glomerulonephritis due to ANCA positive vasculitis.

At the same time, some important studies were successfully conducted. Especially the results of the RAVE and IMPROVE studies, will have an impact on nephrologists' approaches to the treatment of patients suffering from this type of vasculitis.

The following chapter will focus on the new developments and briefly outline our already well established knowledge about ANCA positive vasculitis from a nephrological point of view.

2. Pathogenesis of ANCA positive vasculitis

There has been a long debate about the actual role of ANCA autoantibodies as causative agents of small vessel vasculitis. Although the correlation of ANCA titres with disease activity is not very strong¹², the fact that drug induced ANCA formation in patients treated with propylthiouracil, hydralazine or penicillamine can lead to exactly the same clinical picture of pauci-immune glomerulonephritis as "idiopathic" ANCA disease seems to indicate a causative role of the antibodies³. A well documented case report of a neonate with glomerulonephritis (GN) and pulmonary vasculitis due to Anti-MPO-antibodies that had passed the placental barrier from the maternal circulation⁴ points in the same direction. The ability of these antibodies to cause GN when administered to mice intravenously has also been demonstrated⁵.

The course of events leading to the inflammatory destruction of endothelial cells starts with activated neutrophils, which represents the flu-like initial phase of the disease. Cytokine

activated neutrophils present antigens at their surface which attract IgG ANCA's binding to them, forming local immunocomplexes. Recent results show an essential involvement of the alternative complement pathway in these complexes - C3 and C5 rather than C4 are the main complement fragments involved. C5 knock out mice will not develop Anti-MPO antibody induced vasculitis⁶, depletion of neutrophils also prevents the disease despite ANCA's being administered, as demonstrated in an animal model⁷. T cells play a role in the pathogenesis, and so do B cells -indicated by the fact that anti-B cell agents such as rituximab are highly effective in therapy. Th17 cells are the major effector cells, while Th1, Th1 and regulatory T cells are also involved. Activated B cells produce the ANCA antibodies, and their number correlated with the disease activity. However, the actual role of B cells still needs to be elucidated.

While 70% of ANCA positive patients will show renal manifestations, there are about 10% of patients with the same clinical picture of pauci-immune GN who are ANCA negative. Conceivably other, as yet unknown antibodies might be involved in this patient subgroup. Similarly, the two classical antigens of proteinase 3 (c-ANCA's) and myeloperoxidase (p-ANCA's) are not the only ones, the lysosomal membrane protein lamp-2 which has a homologue protein in renal glomerular endothelial cells, is another important target of ANCA's⁸. In fact this ANCA subtype is present in almost all patients with pauci-immune focal necrotizing glomerulonephritis. Most interestingly, lamp-2 is highly similar to certain bacterial fimbria proteins, as recently reported by Kain et al in Nature Medicine in 2008⁹. Some peptides of proteinase3 resemble epitopes of staphylococcus aureus antigens. Bacterial infections mainly with Klebsiella and Escherichia coli species may therefore trigger systemic ANCA associated vasculitis via a cross-reactivity mechanism.

3. The beginning of the LAMP story

In 1988, isolation and characterization of two human lysosomal membrane glycoproteins was reported by Carlsson et al. and the terms h-lamp-1 and h-lamp-2 introduced ("LAMP" being the acronym for lysosome associated membrane protein). The two major lysosomal membrane glycoproteins were described as major sialoglycoproteins carrying polylectosaminoglycan¹⁰, with apparent molecular weights of 39.5 and 41.5 kDa, respectively. They were purified from chronic myelogenous leukemia cells. Already at this early stage it was noted that the apparent molecular weights differed between cell lines and that "this probably represents differences in the amount of polylectosaminoglycan expressed by each cell line". The first one of the glycoproteins was found to be very homologous to that of a mouse counterpart, m-lamp-1, it was therefore named human lamp-1 (h-lamp-1), while the other glycoprotein was called human lamp-2 (h-lamp-2). After cloning both proteins in the same year¹¹, it became clear that major portions of both h-lamp-1 and h-lamp-2 reside on the luminal side of the lysosome and are heavily glycosylated by N-glycans: h-lamp-1 and h-lamp-2 were found to contain 19 and 16 potential N-glycosylation sites, respectively. Strong homology was noted and a common ancestor gene suggested. Diversion had to have happened at an early evolutionary stage however, since human lamp-1 has more similarity to lamp-1 from other species than to human lamp-2. Both LAMP's are structural proteins without enzymatic activity. By means of in situ hybridization, the gene for human lamp-2 was localized to chromosome 12p133 and the h-lamp-1 gene to chromosome 13q34¹². The authors argued that the fact of two genes on different chromosomes indicates that lamp-1 and lamp-2 diverged early in evolution and

