Cyclins and the cyclin-kinase system—their potential roles in nephrology

Yoshio Terada, Seiji Inoshita, Osamu Nakashima, Michio Kuwahara, Sei Sasaki and Fumiaki Marumo

Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, Japan

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Introduction

Recently a number of major advances in molecular biology have led to the identification of several critical genetic and enzymatic pathways that controls cell cycling. We now know that the progression of a cell through the cell cycle is controlled in part by a series of protein kinases, the activity of which is regulated by a group of proteins called cyclins. Cyclins act in concert with the cyclin-dependent kinases (CDKs) to phosphorylate key substrates that facilitate the passage of the cell through each phase of the cell cycle [1,2]. A critical target of cyclin-CDK enzymes is the retinoblastoma tumour suppressor protein, and phosphorylation of this protein inhibits its ability to restrain activity of a family of transcription factors (E2F family), which induce expression of genes important for cell proliferation. In addition to the cyclins and CDKs, there is an emerging family of CDK inhibitors which modulate the activity of cyclins and CDKs. CDK inhibitors inhibit cyclin-CDK complexes and transduce internal or external growth-suppressive signals which act on the cell cycle machinery.

It is of interest to study how these factors regulate cell cycle and proliferation in renal cells such as mesangial cells and renal tubular cells. Further information on renal cell cycle regulation may provide new insights for our understanding of renal pathophysiology and therapeutic approaches.

In this review we summarize the recent reports which examine the regulatory mechanisms of the cell cycle in cultured renal cells or experimental animal models of renal disease. We place a special focus on the physiological and pathological roles of cell cycle inhibitors in the kidney.

Cell cycle mechanisms in mammalian cells

Progression through the first gap phase (G1) of the mammalian cell cycle is positively and negatively regulated by a variety of extracellular signals. Mitogenic signals such as growth factor stimulation are required for cells before they begin to replace their cellular DNA (S phase), but once cells enter the S phase, they can undergo mitosis (M phase) even if they are deprived of growth factors during the S, G2, and M phase intervals. Contrarily, anti-proliferative stimuli induce G1 phase arrest and in some cases trigger further cellular responses such as terminal differentiation, cell senescence, or apoptosis.

On the basis of current knowledge, control of the G1/S phase transition is largely a matter of regulating a set of specific cyclin-dependent kinase (CDK) activities. In mammalian cells, the G1/S-specific CDK activities are composed of complexes between D-type cyclins and either CDK4 or CDK6, and between cyclin E (and possibly cyclin A) and CDK2 (Figure 1). A variety of internal and external signals regulate G1/S-specific CDKs by modulating cyclin availability, the levels of CDK inhibitory proteins, and the phosphorylation status of CDKs [1,2].

When cells enter the cell cycle from quiescence (G0), D-type cyclins and cyclin E are synthesized sequentially during the G1 interval, both being rate limiting for S-phase entry. Genes encoding D-type cyclins (D1, D2, and D3) are progressively induced as a part of the response to mitogenic stimulation. D-type cyclins assemble with CDK4 and CDK6, and these cyclin D-bound cdks must be phosphorylated on a threonine residue by a cdk-activating kinase (CAK) to acquire catalytic activity. Retinoblastoma protein (pRb) is a key physiological substrate of cyclin D-bound cdks, i.e. CDK4 and CDK6. In turn, pRb binds to and negatively regulates transcription factors such as E2F, whose activities are required for S-phase entry. Cyclin E is expressed periodically at maximum levels...
Role of cell-cycle-regulatory proteins in mesangial cells and glomerular disease

The proliferation of glomerular mesangial cells is a common feature of many glomerular diseases. The cell cycle of mesangial cells is under the control of a large number of humoral factors which either promote or suppress mitogenesis and cell proliferation. Recently Shankland et al. [3] demonstrated that mesangial cell proliferation in the Thy-1 model of experimental mesangial proliferative glomerulonephritis is associated with an upregulation of cyclin A and an increase in the expression and activity of CDK2. They also showed that the normal glomerulus has high endogenous expression of the CKI, p27\(^{Kip1}\), which decreases with the initiation of the mesangial cells’ proliferative response and then normalizes with the resolution of the mesangial cells’ proliferation [3]. Further, they found that p21\(^{cip1}\) has low levels of expression in the normal rat glomerulus, but that resolution of mesangial cell proliferation is associated with an increase in p21\(^{cip1}\) expression [3]. They also observed using p27\(^{Kip1}\), knockout mice that the absence of p27\(^{Kip1}\) was associated with a marked increase in the severity of the glomerular response to injury induced by anti-GBM antibody-induced crescentic glomerulonephritis [4].

Recently, in our own investigation of the mechanisms of the cell-cycle regulation of rat mesangial cells, we produced adenovirus vectors containing coding sequences of cyclin D1, p16\(^{Ink4a}\), and p21\(^{cip1}\), and investigated whether transfer of these genes changes expression of the CKI, p27\(^{Kip1}\), and p18\(^{Kip1}\) (Kip family). Their inhibitory action concerns a large range of cyclin–CDK complexes involved in the G\(_1\) and S phases. We also demonstrated that endothelin-1 induced cyclin D1 expression and stimulated CDK4 activity and cell cycle progression via A-type receptor in rat mesangial cells [6]. These effects were regulated by expression of cyclin D1, p16\(^{Ink4a}\), p21\(^{cip1}\), and phosphorylatable form of pRb. Schoechlmann et al. [7] reported that phosphorylation of pRb is required for PDGF-induced mesangial cell proliferation in vitro. Prevention of pRb phosphorylation by TGFB-β or by overexpressing the non-phosphorylatable form of pRb inhibits mitogen-induced mesangial cell proliferation in vitro [6,7].

Cell-cycle regulation of tubular cells and acute renal failure (ARF) models

DNA replication and proliferation of renal tubular cells occur during recovery from ischaemic acute renal failure (ARF). During this process, quiescent renal cells in the G\(_0\) phase enter a new phase of the cell
cycle, the G1 phase. Some of the immediate early genes such as c-fos and Egr-1 are reported to increase during the G0/G1 transition after ischaemic ARF [8]. However, the types of cell-cycle-related genes expressed in the G1/S phase during recovery from ARF are not fully known.

Recently Megyesi et al. [9] demonstrated increased expression of p21cip1 in three different models of ARF (ischaemia, ureteral obstruction, and cisplatin administration). They also demonstrated that p21cip1 expression is localized exclusively in cells of thick ascending limbs and distal convoluted tubules in ARF. They suggested that p21cip1 gene transcription is a general response to renal injury and could be a key determinant of cell fate in the cells in which it is expressed [9]. They also found that p21cip1 knockout mice display a more rapid onset of the physiological signs of acute renal failure, develop more severe morpohological damage, and have a higher mortality [10]. They speculate that the induction of p21cip1 after acute renal damage by cisplatin is a protective event for kidney cells [10]. They demonstrated that cisplatin administration caused kidney cells to start entering the cell cycle [10]. However, cell-cycle progression is inhibited in wild-type mice, whereas kidney cells in the p21cip1 knockout mice progress into S-phase. They propose that p21cip1 protects kidneys damaged by cisplatin by preventing DNA-damages cells from entering the cell cycle, which would otherwise result in death from either apoptosis or necrosis [10].

Park et al. [11] also demonstrated that the proliferative index increased in the kidney section, and that the mRNA and protein levels of cyclins D1, D3 and B; the mRNA levels of cyclin A; the protein levels of CDK4 and CDK2; and the activities of CDKs (CDK4, CDK2 and cdc2) all increased in the outer medullae of kidneys after ischemic injury. They suggest that the temporal induction of proliferative activity in outer medullary tubules was closely linked with the cyclin/CDK system for regeneration of kidney after ischemic injury [11].

We also demonstrated the expression and regulation of cyclin D1, cyclin D3, CDK4, p21cip1, and p27kip1 during recovery from ischemic ARF [12]. We found that cyclin D1, cyclin D3, and CDK4 increased after reperfusion, while cyclin D2 showed no significant change. Interestingly, among the Kip family members, p21cip1 reached its peak level at 24 h after reperfusion, while p27kip1 showed a decrease at the same point.

These reports have suggested that the control of cell-cycle progression plays critical role in the pathophysiology during the recovery from acute renal failure [8–12]. Thus, the further understanding of the checkpoint control in acute renal failure may lead to new therapeutic target to ameliorate the pathophysiology of acute renal failure.

**Renal tubular cell hypertrophy and cyclin kinase inhibitor**

Renal tubular hypertrophy is observed in many pathological conditions such as diabetes mellitus, loss of renal mass, and protein feeding. The mechanism of renal hypertrophy is largely unknown. Recently two groups reported that the mechanism of tubular hypertrophy is pertinent to cell-cycle-related genes. Franch et al. [13] reported that TGF-β1 converts the EGF-induced growth response from hyperplasia to hypertrophy by causing cell cycle arrest at the restriction point in late G1 via reduction of the cdk2/cyclin E kinase activity. Wolf et al. [14] reported that angiotensin II stimulated p27kip1 protein expression in LLC-PK1 cells, and that this induction of CDK inhibitor is a necessary prerequisite for the subsequent generation of tubular hypertrophy. Our preliminary experiments demonstrated also that Ang II caused hypertrophy of LLC-PK1 cells with increment of p27kip1 protein level, and that overexpression of p21cip1 and p27kip1 using adenovirus caused hypertrophy in LLC-PK1 cells. On the other hand, overexpression of p16ink4a did not cause hypertrophy [15].

