Understanding renal disorders as systemic diseases: the fascinating world of basement membranes beyond the glomerulus*

Oliver Gross

Department of Nephrology and Rheumatology, University of Göttingen, Göttingen, Germany

Keywords: Alport syndrome; chronic renal fibrosis; extracellular matrix; glomerular basement membrane; type IV collagen

In the 27 December 2007 issue of the *New England Journal of Medicine*, Plaisier and colleagues [1] describe fascinating data on a new spectrum of autosomal dominant hereditary collagen diseases involving the COL4A1 gene. This gene codes for the α1-chain of type IV collagen, being the most important structural component of all basement membranes throughout the body. The paper was highly publicized and completes a trilogy of manuscripts about collagen type IV α1-chain mutations causing neonatal porencephaly, adult stroke, perinatal cerebral haemorrhage, skin lesions and nephropathies [1–3].

All basement membranes consist of a network of type IV collagen. Collagen IV monomers contain a long triple helical rod built by >1000 Gly-X-Y repeats, which is terminated at its C-terminal end by a globular NC1 domain, well known to nephrologists due to Goodpasture syndrome (Figure 1). In contrast to α-chains of the fibre forming collagens (types I, II, III and V), collagen IV chains contain interruptions in their Gly-X-Y repeats. These interruptions endow the collagen IV triple helix with a high degree of flexibility compared to fibre-forming collagens. Six genetically distinct α-chains of type IV collagen have been identified, forming a network of α1α1α2(IV), α3α4α5(IV) and α5α5α6(IV) [4]. Whereas the α1α1α2(IV) trimers are widely expressed in all basement membranes throughout the body, the α3α4α5(IV) network localizes to the glomerular basement membrane, lung, eye and lens and the α5α5α6(IV) network to Bowman’s capsule and the oesophagus [5].

Alport syndrome is derived from a mutation of either the COL4A3, COL4A4 or COL4A5 gene, coding for α3, α4 or α5 chain of type IV collagen, i.e. collagen types that constitute basement membranes in the renal glomerulus, the ear and the eye. In knockout mice and humans mutations in COL4A1 have recently been associated with cerebral haemorrhage and porencephaly, a rare autosomal dominant condition characterized by cystic brain cavities and cerebral white-matter lesions [2,3]. Data from COL4A1 knockout mice models extend our view on collagen IV mutations as a systemic disease by describing endoplasmic reticulum and intracellular stress [6] leading to defects of the eye and vascular stability, the brain and kidney function and postnatal viability [7]. The present study by Plaisier et al. [1] completes this type IV collagen story by describing a systemic syndrome involving not only the brain but also all basement membranes including small vessels and large arteries as well as the skin and the kidney. This report opens a fascinating world beyond the well-known basement membrane of the glomerulus.

But do we really know much about the basement membrane? We know it is there and is needed to give cells some orientation, and serves as a part of a filter in the glomerulus. We have known that for over 20 years [8]. But we still do not know much about what the basement membrane proteins really do in the extracellular matrix, how they interact with whom and by which. This might explain why COL4A1 mutations involve a confusing number of different organs. By focussing on a well-known basement membrane disease of the glomerulus, Alport syndrome, nephrologists might explain some of the confusing findings in COL4A1 mutations.

(a) Can nephrologists’ knowledge about the glomerular basement membrane explain the clinical manifestations of COL4A1 mutations?