probably have distinct functions which emerged as soon as eukaryotic cells acquired lysosomes as subcellular compartments. When mouse LAMP-2 had been cloned¹³ it was found that mouse LAMP-2 and human LAMP-2 form one homology class (LAMP-2) that is separated from the LAMP-1 class of proteins. The localization of the polylactosaminoglycans¹⁴ in the two lysosome membrane glycoproteins was analyzed, and in 1990 rat LAMP-2 was purified¹⁵ and found to be present in all rat tissues examined, but at consistently lower concentrations than LAMP-1. The authors reported that their apparent molecular weights differed among the tissues, suggesting different glycosylation patterns. Later a soluble LAMP-2 was detected in rat liver¹⁶. When the exon structure of both protein classes was analyzed¹⁷, it turned out that each of the nine exons encodes almost identical portions of the proteins. Since the amino acid sequence of human lamp-1 is more homologous to lamp-1 of other species than it is to human lamp-2, the two genes were most likely produced by duplication of a primordial gene, which took place early in evolution.

The old age, in evolutionary terms, of the LAMP-2 gene, is in fact not trivial but will shed some light on the pathogenetic role of this protein as the LAMP story unfolds. Homology with another protein outside the LAMP-2 class was already reported in 1993¹⁸, when glycoprotein II (GpII), a heterogenous glycoprotein isolated from the membranes of secretory chromaffin granules in the adrenal medulla was found to show a homology of greater than 70% of the sequence with LAMP-1 and -2. It became clear¹⁹, that the LAMP-2 gene is in fact preserved from birds to mammals and all diversity due to alternative splicing from a single gene. In the following years a number of papers dealt with structural properties of the protein and its processing within the cell. So it was reported, that²⁰ clusters of O-glycans protect LAMP-2 from intraluminal lysosomal proteases - after removal of the asparagine-linked glycans from fully folded lysosomal membrane proteins by endoglycosidase H in cell culture, both LAMP-1 and LAMP-2 are rapidly degraded²¹. Tissue-specific expression of three different LAMP-2 variants due to alternative splicing was reported²² in chicken. In cell culture it was found, that lamp-2, similar to lysosomal acid phosphatase (LAP), shuttles²³ in the endocytic membrane transport system of rat hepatocytes between lysosomes and the plasma membrane. After leaving the rough endoplasmic reticulum, newly synthesized lamp-2 is transported²⁴ to the trans-Golgi and then transferred to at least three compartments - the cell surface, cell peripheral early endosomes and perinuclear late endosomes, before it is finally delivered to the lysosomes. The extent of polylactosamine glycosylation of MDCK LAMP-2 is determined by its Golgi residence time²⁵. Where the molecule will travel is governed by the COOH-terminal residue of its cytosolic tail²⁶. Its plasma membrane variant was discussed as a possible tumour antigen; it was speculated, that LAMP-1 and -2 like several other glycoproteins²⁷ might be important in colon carcinoma adhesion and metastasis by functioning as its endogenous ligands - in fact there is evidence²⁸ suggesting an increase in their cell-surface expression in tumor cells, with some data indicating that the adhesion of some cancer cells to the extracellular matrix is partly mediated by interactions between LAMP's and E-selectin and between Lamps and galectins (endogenous-galactoside-binding lectins). However, its physiological role and main pathophysiological importance remained unclear, until the next major discovery was made.

4. LAMP-2 as an additional autoantigenic ANCA target

While the association between the clinical picture of pauci-immune, necrotizing and crescentic glomerulonephritis (NCGN) with circulating antineutrophil cytoplasmic autoantibodies (ANCA) had been known for some time, only two of the actual targets had been identified