Although these findings from the cell culture system are informative, the in vivo mechanisms of renal hypertrophy are more complex and need to be clarified both in the cell culture system and animal models of renal hypertrophy.

**Summary**

Our understanding of the cell-cycle mechanisms has progressively advanced in the past few years. Cyclins and cyclin-dependent kinases play major roles as positive cell-cycle regulatory proteins and CDK inhibitors; while the Kip family and INK4 family are negative regulatory proteins in mesangial cells and renal tubular cells. An understanding of the cell cycle is essential for the rational design of novel pharmacotherapeutic approaches to suppress the excessive proliferation of mesangial cells in glomerular disease and hypertrophic tubular disease.

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Introduction

For many years catecholamines are known to participate in the regulation of glomerular blood flow and microcirculation, mainly by influencing cellular functions of the renal vascular and the glomerular mesangium [1]. Until recently knowledge about the actions of catecholamines on cells from the glomerular filtration barrier is, due to their unique localization, limited. These cells, i.e. podocytes and glomerular endothelial cells are probably involved in the control of glomerular haemodynamics and filtration. Especially the podocyte seems to be an important regulator of glomerular functions: it stabilizes the glomerular architecture, maintains a large filtration surface, and serves as an immunological barrier to plasma proteins [2]. Very recently Mundel et al. successfully propagated differentiated podocytes in cell culture, thus allowing the study of biological properties of these cells in vitro [3]. This article discusses new insights about the influence of catecholamines on podocyte function and the possible biological and pathophysiological relevance of the findings.

The physiological role of catecholamines in the glomerulus

Stimulation of renal sympathetic nerves produces a frequency-dependent decrease in the glomerular filtration rate, due to an increased glomerular arteriolar resistance, a decreased glomerular hydraulic pressure gradient, and a decreased glomerular ultrafiltration coefficient $K_f$ [4]. Morphological studies have shown that sympathetic nerve stimulation or addition of noradrenaline decreases the diameter of the glomeruli [5]. A decrease in $K_f$ after sympathetic nerve stimulation may at least partially be due to a reduction of glomerular surface area. In mesangial cells, noradrenaline increases the uptake of Ca$^{2+}$ and induces a cell contraction [6,7]. Thus, it has been suggested that noradrenaline-induced mesangial cell contraction might decrease $K_f$ by a reduction of the capillary surface area [7]. However, noradrenaline might not only contract mesangial cells but also podocyte foot processes, which are known to possess a rich contractile apparatus [8]. Noradrenaline-induced contraction of foot processes might also lead to a reduced capillary surface area and decreased $K_f$. It appears difficult to prove this hypothesis, but a detection of noradrenaline-induced changes of podocyte function may support its validity.

Catecholamines modulate cellular functions of glomerular cells

Very recently, we investigated the influence of catecholamines on cellular functions of differentiated cultured podocytes from a mouse carrying a transgene for a thermostensible variant of the SV40 T-antigen [9]. Podocytes from this mouse grown at 37°C exhibit a differentiated morphology and express specific immunological markers of podocytes in vivo [3]. Figure 1 shows an overview of catecholamine-mediated cellular signalling in podocytes: in cultured podocytes noradrenaline and the $\alpha_1$-adrenoceptor agonist phenylephrine increase the intracellular calcium activity ([Ca$^{2+}$]) [9]. Both agonists induced a fast transient [Ca$^{2+}$] transient, which was followed by a sustained [Ca$^{2+}$] plateau. The [Ca$^{2+}$] response to noradrenaline and

New aspects concerning the role of catecholamines in the pathogenesis of glomerular diseases

Hermann Pavenstädt

Department of Medicine, Department of Nephrology, University of Freiburg, Freiburg, Germany

phenylephrine was concentration-dependent with an EC$_{50}$ of $\sim 0.1$ $\mu$M for both agonists. The $\alpha_1$-adrenoceptor antagonist prazosin inhibited the noradrenaline induced [Ca$^{2+}$], increase, whereas an $\alpha_2$-adrenoceptor agonist had no effect, indicating that the [Ca$^{2+}$], increase induced by noradrenaline is mediated via an $\alpha_1$-adrenoceptor. Reduction of the extracellular Ca$^{2+}$ concentration did not affect noradrenaline mediated [Ca$^{2+}$], peak, whereas the [Ca$^{2+}$], plateau was inhibited, indicating that noradrenaline mobilizes Ca$^{2+}$ from intracellular stores, but also induces a Ca$^{2+}$ influx from the extracellular space. The $\alpha_1$-type Ca$^{2+}$ channel antagonist nicardipine did not inhibit the increase of the [Ca$^{2+}$], induced by noradrenaline. In addition, an increase in extracellular K$^+$, which should lead to an influx of Ca$^{2+}$ via $\alpha_1$-type Ca$^{2+}$ channels did not increase [Ca$^{2+}$], in podocytes, suggesting that noradrenaline-induced Ca$^{2+}$ influx in podocytes is not mediated by a $\alpha_1$-type Ca$^{2+}$ channel, but may be due to the activation of a receptor-operated or store-controlled Ca$^{2+}$ or non-selective cation channel. In subsequent experiments, we demonstrated that phenylephrine, noradrenaline, and the $\beta$-adrenoceptor agonist isoproterenol activate a Cl$^-$ conductance in podocytes leading to depolarization [9]. The rank order of potency for the adrenoceptor agonists in depolarizing podocytes was isoproterenol > noradrenaline > phenylephrine. A specific $\beta_2$-adrenoceptor antagonist inhibited the effect of isoproterenol, indicating that podocytes do not only express $\alpha_1$-adrenoceptors but also $\beta_2$-adrenoceptors. The depolarization of podocytes in response to isoproterenol is probably mediated by an increase in cAMP, because forskolin, a direct activator of adenylate cyclase, also depolarized podocytes and the addition of isoproterenol to podocytes resulted in an increase in cAMP. The physiological significance of the $\beta_2$-adrenoceptor mediated changes in conductance is not yet clear. Infusion of isoproterenol into the renal artery did not change glomerular haemodynamics [10]. However, these experiments have been performed in rats and infusion of isoproterenol into the kidney stimulates several hormone systems which might prevent a direct effect of isoproterenol on podocyte function. Under pathological conditions, an attenuated cAMP increase in response to glomerular $\beta$-adrenergic agonists has been observed in spontaneously diabetic rats [11]. A loss of podocytes is associated with the development of diabetic nephropathy and therefore a defective response to isoproterenol in podocytes might contribute to the pathogenesis of this disease [12].

**The contribution of podocytes in noradrenaline-induced acute renal failure**

The findings discussed above indicate that noradrenaline directly influences podocyte function. This might not only play a role under physiological conditions but may also be important for the pathogenesis of renal diseases such as acute renal failure (ARF). The pathophysiological mechanisms of ARF are not clearly understood, but renal vasoconstriction, tubular obstruction, back leakage of filtrate, and decrease in glomerular capillary permeability are involved. Podocytes maintain a large filtration surface through the slit membranes and are responsible for $\sim 40\%$ of the hydraulic resistance of the glomerular filtration barrier [13]. They might therefore be involved in the decrease of capillary permeability occurring in ARF. It has been reported that infusion of noradrenaline into the renal artery of dogs induces ARF, which was not due to vasoconstriction, tubular leakage, or tubular obstruction [14]. However, after infusion of noradrenaline filtration barrier damage has been observed.

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**Fig. 1.** Overview of catecholamines-mediated cellular signalling in podocytes.
Podocytes showed marked abnormalities including flattening of cell body and obliteration of foot processes [14]. Although a subsequent study using the same model found a lower degree of podocyte damage [15], injury of podocytes may play a role in noradrenaline-induced ARF.

Involvement of catecholamines in glomerular diseases

Different forms of primary glomerular injury often trigger a destructive glomerular process, which leads to a continuous decline in renal function. The histological hallmark of these pathological alterations observed in chronic glomerular diseases is glomerulosclerosis with tubulointerstitial fibrosis. Results from experimental models of chronic renal failure support the idea that the podocyte initiates and maintains the progression of glomerulosclerosis [16]. The progression of glomerulosclerosis is influenced by several factors including hypertension, magnitude of proteinuria, serum lipid concentrations, dietary protein intake, and smoking [17,18]. Regarding the progression factor ‘hypertension’, it is known that noradrenaline levels are increased in patients with chronic renal failure [19] and renal afferent denervation prevents in large part the development of hypertension in rats with chronic renal failure [20]. Vasoactive hormones not only increase systemic and intraglomerular pressure but also seem to modulate cellular functions of the filtration barrier [21]. One may therefore speculate whether noradrenaline accelerates the progression of glomerulosclerosis by directly influencing podocyte function. Is there any evidence for this hypothesis? Recently, Amann et al. have reported that glomerular and tubulointerstitial damage after subtotal nephrectomy are prevented by treatment with the central antisypathotrophic agent moxonidine and the ACE inhibitor ramipril, but not with the Ca$^{2+}$ channel antagonist nifedipine [22]. Moxonidine reduced the proportion of the sclerosed area of glomerular tuft to the same extend as ramipril, indicating that the effect of moxonidine on glomerular tuft lesions might be due to an inhibition of noradrenaline-mediated effects on podocytes, which are major players in the pathogenic events occurring after subtotal nephrectomy. On the other hand, unlike ramipril, moxonidine did not change podocyte hypertrophy after subtotal nephrectomy, indicating different abilities of these drugs to influence cellular morphology of the injured podocyte [22].