COL4A1 mutations lead to a severe systemic disease; how can we explain the very different phenotypes (angiopathy, nephropathy, aneurysms and muscle cramps) described? Goodpasture syndrome is limited to the lung and kidney; Alport syndrome is limited to the glomerular basement membrane, the inner ear and lens. Mutations involving the α5- and α6-chain of type IV collagen result in Alport syndrome plus leiomyomatosis of the oesophagus. Therefore, as nephrologists we know about the tissue-specific contribution of different type IV collagen chains. This knowledge even helps us to understand why COL4A1 mutations...
All human families with \textit{COL4A1} mutations have missense mutations in exons 24 or 25 leading to substitution of glycine to another amino acid. Is this just a coincidence? No, we know from Alport syndrome that glycine-X-Y-missense mutations are most common (~40%) and lead to a relatively benign phenotype depending on their distance from the NCI-domain [9]. As \textit{COL4A1} mutations lead to a more systemic disease, one can expect mutations with a larger impact on protein function to be lethal. These data were confirmed in \textit{COL4A1} knockout mice [2,3]. Only smaller impacts on protein integrity such as missense mutations could lead to a (mis-)functioning mis-folded protein that can still be incorporated in the basement membrane. This mutated protein is likely to be degraded faster. In conclusion, only embryos with a milder missense \textit{COL4A1} mutation can survive organogenesis. Only newborns with a mildly altered protein, which still can be incorporated within the basement membrane, can survive their basement membrane defects for a certain time. Similar to Alport syndrome focusing on glomerular (vascular) damage, the phenotype of \textit{COL4A1} mutations focuses on areas with the most mechanical stress, such as the vessels.

(b) Can nephrologists’ knowledge about the glomerular basement membrane predict the phenotype–genotype correlation in \textit{COL4A1}-mutations?

All human families with \textit{COL4A1} mutations have missense mutations in exons 24 or 25 leading to substitution of glycine to another amino acid. Is this just a coincidence? No, we know from Alport syndrome that glycine-X-Y-missense mutations are most common (~40%) and lead to a relatively benign phenotype depending on their distance from the NCI-domain [9]. As \textit{COL4A1} mutations lead to a more systemic disease, one can expect mutations with a larger impact on protein function to be lethal. These data were confirmed in \textit{COL4A1} knockout mice [2,3]. Only smaller impacts on protein integrity such as missense mutations could lead to a (mis-)functioning mis-folded protein that can still be incorporated in the basement membrane. This mutated protein is likely to be degraded faster. In conclusion, only embryos with a milder missense \textit{COL4A1} mutation can survive organogenesis. Only newborns with a mildly altered protein, which still can be incorporated within the basement membrane, can survive their basement membrane defects for a certain time. Similar to Alport syndrome focusing on glomerular (vascular) damage, the phenotype of \textit{COL4A1} mutations focuses on areas with the most mechanical stress, such as the vessels.

(c) If nephrologists understand the glomerular matrix, will we understand the fascinating world beyond?

Despite knowing most of the different matrix components for >20 years [8], we can only speculate about their function by investigating their malfunction in type IV collagen diseases such as Alport syndrome. One key point might be the cell–matrix interaction via type IV collagen receptors. These receptors are tyrosine kinase receptors binding collagens at the cell surface, passing signals through the plasma membrane to the nucleus. By this they regulate cell proliferation, cell transformation, cell migration, ageing of cells as well as apoptosis [14] in almost every single cell of our organism such as epithelial, mesenchymal, endothelial cells, fibroblasts, haemapoetic cells, etc. We know that these receptors influence implantation of blastocytes and maturation of mammalian glands. We know that collagen can activate macrophages via collagen receptors through a p38-MAPK- and NFκB-dependent upregulation of IL-8, macrophage inflammatory protein-1α and monocyte chemoattractant protein-1 [15]. Chronic fibrosis can be delayed in mice lacking the DDR1-collagen receptor [16]. We have recently started to understand how the matrix and its receptors influence tumour angiogenesis and metastasis [17]. The complex mechanisms of tumour invasion beyond the matrix barrier and the tissue-specific growth of metastasis are closely linked to type IV collagen and its receptors.

For many of us being nephrologists the glomerulus might be the centre of the world. If we understand more about the matrix holding this small glomerular world together, will we learn about functions of the basement membrane beyond?

Oh yes, we can. We certainly can learn a lot about the fascinating basics of embryogenesis, organogenesis, acute and chronic organ damage and healing, chronic fibrosis, tumour invasion and metastasis and how to treat and cure numerous chronic diseases. We have now started to accept that the matrix is not a virtually unorganized, dead mass lying under cells.

Acknowledgements. This editorial comment on the extracellular matrix and its receptors is in memory of my friend Wolfgang F. Vogel, a young excellent and enthusiastic researcher in this field, who passed away recently.

Conflict of interest statement. None declared.

References


Received for publication: 13.2.08
Accepted in revised form: 18.2.08