until 1995: proteinase 3 (mainly associated with c-ANCA) and myeloperoxidase (mainly associated with p-ANCA). Then the group of Renate Kain et al. reported LAMP-2 to be another antigen targeted by ANCA, and they also found the link to the underlying disease mechanism when they identified gp130, a glycoprotein in the endothelial membranes of renal glomeruli, to be highly homologous to LAMP-2²⁹. The same group later showed, that almost all patients with pauci-immune focal necrotizing glomerulonephritis have ANCA's against LAMP-2, so that their prevalence is almost twice that of Anti-proteinase 3 and myeloperoxidase ANCA's. They also demonstrated³⁰ the pathophysiological significance of these antibodies, since Anti-LAMP-2 ANCA's injected into rats caused the same histological picture of pauci-immune focal necrotizing glomerulonephritis. In vitro, these antibodies cause apoptosis in microvascular endothelium. When studying the epitope, to which the ANCA's commonly bound, it turned out that this part of the LAMP-2 protein had a 100% homology with to the bacterial adhesin FimH, a protein present in bacterial fimbria. The terminology of p- and c-ANCA refers to the distinct staining patterns due to the intracellular localization of the respective antigens. LAMP-2 is also localized in specific lysosomal fractions - together with Lamp-1 it is present in the specific-granule-enriched fraction and in the light-membrane fraction³¹, but not in the azurophil granules. These further studies, fuelled by the increased interest in the LAMP's as intracellular antigens, began to clarify their physiological role: Separation of secretory vesicles from plasma membranes disclosed that the light-membrane LAMP's are present primarily in the secretory-vesicle-enriched fraction, and during phagocytosis both Lamp-1 and Lamp-2 become markedly concentrated around the ingested particle. Both appear on the cell surface when the secretory organelles are mobilized. This fact sparks the ongoing interest in Lamp-2 as a tumour marker, because - other than in the lysosomal membrane - Lamp-2 proteins are expressed at the plasma membrane of cells in a differentiation dependent and activation dependent manner³². Murine Lamp-2c expression is pronounced in mesenchyme early in development, in limb connective tissue, and in lung parenchyma, whereas m-Lamp-2a is prevalent in the liver, the pancreas, and in differentiating kidney epithelium, and becomes increasingly prominent in the epithelial lining of the digestive and the respiratory tract during development. Their expression pattern becomes more tissue and cell type specific as differentiation progresses. In adults, tumour cells undergoing dedifferentiation again have detectable amounts of LAMP-2 at their cell surface, where they might play a role in cell adhesion, metastasis or tumour progression, as a study about LAMP-1 in pancreatic carcinoma³³ suggests. Since morphogenesis often requires apoptotic removal of cells, an important role of phagolysosome activities and lysosomal proteins in these processes is evident.

5. Learning from rare genetic deficiencies: Danon's disease and LAMP-2

The first time, when a rare genetic condition provided insight into the physiological role of LAMP-2, was when control platelets and those from an individual with Hermansky-Pudlak³⁴ syndrome were compared³⁵ regarding the presence of LAMP-2 expression: It turned out that LAMP-2, like CD63, is normally present not only in lysosomes but also in dense granules of platelets. Apart from oculocutaneous albinism, this autosomal recessive condition is characterised by platelet dense granule deficiency, prolonged bleeding time, a storage pool deficiency of platelets and lysosomal accumulation of ceroid lipofuscin. A major breakthrough in the understanding of the physiological role of LAMP-2 came with studies of knock-out lab animals and the discovery of Nishino, DiMauro et al. that the rare

condition of Danon's³⁶ disease is due to LAMP-2 deficiency. It became evident, that a deficiency of this protein mainly impairs autophagy, i.e. the removal of aged cell material, lysosome biogenesis and cholesterol homeostasis³⁷ – being a structural protein it has no enzymatic activity of its own, but a deficiency leads to partial mistargeting of a subset of lysosomal enzymes³⁸. Lysosomal cholesterol transport³⁹, the ability of lysosomes to migrate by means of dynein-mediated transport and the fusion with autophagosomes and phagosomes depend on the LAMPs⁴⁰. Therefore phagocytosis is also affected, and pathogenic *Neisseria* have been found to excrete a protease which selectively cleaves LAMP-1⁴¹. In the unicellular eukaryote *Paramecium* LAMP-2 was found to be required for phagosome maturation⁴². Since antigen presenting B-cells rely on normal lysosomal function, MHC class II antigen presentation to CD4 T-cells and the balance between endogenous and exogenous antigen presentation is impaired⁴³ in LAMP-2 deficiency.