Conclusion and future perspectives

There is great body of evidence that catecholamines modulate glomerular cell function under physiological conditions and during disease. Future studies should clarify:

(i) Which factors are involved in the response of glomerular cells to catecholamines, i.e. whether catecholamines induce the release of inflammatory substances such as prostaglandines or oxygen radicals.

(ii) The role of protein kinase C in noradrenaline-mediated effects. Vasoactive hormones such as noradrenaline are known to stimulate protein kinase C, an important mediator of cellular functions, such as cell differentiation or growth. Inhibition of a protein kinase isozyme has been reported to reduce hyperfiltration and proteinuria in experimentally induced diabetes mellitus. Thus it seems reasonable to investigate whether protein kinase inhibitors might also reduce the development of glomerulosclerosis in chronic glomerulonephritis.

(iii) The functional meaning of the effects of noradrenaline in vivo. The immunological characteristics of the mouse podocytes in culture fit very well to the properties of podocytes in vivo, but functional changes of the podocyte may occur during cell culture. In addition, it is likely that there is an interaction between glomerular cells, which might lead to a different regulation of intracellular signaling systems and a distinct expression of hormone receptors. Therefore, it is necessary to investigate biological effect of vasoactive hormones on cells in the intact glomerulus. This project is presently under investigation in our laboratory.

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References
Familial Mediterranean fever: from inflammation to amyloidosis

Gilles Grateau

L’Hôtel-Dieu, Paris, France

Familial Mediterranean fever (FMF) is a fascinating disease which has been recognized recently [1]. The mode of inheritance was disputed, and finally defined as autosomal recessive with variable penetrance and high gene frequency in affected populations. FMF mainly affects populations of Mediterranean origin: Arabs, Armenians, Druses, non-Ashkenazi and less frequently Ashkenazi Jews, Turks, and probably many others. Clinical signs reflect two processes: 1) acute inflammatory crisis with fever and localized inflammation, and 2) amyloidosis of the AA type representing the most severe manifestation of the disease. The pathological mechanisms associated with these two processes are still poorly understood. The gene whose mutations are responsible for FMF has now been cloned and this should result in improved understanding of the disease [2,3].

**FMF is a non-periodic acute polyserositis sensitive to colchicine**

The most common sign of FMF is acute peritoneal inflammation resulting in severe abdominal pain and high fever. One out of three patients with these signs undergoes surgical intervention. The inflammatory process can involve all serous cavities: pleura, pericardium and testicular vasa. However, this tropism is relative and other tissues can also be involved, such as articular synovia, skin and muscle. Some observations of cutaneous and large tree vasculitis suggest that vascular inflammation can occur. Most of the attacks are two to three days long and the patients are well between them. Patients commonly have leucocytosis, increased erythrocyte sedimentation rate and increased serum concentrations of acute phase proteins.

Despite ignorance regarding the exact cause and pathological mechanisms leading to FMF, clinicians have a very efficient treatment which prevents the recurrence of most of the inflammatory crises and amyloid deposition [4]. Colchicine is the standard treatment for FMF, even though long-term use of colchicine is not innocuous. Recent genetic advances offer the theoretical opportunity for the long-term discovery of more specific molecules.

**FMF as a familial disorder: a new success of positional cloning**

Four decades of research have aimed at identifying a specific defect for FMF in the inflammatory reaction. The most convincing abnormality likely to be implicated in the mechanisms of FMF is a tissue-specific lack of a putative inhibitor of a proinflammatory protein of the complement pathway, the C5a fraction [5]. This inhibitor is still not well characterized.

The first step, primary location of the gene, was achieved in 1992 [6]. The gene responsible for FMF, MEFV, is located on the short arm of chromosome 16 (16p13.3). After five years of positional cloning, two groups independently and simultaneously discovered...
MEFV. It encodes a protein named marenostrin by the French group, referring to mare nostrum, the Latin name of the Mediterranean Sea, and pyrin by the American group, referring to pyros, the Greek name for fever [2,3]. The gene is 10 kb long, consists of 10 exons, and its mRNA is 3.7 kb long. The latter seems to be specific for the neutrophil. The genomic sequence of MEFV predicts a basic protein consisting of 781 amino acid residues and shares some similarities with proteins of the RoRet or B30.2 family, to which belong several transcription factors. Thus, marenostrin/pyrin may be a neutrophil-specific transcription factor. Of course, this has to be demonstrated by further cellular and molecular biology studies. Four missense mutations were identified in the distal part of exon 10 of the marenostrin/pyrin gene, in about 75% of the patients selected for the genetic study. We can easily hypothesize that a lot of other mutations will be discovered in years to come, associated with the varied forms of clinical presentation and across the diverse populations. The availability of a genetic test which identifies these four mutations will improve clinical diagnosis, and utilization of the colchicine treatment.

Marenostrin and the Mediterranean

Haplotype analysis of the disease-bearing chromosomes showed the existence of one or more founder effects in all the populations studied thus far. Of major interest is the fact that two of these four mutations, and the corresponding haplotype, are found in different populations. For instance, the M694V mutation, which is strongly predominant in non-Ashkenazy Jews is also present in Arabs, Armenians and Turks, suggesting a common origin for a part of these populations. These data provide new perspectives regarding the genetics of these populations.

Pyrin and fever

In all genetic diseases with a recessive mode of inheritance, we have to understand the mechanisms leading to a high frequency of the disease in the affected population. One possibility is the existence of a putative acquired advantage for heterozygotes. What could be (or could have been) the advantage of heterozygosity for a marenostrin/pyrin mutation? We have to think on the great scourges of the past, and of the future, i.e. infectious diseases. We propose that heterozygotes would be more resistant to infectious diseases because they are able to react against the microbial aggression with a more intense fever and inflammatory response. It is not long ago that Wagner-Jauregg received the Nobel prize for medicine for treating patients who were affected by neuro-syphilis with fever by giving them malaria. Marenostrin/pyrin probably controls an important pathway of the inflammatory response and reminds us that fever and inflammation are necessary to fight against infection.

FMF and amyloidosis: what is the missing link?

Amyloidosis of the AA type is the major problem of FMF. There is compelling evidence that amyloidosis is not only a complication of the inflammatory response but is rather, at least in part, an associated phenomenon. Firstly, there is no close link between the severity of the inflammatory crisis and the outcome of amyloidosis. Indeed, some patients present with amyloidosis without any previous inflammatory event or subclinical crises (so-called phenotype II). Secondly, it was clearly demonstrated that colchicine prevents the development of amyloidosis in every patient, whereas the inflammatory crises were not completely suppressed. Thirdly, the prevalence of amyloidosis varies among the Mediterranean populations. The role of the marenostrin/pyrin protein in the amyloid pathway is not as obvious. Some authors have suggested that MEFV encodes the human equivalent of the amyloid enhancing factor (AEF), an important molecule implicated in experimental amyloidosis, which is not yet well characterized [7,8]. Further studies would help to determine whether marenostrin/pyrin plays a direct role in the mechanisms of amyloidosis and, therefore, whether it is the missing link between inflammation and amyloidosis. Conversely, as is suggested by some authors, the absence of the ‘mythic ‘missing link’ is not a hindrance to the coherence of the Darwinian theory of evolution. If that is the case, other genetic or environmental factors are necessary to explain all the aspects of amyloidosis in FMF patients.

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Factor H—US?

Paul Warwicker, Judith A. Goodship and Timothy H. J. Goodship

Renal Unit, Lister Hospital, Stevenage and Departments of Medicine and Human Genetics, University of Newcastle upon Tyne, UK

It is now accepted that most cases of diarrhoeal haemolytic uraemic syndrome [(D+) HUS] are caused by verocytotoxin producing bacteria such as E. coli 0157:H7, however the cause of non-diarrhoeal HUS has historically remained elusive. The most plausible and enduring theories have involved abnormalities of prostacyclin metabolism [1] or of the amount and structure of von Willebrand factor [2].

Why is it important to define the cause of D−HUS? Firstly the disease still carries a significant burden of morbidity and mortality. Death rate, estimated at 9% and 29% in two recent studies [3,4], may be ‘over optimistic’ because of the inclusion of undefined numbers of patients with the closely related thrombotic thrombocytopenic purpura (TTP) which is more amenable to treatment. Secondly with the exception of plasma exchange few treatments have been demonstrated to be effective.

We propose a complement-based theory of microangiopathy, critically involving complement factor H, and speculate on possible future treatments.

Complement and HUS

Evidence implicating the complement system, and in particular the alternative pathway, exists for all forms of HUS. Low C3 levels were first described in D+HUS in the early 1970s and it has also been reported that persistently low levels are predictive of a poor prognosis [5,6]. These findings have been subsequently confirmed and further evidence of alternative pathway activation presented in studies which demonstrated increased breakdown products of C3 and factor B [7–9].

In D−HUS C3 is sometimes deposited in the renal arterioles, and C3 levels are often depressed [10]. In recurrent D−HUS profound depression of C3 is seen, particularly during relapses, but also in disease-free intervals [11–13]. An association with the hypomorphic fast allele of C3 has been reported in D−HUS [14], but no difference in complement activity between the alleles has been demonstrated [15]. In familial D−HUS alternative pathway activation has also been reported [12,16,17].

In a recent study we have found that in three families HUS maps to a region of chromosome 1q containing the gene for complement factor H. In one of these families and also in a case of sporadic D−HUS we have identified mutations in the factor H gene [18]. Although mutations in factor H have also recently been reported in mesangiocapillary disease [19], this is the first report in HUS.