The condition was first characterized by Moris J. Danon and Shin J. Oh in two patients as a 'lysosomal glycogen storage disease with normal acid maltase' in 1981⁴⁴– the clinical picture involves hypertrophic cardiomyopathy (often associated with Wolff-Parkinson-White syndrome), myopathy and variable mental retardation. It was initially thought to be mainly X-linked, but as DiMauro et al. recall in their review⁴⁵, in 1993 they wrote that an "autosomal dominant inheritance cannot be ruled out". In the meantime more than 20 autosomal mutations of the LAMP-2 gene (chromosome 12) have been reported: in exon 7 resulting in the syndrome and with the patient requiring heart transplantation at 41 years of age⁴⁶, in intron 6⁴⁷, in intron 8⁴⁸ with additional hepatopathy, in exon 5⁴⁹ and in exon 4 with several both male and female family members being affected⁵⁰. Another missense mutation in the LAMP-2 gene caused a much milder clinical picture with exercise intolerance, persistent HyperCKemia and hypertrophic cardiomyopathy, but no mental retardation or severe heart failure⁵¹. Other genes have to be involved, suggested not only by the fact that the disease is always much more severe in male patients than in females, but also by marked phenotypic variation in unrelated patients with the same LAMP-2 gene mutation⁵² – in a family with a mutation in exon 2 of the *Lamp-2* gene⁵³, females developed isolated cardiomyopathy in adulthood, whereas males presented with cardiomyopathy, myopathy, and mental retardation before the age of 20 years. Intrafamilial variability of affected family members does occur⁵⁴. Moreover, a case with quite the same clinical picture of Danon's disease but normal LAMP-2 staining in the muscle biopsy has been reported⁵⁵. In mice, LAMP-2 deficiency increases mortality between 20 and 40 days of age⁵⁶, the surviving mice are fertile and have an almost normal life span. Only the additional knock-out of LAMP-1 and -2 results in a lethal phenotype at embryonic stage⁵⁷. Many tissues including liver, pancreas, spleen, kidney and skeletal and heart muscle accumulate autophagic vacuoles. In hepatocytes, the autophagic degradation of long-lived proteins is severely impaired. Cardiac myocytes are ultrastructurally abnormal and heart contractility is severely reduced. The reason for this reduced contractility is not completely understood yet; calcium handling by the cardiomyocytes is normal⁵⁸. Finally, when cases of Danon patients with oculocutaneous albinism were reported in 2006⁵⁹, it became clear that features of Danon and Hermansky-Pudlak syndromes may sometimes not be separable.

6. Conclusion

Recent years have seen a number of breakthroughs in our understanding of glomerulonephritis. The common theme in all of these cases is that disease entities, which

used to be defined simply by histomorphological criteria or clinical pictures, could be traced down to the underlying causative agent. In ANCA positive vasculitis, as in polyarteriitis nodosa, hitherto unknown roles of infective agents that give rise to the disease-defining immunological responses were identified: while most polyarteriitis nodosa cases are related to the hepatitis B virus⁶⁰, fimbriated bacteria causing cross-reactions against lysosomal membrane proteins are involved in a majority of ANCA positive vasculitis cases.

The story of LAMP-1 and -2 (or CD107a and b, as they have also been referred to⁶¹) continues. More splice variants were detected, so a whole new nomenclature was introduced⁶², the new class of LAMP-3 and the LIMP's (lysosomal integral membrane proteins) entered the stage. Possible additional roles of LAMP-2 as a diagnostic marker need to be investigated further – conceivably it might play a role as a tumour marker as well as in screening of newborns for presymptomatic lysosomal storage disease: In a study LAMP-2 plasma concentrations were increased in >66% of patients with lysosomal storage disorders⁶³, and the increases coincided with increased LAMP-1 concentrations. Increased LAMP-1 and -2 levels have been associated with normal mast cell activation⁶⁴, increased LAMP-2 expression in peripheral leucocytes with coronary artery disease⁶⁵. There seems to be the possibility of a non-genetic, acquired LAMP-2 deficiency in alcoholic acute pancreatitis or severe endotoxemia⁶⁶. Whether all these associations, or the report of Anti-LAMP-2 ANCA's in pyoderma gangrenosum⁶⁷, or indeed the slowing down of aging processes by restoration of chaperone-mediated autophagy in aging cells ("Live longer with LAMP-2!"⁶⁸) will gain clinical significance in the future, remains to be seen.

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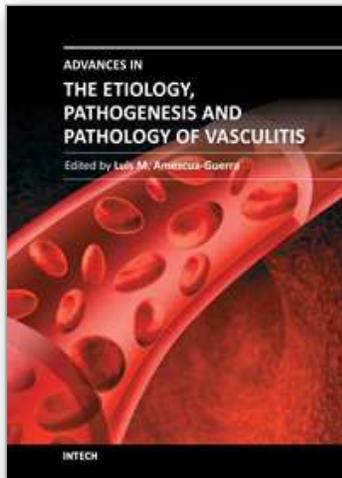
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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of-the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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