Our findings are not unexpected as three previous studies have demonstrated an association between factor H deficiency and D−HUS. Thompson and Winterborn in 1981 [20], reported an 8 month old boy who presented with HUS; both he and his healthy 3 year old brother had 5–10% normal levels of factor H, inherited in an autosomal recessive fashion from consanguineous parents, each of whom had approximately 50% normal levels. Roodhooft et al. in 1990 [13] described a female infant who suffered three episodes of HUS (including an ultimately fatal recurrence following renal transplantation) with 48% normal levels of factor H probably inherited from her unaffected father who had 34% normal levels. Pichette et al. in 1994 [16] reported a family in whom two siblings suffered HUS: one died at an early age from diarrhoea-associated HUS (E. coli serotype 0119:B14) and the other suffered three episodes of HUS from the age of 19 and was shown to have 5% normal factor H levels. An asymptomatic sister also had 5% levels and several members of the extended family had approximately 50% levels.

What does complement factor H do?

Factor H is the most important plasma bound regulator of the alternative pathway [21]; it does this firstly, by binding with C3b, preventing the formation of the C3bBb (C3 convertase) complex and accelerating the dissociation of Bb from the active C3 convertase (so called decay-accelerating activity) [22,23]; secondly, by acting as a cofactor for factor I, a serine protease, which degrades C3b by cleaving the alpha chain of C3, converting it into the major opsonic form, iC3b [23]; and thirdly, by distinguishing between activator and non-activator surfaces [24].

Factor H is a plasma protein produced primarily by the liver with a concentration of approximately 300–600 mg/l. Deficiency or malfunction causing HUS is therefore consistent with the therapeutic response to plasma exchange.

The interaction of factor H and renal endothelium

It is interesting that recurrent episodes of thrombotic microangiopathy are not seen in HUS patients under-
What other diseases have been associated with abnormalities of factor H?

Deficiency of factor H is rare [21], and relatively few cases have been reported. Several cases of deficiency have been reported to have the clinical and histological features of type II mesangiocapillary glomerulonephritis (MCGN) [27,28] and in a pig model of inherited factor H deficiency homozygotes develop a lethal mesangiocapillary glomerulonephritis [29].

It is interesting that C3 nephritic factor, an IgG autoantibody that stabilizes C3 convertase (C3bBb) thus protecting it from dissociation by factor H, is also associated with MCGN type II. West has recently hypothesized that this form of glomerulonephritis is a function of a systemic state of complement activation [30].

The genetic and cellular basis of factor H-associated hypocomplementaemic MCGN in a child has recently been reported [19]. Using the techniques of immunofluorescent staining and confocal microscopic imaging of cultured fibroblasts, it was demonstrated that factor H secretion rather than the production was impaired. Two mutations affecting cysteine residues on each allele were shown to be responsible for this deficiency.

Susceptibility to bacterial infections, particularly Neisseria meningitidis, is a feature of factor H deficiency [27,28,31,32], as are, more rarely, SLE like syndromes [32,33], splenomegaly [34] and IgA nephropathy [34].

A complement theory of microangiopathy

The features of HUS, sometimes known as thrombotic microangiopathy, are seen in a variety of other conditions notably the renal crisis of systemic sclerosis—a situation histopathologically, haematologically and clinically similar to HUS. Comparing vascular endothelium from patients with systemic sclerosis with endothelium from patients with a variety of inflammatory diseases as well as normal controls, Venneker has demonstrated a markedly reduced (and often undetectable) expression of the membrane-bound complement regulatory proteins MCP (membrane cofactor protein) and DAF (decay accelerating factor or CD59) [35]. He postulates that this deficiency may contribute to vascular damage, resulting in intimal proliferation and finally fibrosis.

The combination of renal failure, thrombocytopenia and anaemia (albeit with derangement of coagulation) is also seen in pre-eclampsia. A recent immunohistopathological study demonstrated subendothelial deposits of IgG, IgM and notably C3, and it is interesting that the authors noted the similarity of the light microscopic features to mesangiocapillary glomerulonephritis [36].

On the basis of our findings in HUS and these studies we should like to propose a unifying theory of microangiopathy, based on deficiency or dysfunction of complement control molecules.

Prospects for treatment

Plasma exchange is complicated by allergy, isoimmunization, infection, vascular access and the necessity for large volume colloids infusions in oliguric patients. If, in plasma, factor H is the ‘active component’ (and a study has suggested that plasma administration rather than exchange is the critical step [37]) then purified factor H might be more convenient, safer and effective.

Recombinant CR1 (complement receptor 1), a solubilized form of the usually membrane-bound modulator of complement activity has been safely administered to patients to protect against complement driven reperfusion injury post-cardiac surgery [38].

Could factor H or other modulators of complement activation be used therapeutically in HUS? In the porcine model of factor H deficiency, the otherwise fatal mesangiocapillary glomerulonephritis could be reversed with porcine factor H concentrate [39]. It seems improbable that factor H therapy would reverse the pathology of established D—HUS but early intervention or prophylactic use post-transplantation might be beneficial.

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Tricking the parathyroid gland with novel calcimimetic agents

Edward F. Nemeth and Sharon A. Bennett

Introduction

The cloning and structural characterization of the parathyroid Ca\(^{2+}\) receptor by Brown and colleagues [1] constituted a breakthrough in our understanding of the mechanism by which parathyroid cells sense changes in the concentration of extracellular Ca\(^{2+}\). The Ca\(^{2+}\) receptor is a relatively new member of the G protein-coupled receptor superfamily and shares limited sequence homology with the metabotropic glutamate receptors. Activation of the Ca\(^{2+}\) receptor by elevations in the circulating levels of extracellular Ca\(^{2+}\) inhibits parathyroid hormone (PTH) secretion.

Genetic studies have shown that mutations in the Ca\(^{2+}\) receptor are the molecular lesions underlying inherited disorders of systemic Ca\(^{2+}\) homeostasis, such as autosomal dominant hypocalciuria, familial benign hypocalciuria hypercalcaemia, and neonatal severe primary hyperparathyroidism [2]. Furthermore these
All known type I calcimimetics are inorganic or organic compounds. The Potential benefits from the use of calcimimetic agents include an increased sensitivity of the Ca\(^{2+}\) receptor to activation by extracellular Ca\(^{2+}\). What are calcimimetic agents? Ligands that mimic or potentiate the effects of extracellular Ca\(^{2+}\) at the Ca\(^{2+}\) receptor have been termed calcimimetics, and there are at least two pharmacologically distinct types. Type I calcimimetic compounds are agonists, whereas type II calcimimetics are positive allosteric modulators that increase the sensitivity of the Ca\(^{2+}\) receptor to activation by extracellular Ca\(^{2+}\). All known type I calcimimetics are inorganic or organic polycations that lack the appropriate pharmaceutical properties necessary for in vivo testing. In contrast, the first-generation type II calcimimetic compounds, typified by NPS R-568, are small organic compounds that are potent and selective activators of the Ca\(^{2+}\) receptor and are suitable for in vivo testing. Calcimimetic compounds trick the parathyroid cell into sensing a hypercalcemic condition when in fact plasma levels of Ca\(^{2+}\) are normal. Calcimimetic compounds therefore offer a means of rapidly and directly suppressing the secretion of PTH without increasing the plasma level of Ca\(^{2+}\).

Is the hyperplastic parathyroid gland able to sense a calcium overload? An early issue in the development of calcimimetic compounds for hyperparathyroidism was whether the Ca\(^{2+}\) receptors in adenomatous or hyperplastic tissues are 'normal'. So far, comparisons between normal and pathological parathyroid tissues have not revealed any structural differences in the Ca\(^{2+}\) receptor cDNA [3]. What has been noted consistently, however, is an apparently lower level of expression of the Ca\(^{2+}\) receptor in hyperplastic and adenomatous parathyroid tissues [4,5]. Nonetheless there appear to be sufficient quantities of Ca\(^{2+}\) receptor remaining to regulate PTH secretion, because calcimimetic compounds have now been shown to suppress plasma levels of PTH rapidly in patients with primary or secondary hyperparathyroidism.

Initial clinical experience with calcimimetics

In postmenopausal women with primary hyperparathyroidism, there is a time- and dose-dependent reduction in plasma levels of PTH and Ca\(^{2+}\) following the oral administration of NPS R-568 [6]. By activating the Ca\(^{2+}\) receptor and decreasing secretion of PTH, calcimimetic compounds directly target the underlying hormonal imbalance leading to the signs and symptoms of primary hyperparathyroidism. In patients with this disease, a calcimimetic compound could conceivably constitute a stand-alone therapy.

A small study in renal dialysis patients with secondary hyperparathyroidism has also demonstrated the ability of NPS R-568 to lower plasma levels of PTH rapidly [7]. Elevated levels of PTH are just one of the problems, however, in the hyperparathyroidism that is secondary to renal failure and, in this setting, it is anticipated that therapy with calcimimetic compounds will be adjunctive. Supplementation with 1,25-dihydroxyvitamin D \(_3\) will be necessary to maintain proper systemic Ca\(^{2+}\) homeostasis and it will also be important to control plasma phosphate levels.

Potential benefits from the use of calcimimetic agents

Hypocalcaemia, in addition to lowered levels of 1,25-dihydroxyvitamin D \(_3\) and hyperphosphataemia, has long been known to stimulate hyperplasia of the parathyroid glands. The Ca\(^{2+}\) receptor might mediate this effect of extracellular Ca\(^{2+}\) on cellular proliferation. Indeed, daily treatment of rats with a calcimimetic compound prevented proliferation of parathyroid cells caused by subtotal nephrectomy [8]. If treatment with a calcimimetic compound is started at the time of subtotal nephrectomy, rats do not develop secondary hyperparathyroidism. Similar antiproliferative effects have been achieved by treating with calcitriol or by maintaining normal phosphate levels. Calcimimetic compounds, however, prevent parathyroid cell proliferation despite low levels of 1,25-dihydroxyvitamin D \(_3\) and chronic hyperphosphataemia. Thus, at least in rats it appears that Ca\(^{2+}\) receptor activation can override the stimuli to cellular proliferation triggered by lowered 1,25-dihydroxyvitamin D \(_3\) and elevated phosphate levels.

One appealing aspect of cotherapy with a calcimimetic compound lies in its potential to treat secondary hyperparathyroidism without the risk of causing hypercalcaemia. Another is the ability to titrate the dose of calcimimetic compound rapidly to achieve the desired level of PTH. One or both of these features are lacking in the treatment options currently available. In many patients with secondary hyperparathyroidism, calcitriol simply fails to lower plasma levels of PTH, and in many others it does so only at doses that cause hypercalcaemia and/or hyperphosphataemia. Some of the newer ‘noncalcaemic’ vitamin D analogues might overcome the limitations imposed by bouts of hypercalcaemia and/or hyperphosphataemia. It is not known if these new analogues will improve the percentage of patients that respond to treatment, which varies from 30 to 70% following treatment with calcitriol. So far...
there have not been any ‘non-responders’ following treatment with NPS R-568, but the patient population studied is small and the effects of calcimimetic compounds have not been tested in patients with severe hyperparathyroidism.

Differences between treatment with vitamin D metabolites and calcimimetics

There is, however, a fundamental difference between the mechanism of action of vitamin D metabolites (or phosphate binders) and calcimimetic compounds that enable the latter to alter plasma PTH levels in a manner not previously possible. Vitamin D metabolites act genocmically to decrease the synthesis of PTH. In those instances where calcitriol does lower plasma levels of PTH, the effects are slow in onset (often weeks to months) and persist for weeks after treatment is stopped. In contrast, calcimimetic compounds act on the mechanisms (the Ca\(^{2+}\) receptor) that regulates the moment-to-moment secretion of hormone.

Calcimimetic compounds can lower plasma levels of PTH within 20 min after oral dosing, and levels return to pre-dosing levels within 24 h. These different mechanisms of action result in very different profiles of change in plasma levels of PTH (Figure 1). Calcimimetic compounds allow, for the first time, daily intermittent decreases in plasma levels of PTH. The amplitude (or maximal decrease) in PTH levels is largely dependent on the dose of compound. The frequency and the waveform of the changes in plasma PTH can be varied by altering the pharmacokinetic properties of the compound and by altering the dosing regimen. In contrast, treatments that affect the synthesis of PTH often do not cause large changes in amplitude, and they cannot cause daily oscillations in plasma levels of PTH. The additional clinical benefits of intermittent changes in PTH levels, when compared to those of current therapies, is speculative but intriguing. It is conceivable that intermittent decreases in abnormally elevated levels of PTH might have positive effects on bone akin to those achieved by intermittent increases in otherwise normal levels of PTH.

In an animal model of secondary hyperparathyroidism with high-turnover bone lesions, pulsatile decreases in plasma levels of PTH (achieved by daily oral dosing with NPS R-568) reversed osteitis fibrosa and improved bone biomechanical strength [9]. At least in this animal model, intermittent decreases in abnormally high levels of PTH improved bone quality.

Perspectives

It is the ability of calcimimetic compounds to cause both short- and long-term changes in plasma levels of PTH that set them apart from all other current therapies. Whether such compounds will eventually become a mainstay in the management of hyperparathyroidism is still to be determined. At the very least, compounds that act on the Ca\(^{2+}\) receptor will constitute important pharmacological probes to discern the functions of the Ca\(^{2+}\) receptor and the skeletal mechanisms of action result in very different profiles of change in plasma levels of PTH.

Fig. 1. Contrasting effects of vitamin D analogues and metabolites, and calcimimetic compounds on plasma levels of PTH. The frequency, waveform, and amplitude of plasma PTH levels can be varied by altering the pharmacokinetic properties and dosing regimen of the calcimimetic compound. Omitted for the sake of clarity are pulsatile (episodic) changes in plasma levels of PTH, which occur with a frequency of about seven per hour, and small circadian variations.

References

Protein intake—new evidence for its role in diabetic nephropathy

Monika Toeller and Anette E. Buyken
Clinical Department, Diabetes Research Institute at the Heinrich-Heine-University, Düsseldorf, Germany

Introduction

Blood pressure and glycaemic control are well established factors influencing the development and progression of diabetic nephropathy. However, regarding the involvement of protein intake in the aetiology of renal disease, state-of-the-art lectures mostly summarize current evidence with a question mark. Indeed, the role of protein intake in the prevention or progression of nephropathy remains ambiguous, with many questions still awaiting conclusive answers. Recent findings from large-scale intervention studies in non-diabetic subjects indicate that the effort to reduce protein intake is rewarded by only small benefits for the progression of nephropathy [1,2]. However, studies in people with clinically overt diabetic nephropathy suggest that the situation may be different in individuals with type 1 diabetes [3,4]. Is protein intake thus more relevant for diabetic nephropathy? Hence, are low protein diets effective in slowing its progression? In that case, can an early introduction of low protein diets even prevent renal disease [5,6], which individuals with type 1 diabetes are so prone to develop [7]? Should we, therefore, promote a low protein diet for individuals with diabetes mellitus and if so at which stage of the disease? Should we advise type 1 diabetics to restrict their protein intake when a macroalbuminuria is diagnosed, or already when they present a microalbuminuria or even long before that? How low do low protein diets need to be? Or conversely: which upper limit of protein intake should not be exceeded? Is there a specific level above which protein intakes need to be discouraged?

Some new aspects of the protein issue

Recent evidence from individuals with type 1 diabetes suggests that protein intakes do indeed matter for the development and/or progression of renal disease because they are associated with urinary albumin excretion rates (AER). We found a significant relation to levels of AER for both total and animal protein intakes (% of energy) in type 1 diabetic patients from the EURODIAB IDDM Complications Study. This cross-sectional, clinic-based study in 31 European centres, was designed to explore risk factors for diabetic complications. Nutritional intake was assessed in >2800 type 1 diabetic patients. Presumably due to the size of the stratified sample could we demonstrate a clear association between AER and protein intakes [8], which former smaller studies were not able to identify.

More detailed analysis revealed that the trend of AER to increase with higher intakes of protein was largely due to higher levels of AER in those individuals who consumed >20% of their dietary energy as protein. For type 1 diabetic persons with protein intakes up to 20%, mean AER remained <20 μg/min, but in individuals with a protein consumption >20% of food energy intake mean AER levels were in the microalbuminuric range (≥20 μg/min) [8].

In comparison to the key approaches for an effective prevention of diabetic nephropathy—the optimization of blood pressure and glycaemic control—the association of protein intake to the progression of nephropathy is much weaker. This is commonly raised as an argument against an early consideration of protein restriction. However, in the EURODIAB IDDM Complications Study we could show that the trend of AER to increase with higher dietary protein intakes was particularly pronounced in patients with hypertension and/or elevated HbA1c values [8].

Protein consumption is two times higher than required

Debates on the relevance of protein restriction for the progression of renal disease often relate to the efficacy of a diet providing 0.8 g protein/kg body weight per day in comparison to a diet with 0.6 g protein/kg body weight. Meanwhile the vast majority of European individuals with type 1 diabetes consume more than twice as much dietary protein. In the EURODIAB IDDM Complications Study average protein intake was 1.5±0.5 g protein per kg body weight, which amounts to 17.6±3.5% of total energy intake. About one out of four type 1 diabetic patients consumed >20% of protein [8,9]. Throughout Europe animal protein provided ~70% of the protein consumption and protein intakes of the type 1 diabetic individuals were uniformly higher than commonly observed in the general population of the respective country.

Once patients presented micro- or macroalbuminuria they tended to even further increase their protein intake: particularly persons with macroalbuminuria,
but also subjects with microalbuminuria consumed more total protein and more animal protein than individuals with normoalbuminuria [8].

Should current recommendations for protein intake be updated?

The Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes and the American Diabetes Association (ADA) recommend a protein intake ranging between 10% and 20% of total energy to people with diabetes mellitus. Patients with incipient or manifest nephropathy should be advised to reduce their protein intake to the lower end of this range (0.7–0.9 g/kg body weight). The Associations felt that not enough scientific evidence was available to generally recommend a lower protein intake for all individuals with diabetes [10,11].

The rationale for the recommendation not to exceed a protein intake of 20% was largely based on the consumption commonly observed in the general population [11]. This recommendation is now confirmed by our finding that protein intakes >20% are associated with elevated levels of AER in European individuals with type 1 diabetes. However, since mean AER increased to levels in the microalbuminuric range when the patients’ protein intakes exceeded 20% of energy, more attention should be directed towards the avoidance of such high protein intakes. Dietary advice given to individuals with diabetes should always discourage excessive protein intakes, regardless of albuminuria. For persons who already present a micro- or macroalbuminuria a routine screening for protein intake appears to be essential, particularly when arterial pressure is raised and/or diabetic control is poor. Those individuals whose protein intake exceeds 20% of total energy should be advised by a dietician on how to avoid undesirably high amounts of dietary protein.

How can high dietary protein intakes be avoided?

What practical dietary advice can we give patients to help them reduce their protein intake and maintain a lower protein consumption for years or even for the rest of their lives? Generally, a modification of protein intake should be explored as a feasible therapeutic approach to reduce the adverse effects of a high protein ingestion, since specifically animal protein appears to exert deleterious effects on renal function [6,8,12]. Therefore, substitution of vegetable protein for protein from animal sources should be considered. Such a modification of protein supplying food groups would also reduce the intakes of total fat and saturated fatty acids. High intakes of saturated fatty acids—as observed in individuals with type 1 diabetes from most parts of Europe [9]—are considered to be a risk factor for cardiovascular disease, from which a large number of the patients with diabetic nephropathy will eventually suffer and die [13]. Thus, a concomitant reduction of saturated fat intake is a meaningful ‘side effect’.

The main dietary sources for animal protein require particular attention. The consumption of meat should be restricted to one serving per day (~125 g). Also, cold meat and cheese need specific consideration and should only be consumed in small amounts. Furthermore, two daily servings of milk or milk products (e.g. one yoghurt and one glass of milk) are sufficient to meet nutritional needs. The consumption of large amounts of curd—as recommended to individuals with diabetes mellitus until the early 80s in order to achieve satiety—should no longer be advised, even if it is low in dietary fat. Instead, the consumption of protein from vegetable sources, which are also rich in dietary fibre, should be encouraged.

References

The acute renal effects of Angiotensin II receptor blockers

Roland Veelken¹, Karl F. Hilgers¹ and Johannes F. E. Mann²

¹Medizinische Abteilung, Krankenhaus Schwabing, Akademisches Lehrkrankenhaus der LMU, München and ²Medizinische Klinik IV, Universität Erlangen-Nürnberg, Germany

Introduction

Angiotensin II (ANG II) has a wide range of effects on resistance vessels, kidney and heart through type 1 and type 2 (AT1, AT2) receptors [1]. Effects through AT1 receptors on vessels, glomeruli and tubules of the kidney include vasoconstriction, cell proliferation, and matrix protein synthesis. Activation of AT2 receptors leads to vasodilatation, inhibition of cell proliferation and presumably programmed cell death (apoptosis). The latter effects oppose to a certain extent the consequences of a AT1 receptor stimulation.

Recently developed non-peptide antagonists for type 1 receptors of angiotensin II (ATA) will be more and more widely used in the treatment of patients with primary or renal hypertension, and possibly in patients with heart or kidney failure. Another class of drugs that blunt the effects of the renin–angiotensin system through inhibition of angiotensin II formation are the ACE inhibitors (ACEI), which potently increase bradykinin levels as well. Much is known about the acute effects of ACEI on the kidney. Some of these actions are desirable like antiproteinuria and natriuresis, others are unwanted, most notably acute falls in glomerular filtration rate (GFR).

What about the acute renal effects of the new ATA and how do they compare with the ACEI?

Studies in animals

Early experimental studies with ATA in rats with renal diseases offered some surprises. In a number of settings, the acute renal effects of ATA proved to be clearly different from ACEI. Thus, in rats with severe volume depletion, resistance of the efferent glomerular arteriole was reduced to a much greater extent by ACEI than by ATA. In parallel, the intraglomerular hydraulic pressure and the single–nephron GFR fell with the ACEI, being maintained on the ATA. The action of the ACEI was blunted by blockade of bradykinin receptors [2]. Bradykinin, the metabolism of which is blunted by ACEI but not by ATA, may contribute to the control of glomerular haemodynamics, thus being responsible for the differences between the two classes of ANG II inhibiting drugs. These results support to a certain extent the hypothesis that ATA are less likely than ACEI to induce acute renal failure as an unwanted side-effect in patients. Controlled trials comparing the two classes of inhibitors of the renin system in man with conditions such as renal artery stenosis or volume depletion are as yet lacking.

One should keep in mind that the contribution of bradykinin to the control of glomerular haemodynamics differs vastly between species; furthermore, the study mentioned above investigated rats with very severe volume depletion [2]. In other rat models with diabetic hyperfiltration and with experimental nephritis results were comparable to the dehydrated animals. In the diabetic rat with high GFR [3], ACEI were more effective than an ATA to acutely normalize GFR. Again, a bradykinin antagonist inhibited the action of the ACEI in this situation. In experimental nephritis [4], an ATA was much less effective than an ACEI to reduce proteinuria. Despite those consistent differences of ATA and ACEI on acute renal changes in rats, there are many reports about quite comparable long-term renal effects of those two types of angiotensin inhibitor drugs [3,5,6] but this is outside the scope of the present communication.

Studies in men

How about patients? Doig studied severely volume-depleted healthy volunteers and showed a clear-cut, reversible decrease in GFR by almost 50% when an ATA was added [7]. This study was controlled by placebo but not by ACEI or other antihypertensive agents. Controlled trials comparing ATA and ACEI in patients at risk of acute renal failure are as yet lacking except for the ELITE study [8]. More than 700 patients with heart failure were randomly assigned to an ATA or an ACEI; a similar incidence (about 10% in each group) of an acute decrease of GFR was established. One unpublished study by Mimran et al. in 17 patients with renovascular hypertension and moderately impaired renal function showed an identical decrease.

Correspondence and offprint requests to: Prof. Dr Johannes Mann, Krankenhaus Schwabing, 6. Medizinische Abteilung (Schwerpunkt: Nieren- & Hochdruckkrankheiten), D-80804 München, Germany.
in GFR with captopril (50 mg) or with losartan (200 mg). In one case report, however, a transplanted patient tolerated ATA without an decrease in GFR while acute renal failure developed during ACEI treatment [9].

How about proteinuria? In the absence of long-term studies in men, the effect of ATA on protein excretion may to a certain extent be a surrogate marker for nephroprotective potential of these drugs. Gansevoort et al. [10] demonstrated similar effectiveness of ATA and ACEI in patients losing several grams of protein per day on a low-sodium diet. The data indicate that the antiproteinuric action of the ATA was slower in onset than that of ACEI. There also appear to be subtle differences in the natriuretic effect which are quite apparent in rats [11]. In patients the latter action of ACEI is sustained over several days and quite substantial, comparable to a standard dose of hydrochlorothiazide [12]. With ATA, there is also an initial natriuresis in volunteers [13], but the effect apparently is not sustained. In other words, it remains to be shown whether ATA can induce a negative sodium balance, as the ACEI do.

Clinical implications

What are the conclusions for patient management? The results in rats suggest that ATA may provide similar renal protection as ACEI with less risk of acute renal failure. However, men appear to be different from rats, again [7]. The cautious physician will use ATA in renal patients with the same care that is mandatory for ACEI. In other words, renal function must be carefully checked whenever there is a risk of acute renal failure. The major reasons for side-effects are intravascular volume depletion, overzealous use of diuretics, renovascular hypertension, renal artery stenosis/bilateral; single kidney aid transplants. Most patients, however, will show similar changes in GFR with an ATA and an ACEI if the baseline conditions are the same. Nevertheless, in an individual who clearly profits from an ACEI (e.g. decrease in proteinuria or improvement in cardiac function) but presents with an acute decrease in renal function, a very cautious trial of an ATA is justified. This recommendation is based on the animal studies and on some anecdotal observations [9].

Perspectives

Many questions will have to be answered in the future. Is the vigorous stimulation of AT2 receptors that occurs during ATA treatment safe, or are the high circulating levels of angiotensin II potentially harmful in some circumstances? Is bradykinin, the tissue concentration of which is likely to be increased during ACEI treatment, an important cofactor in ameliorating end-organ damage in e.g. hypertension? Or should we assume that the putative role of bradykinin for cough and angioneurotic oedema is a sufficient cause to eventually eliminate ACEI altogether? Further research to address these questions on the chronic effects of ATA could possibly yield guidelines for differential therapies with ATA and ACEI, depending on the pathophysiology of the disease and the individual circumstances of the patient to be treated.

References

Calcium channel blockers in diabetic nephropathy—is there life after the ABCD trial?

Pietro Zucchelli
Malpighi Department of Nephrology, Policlinico S. Orsola-Malpighi, Bologna, Italy

The appropriate blood pressure control in diabetes (ABCD) trial was designed to test the primary hypothesis that intensive blood pressure control, as compared to usual blood pressure control, prevents or slows down progression of diabetic nephropathy, neuropathy, retinopathy and cardiovascular disease in non-insulin-dependent diabetes mellitus (NIDDM). In a recent publication [1] data on a secondary end-point were reported, i.e. the incidence of (fatal or non-fatal) myocardial infarction in a subgroup of ABCD patients who had hypertension. In this cohort a significantly higher incidence was noted among those assigned to the short acting calcium channel blocker (CCB) Nisoldipine compared to those assigned to receive the ACE-inhibitor Enalapril: 25 vs 5 events during 5 years of follow-up, yielding a risk ratio of 9.5.

The data will undoubtedly lead to uncertainty and doubts concerning the proper use of CCBs in the treatment of renal patients, particularly those with diabetic nephropathy. I shall try to interpret critically this important nephrological topic.

Control of arterial pressure in diabetic nephropathy

Arterial hypertension and renal disease are closely interrelated in many ways: hypertension may precede renal disease, but also be caused by, or aggravated by, renal disease: it is a strong predictor of all causes of morbidity and mortality and, last but not least, it accelerates progression of renal disease. The risk of developing nephropathy, one of the most common causes of end-stage renal disease (ESRD) in many Western countries, seems to be linked, at least in part, to an inherited predisposition to hypertension [2]. In addition, there is overwhelming evidence from experimental models and clinical observations that elevated blood pressure is a potent progression promotor. Systemic hypertension probably acts through elevation of filtration pressure; this results from loss of glomerular autoregulation in the diabetic milieu. Elevated glomerular fluid shear stress is thought to initiate a cascade of events ultimately leading to glomerulosclerosis and tubulo-interstitial scarring [3]. Angiotensin II seems to play a central role. This notion finds support in data showing that ACE inhibitors and possibly also angiotensin II receptor antagonists, cause important reduction in proteinuria and disease progression, more than explained by lowering of blood pressure [2]. On the other hand, a large body of evidence indicates that optimal blood pressure control per se to values of less than 140/90 mmHg reduces albuminuria and attenuates the rate of loss of GFR [4] independent of the type of antihypertensive used.

Consequently, in patients with diabetic nephropathy, as in patients with non-diabetic renal disease, optimal blood pressure control is mandatory [5].

Monotherapy or combination of antihypertensive agents

Monotherapy with low or standard doses is the ideal way to control sustained hypertension. However, some clinical studies evaluated to what extent normalization of blood pressure can be achieved with monotherapy in patients without and with renal disease. It was noted that target diastolic blood pressure could be reached in no more than 37% of cases [6] and this is particularly true for hypertensive patients with diabetic or non-diabetic renal disease. In fact, in many studies of patients with serum creatinine levels between 2 and 4 mg/dl, up to four classes of antihypertensive drugs were required [2,4]. Therefore, appropriate combinations of different antihypertensive drugs are necessary to obtain appropriate lowering of blood pressure without incurring unacceptable side effects. In the ABCD trial, 30–50% of hypertensive patients with NIDDM required one or two additional antihypertensive drugs [1].

Calcium channel blockers in diabetic nephropathy

CCBs are a heterogeneous group of agents interfering with transmembrane calcium influx. They are widely used because they are effective antihypertensive drugs. The antihypertensive action seems to be associated, amongst others, with the property of CCBs to act as non-specific post-receptor antagonist of several vasoconstrictive agents, including angiotensin II. In addition, CCBs have antiproliferative and cytoprotective...
properties and retard experimental atherosclerosis [7]. In experimental models as well as in humans with renal diseases, particularly in patients with diabetic nephropathy, the result of the administration of CCBs on progression has remained controversial. In fact, CCBs cause preferential afferent vasodilation and impairment of renal autoregulation. As a result, a greater proportion of systemic blood pressure is transmitted to the glomerular vascular bed [8]. The antiproteinuric and nephroprotective effects of CCBs are directly related to their ability to normalize systemic blood pressure. Many of the discrepancies in experimental and clinical studies can be explained as the result of different levels of blood pressure reduction. Moreover, CCBs are heterogenous: their effect to block the five subclasses of L-type calcium channels differs, and this point may also be responsible for some of the discrepancies.

In conclusion, CCBs are only nephroprotective if adequate blood pressure control has been achieved. Possibly, non-dihydropyridine CCBs offer better renal protection compared to dihydropyridine CCBs. In a randomized study on 52 patients with NIDDM, diabetic nephropathy and hypertension, similar levels of blood pressure control were achieved with either ACE inhibitors or non-dihydropyridine CCB. Both agents significantly reduced proteinuria and slowed down the progression of renal disease to a similar extent [7].

So in the past it was argued that there are many good reasons for combining ACE inhibitors and CCBs. The arguments include not only the fact that additional antihypertensive action can be obtained with possibly less side effects, but also the above mentioned point that additional beneficial effects may be achieved.

**Do we have to modify this statement after the ABCD report?**

A peculiar clustering of adverse cardiovascular outcomes was observed in hypertensive diabetic patients, in the ABCD study [1], as well as in one other randomized trial [9]. These observations would be consistent with the idea that in these high risk patients, CCBs cause an excess of adverse events.

Several observations, however, militate against this interpretation. First, many recent case control studies and several prospective randomized placebo-controlled trials found no increase in adverse cardiovascular outcomes when long acting CCBs were used as recently summarized by McMurray and Murdoch [10]. On the contrary, the relative risk of death tended to be lower. Second, the ABCD study found an increased incidence of fatal and non-fatal myocardial infarction, but not of overall cardiovascular death or death from any cause. Fatal and non-fatal myocardial infarction was only a secondary endpoint. This raises the suspicion that this may have been a spurious finding: patients were not randomized according to their cardiac status, thus raising the possibility of a chance difference between the two groups.

Finally, in the ABCD trial, a group on placebo treatment was not studied. Thus, we do not know whether CCBs were just less effective than ACE inhibitors or truly deleterious. To interpret the absolute rates of myocardial infarction or cardiovascular death, one has to compare the observations with data published in literature. The rate of myocardial infarction in the ABCD study was by no means greater than might be expected in such a high risk population. Their high risk is illustrated by the fact that 33% had LVH by electrocardiography. An illustrative example of the risk to draw the wrong conclusion from analyzing a secondary end-point is provided by the recently published AIPRI (Ace Inhibition in the Progressive Renal Insufficiency) trial. This was a randomized, multicentre study that demonstrated the value of ACE inhibitors in slowing the progression of renal disease. An unexpected difference of mortality, i.e. of a secondary end-point, was noted: nine deaths occurred during the 3-year follow-up in the benazepril group and only one in the placebo group. This result was actually explained by an abnormally low mortality rate in the placebo group. In fact, the recently published extension study concerning the large majority of patients who had originally been randomized to benazepril or placebo showed that the difference in mortality had completely disappeared after a median total follow up of 6.6 years. In contrast, the long-term beneficial effect of benazepril on progression was completely confirmed [11].

**Conclusion**

In patients with diabetic nephropathy as well as in patients with non-diabetic renal disease, proteinuria and preservation of renal function are primarily a function of blood pressure reduction. Because of their documented effect in improving renal survival and reducing cardiovascular events, ACE inhibitors (with or without diuretics) should be used as the first line agent in patients with diabetes and hypertension. Long-acting CCBs should be added, however, as a second step if target blood pressure values cannot be achieved with the administration of ACE inhibitors alone.

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Comment to the editorial of P. Zucchelli

Robert W. Schrier and Raymond O. Estacio

Department of Medicine, University of Colorado School of Medicine, Boulder, CO, USA

Zucchelli’s comment on our recent New England Journal of Medicine (NEJM) article entitled ‘The effect of nisoldipine as compared to enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension’ made some key points. Certainly the control of arterial blood pressure in diabetic patients is important in preventing or slowing progression of diabetic complications including nephropathy. The optimal level of blood pressure to prevent or slow diabetic complications however has not been established. The appropriate blood pressure control in diabetes (ABCD) clinical trial was based on the hypothesis that the accepted upper limit of normal blood pressure, 140/90 mmHg, may not be optimal to prevent or slow the progression of diabetic complications given the underlying abnormalities which occur in the capillary basement membranes throughout the body. A secondary hypothesis of the ABCD trial was that the level of blood pressure, intensive vs moderate, rather than the first line of antihypertensive agent, namely nisoldipine vs enalapril, would be significant. As reported in our NEJM paper, the secondary hypothesis of equivalency between nisoldipine and enalapril was rejected. After 5 years of follow-up in the hypertensive cohort the Data and Safety Monitoring Committee (DSMC) of the ABCD trial recommended that the nisoldipine patients be changed to enalapril because of the difference in the incidence of myocardial infarctions (MI) between the two groups (nisoldipine (25 of 235 patients) vs the enalapril (5 of 235 patients). We have emphasized in the paper that this was a secondary endpoint. Whether a primary or secondary endpoint, however, it can always be argued that a significant finding might not persist with a longer follow-up. The hypertensive diabetic cohort in the ABCD Trial had been followed for 5 years, and was within one year of the closure of the study on June 30, 1998. The members of the DSMC did not feel that the safety of the hypertensive diabetic patients should be jeopardized by following them on nisoldipine for the remaining year of the study.

It is correct that the termination of the comparison between nisoldipine vs enalapril in the hypertensive cohort was based on a morbidity result, i.e. MIs, rather than mortality endpoint (10 deaths in the nisoldipine vs 5 deaths in the enalapril group, P=NS). As we emphasized in the NEJM article, the number of MIs per year in the nisoldipine group over the 5-year follow-up of the hypertensive cohort was not significantly greater than historic controls published in the literature in type 2 diabetic patients. Thus, this finding would support a cardioprotective effect of the angiotensin converting enzyme inhibitor, enalapril, rather than any deleterious effect of the calcium channel blocker, nisoldipine. However, since we did not have a placebo control this must be a tentative conclusion. It should be emphasized, however, that a placebo control would not be ethical in a hypertensive diabetic group of patients.

Before submitting our paper for consideration of publication to the NEJM, we analysed many potential factors which could explain the difference in MIs between the nisoldipine and enalapril treated patients in the hypertensive cohort rather than the drugs per se. In this regard, the only differences in the baseline characteristics were a slight, but statistically significant, higher mean HDL concentration and lower prevalence of abnormal ankle-to-brachial indices, as evidence of less peripheral vascular disease, in the nisoldipine group. These differences were therefore in the wrong direction to account for the observed difference in MIs between the nisoldipine and enalapril-treated hypertensive diabetic patients. There were no significant
differences in baseline cardiovascular events between the nisoldipine and enalapril treated hypertensive patients. During the 5 years of the study, no differences emerged between these two antihypertensive groups with respect to fasting blood glucose concentrations, glycahaemoglobin, plasma lipids, smoking, systolic and diastolic blood pressures. With respect to other medications, there was no difference between treatment with HMG-CoA reductase inhibitors, oral hypoglycemic agents or insulin use.

Zucelli is quite correct that while monotherapy is best for compliance purposes, frequently second-line antihypertensive medications are needed to reach the appropriate blood pressure goals. This was particularly true in the ABCD trial in those patients randomized to the intensive blood pressure treatment group. While there was no significant differences in the hypertensive cohort in the use of beta adrenergic blocking agents between the nisoldipine and enalapril treatment groups, the enalapril-treated patients received diuretics 49% of the time while the nisoldipine treated patients received diuretics 40% of the time. When adjusted statistically for this variable, the statistical difference in MIs between the nisoldipine and enalapril treatment groups remained. The statistical difference of MIs was also present when the intensive and moderate antihypertensive treatment groups were analyzed separately. We would therefore conclude from the results of our ABCD trial that ACE inhibitors should be the first line agent in treating hypertension in type 2 diabetes based on the observed effects in decreasing cardiovascular complications. Addition of diuretics, beta blockers and calcium channel blockers to optimally control blood pressure should also be considered.

Recurrent IgA nephropathy after kidney transplantation: not a benign condition

Jürgen Floege, Michael Burg and Volker Kliem

Division of Nephrology, Medical School, Hannover, Germany

Introduction

IgA nephropathy (IgAN) is the most common type of glomerulonephritis in the Western world [1]. Up to 25% of patients develop end-stage renal failure. When such patients receive a kidney graft, up to 60% will experience a histological recurrence of the disease. Until recently, it has been assumed that such recurrence of IgAN after transplantation is a relatively benign condition and hardly ever results in progressive graft failure. This assumption was derived from case reports and early studies on this subject [2,3]. Several recent studies [4–7] have re-investigated the above notion and will be the topic of this review. However, before embarking in details of these more recent studies, it appears useful to first analyse how clinically relevant recurrence of IgAN can be identified in renal transplant patients.

Chronic renal graft dysfunction has a multifactorial origin and results from both immunological mechanisms, in particular chronic allograft rejection, as well as non-immune mechanisms such as hypertensive damage, hyperlipidaemia, cyclosporine nephrotoxicity, etc. [8]. Usually, detailed clinical data and biopsy findings (in particular when examined by immunohistology and electron microscopy) can allow with some likelihood the differentiation between the relative contribution of dysfunction due to recurrent disease and other reasons, in particular chronic alloreactive damage. Clinically manifest recurrent IgAN is often associated with persistent microhaematuria and proteinuria exceeding 0.5 g/day as well as the demonstration of mesangioproliferative glomerulonephritis, i.e. not just recurrent mesangial IgA deposits, upon graft biopsy. Even when all these findings are present, however, the available data on recurrent IgAN need to be interpreted with the caveat in mind, that other mechanisms may have amplified recurrence-related graft damage in an additive or even synergistic manner. These considerations also imply that caution should be applied when interpreting studies, in which few clinical data are provided [9–11].

How frequent is recurrence of IgA glomerulonephritis in the graft?

In 1994 Odum et al. [4] published their observations in 46 transplanted IgAN patients followed for 3–183
Table 1. Summary of recent studies on the clinical relevance of recurrent IgAN after transplantation

<table>
<thead>
<tr>
<th>Authors [reference no.]</th>
<th>Patients (n)</th>
<th>Follow-up in the whole study population (mean and range; months)</th>
<th>Graft dysfunction/loss due to recurrence</th>
<th>Follow-up in patients with graft dysfunction/loss due to recurrence of IgAN (mean and range; months)</th>
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</thead>
</table>

*aOnly patients who received a transplant biopsy because of graft dysfunction or urinary abnormalities are included in the data shown. Five patients suffered from underlying Henoch–Schönlein purpura.

*bFour patients suffered from underlying Henoch–Schönlein purpura.

N.A., not available.

months. Histological recurrence was detected in 17 of 29 biopsied grafts (59%) and was only predicted by the length of time post-transplantation but no other clinical variables. Recurrence was associated with urinary abnormalities (microhaematuria and/or proteinuria) only in six of these patients, whereas five further patients showed both urinary abnormalities and progressive graft failure felt to be due to mesangioproliferative nephritis (Table 1). One of these five patients required dialysis at 74 months after receiving the transplant.

In 1996 Kessler et al. [5] reported on 71 patients who were followed for 4–120 months. Detailed data, however, were only provided for 28 patients who underwent graft biopsies (23 had underlying IgAN, five had suffered from Henoch–Schönlein purpura; HSP). Within these 28 patients histological recurrence of IgAN was detected in 13 grafts (46%). The histological recurrence was associated with urinary abnormalities and progressive graft failure due to mesangioproliferative glomerulonephritis in six patients. Out of these six patients four developed end-stage renal disease at 69–119 months after transplantation (Table 1). All four patients had exhibited a nephrotic syndrome prior to graft failure.

In 1997 Frohnert et al. [6] described the Mayo Clinic data in 51 grafted patients with underlying IgAN. Clinical recurrence of IgAN (defined as repeated persistent haematuria or proteinuria that was not explained otherwise) was noted in 26% of the patients. In 10 patients (19%) IgAN recurrence was documented by renal biopsy. These 10 patients also showed progressive loss of renal function and in three cases grafts were lost after 34, 83, and 175 months (Table 1). Interestingly, in two of these later cases, subsequent graft nephrectomies at 3 and 19 months after graft failure no longer revealed glomerular IgA deposits. Nevertheless, an adverse role of recurrent IgAN was suggested by the observation that 71% of the patients with recurrence but only 14% of the patients without recurrence lost a significant share of their GFR (>25%) during a median follow up of 3 and 4 years, respectively.

The Hannover experience

Also in 1997 we have reported our single centre experience in 61 patients with IgAN or HSP (n = 4) who had received 71 grafts and had been followed for 7–127 months [7]. Histological recurrence of IgAN was present in 61% of the 33 patients who underwent graft biopsy. In 23% of the whole patient population with IgAN graft dysfunction was felt to be due to recurrence of IgAN (Table 1). In patients with graft dysfunction due to other reasons it became apparent that the observation period was on average 1.5 years shorter than in the patients with clinically relevant recurrence. This suggests that the relevance of recurrent IgAN may have been masked in these latter patients by the more rapid manifestation of chronic allograft rejection and/or other reasons for graft failure. Neither clinical and laboratory findings prior to transplantation, the ACE I/D-gene polymorphism, the type of immunosuppression nor the course after renal transplantation were able to predict graft failure due to recurrent IgAN. Recurrence of clinically relevant IgAN did not appear to occur more frequently in the HSP patients (one recurrence in four grafted patients). Another important finding was that out of five patients who were re-transplanted after graft failure due to recurrent IgAN, three (including the one with initial HSP) again developed end-stage renal disease at 21–51 months due to repeated recurrence of the primary disease.

What conclusions can be drawn?

The above observations provide four important insights into progressive IgAN.

1. Recurrent IgAN after transplantation is not a
benign condition. A growing number of reports is now available to show that at ~5 years after transplantation recurrent disease does become a relevant clinical problem unless it is masked by prior graft failure due to other immune or non-immune mechanisms, in particular allograft rejection.

2. Conventional immunosuppression with low dose corticosteroids, azathioprine and/or cyclosporine A does not prevent recurrent IgAN, both on a histological and a clinical level. Based on this observation, one may also extrapolate to the primary disease, in which the above immunosuppressive approaches generally have not yielded satisfactory therapeutic efficacy.

3. Clinically relevant recurrent IgAN appears to represent largely a function of time post-transplantation and can not be predicted by other variables. In this respect the recurrent disease exhibits considerable clinical similarities with the original course of progressive IgAN.

4. Patients who have already lost a graft due to recurrent IgAN may be at particularly high risk for repeated graft loss due to recurrence upon re-transplantation.

Should transplantation be discouraged in patients with underlying IgA glomerulonephritis?

Long term stable courses of up to 183 months even in the face of histologically proven IgAN recurrence have been documented after transplantation [4–7]. Compared to many other patients suffering from systemic disorders who enter dialysis, those with IgAN generally have little co-morbidity and as such present ideal candidates for transplantation. Graft and patient survival in the first years after transplantation is reported to be superior to that of other transplant patients, possibly related to the increased occurrence of alloreactive IgA anti-HLA antibodies in such patients and their overactivity of the IgAN system. These IgA anti-HLA antibodies may be less pathogenic than IgG anti-HLA antibodies [12]. Given all these observations, primary IgAN definitely should not prevent transplantation, in particular, since even clinically manifest recurrences are usually insidious and not potentially life-threatening (in contrast to, for example, recurrent severe nephrotic syndrome in patients with underlying focal segmental glomerulosclerosis). However, it appears important that both physicians as well as patients with underlying IgAN (particularly those who have already lost a graft due to recurrence) are aware of the fact that recurrent disease may cause graft loss after ~5 years onward. Recent data from the Mayo Clinic [6] also do not support the notion that living-related donor transplantation should be discouraged in patients with IgAN, as these grafts exhibited no higher rates of recurrence or failure than cadaveric transplants.

Can clinically relevant recurrence of IgA glomerulonephritis be prevented?

Currently, there is no established preventive treatment. However, in this respect the recent introduction of mycophenolate mofetil (MMF) into clinical transplantation offers some hope. MMF, unlike currently available immunosuppressive agents, has considerable activity on B-lymphocytes in addition to T-lymphocytes and thereby may reduce the exaggerated IgA production in IgAN patients. Also, recent data suggest that MMF has direct anti-proliferative on mesangial cells in vitro [13]. Finally, Nowack et al. [14] describe a case of a patient with recurrent, progressive IgAN following transplantation, in whom the institution of MMF therapy led to a stabilization of the course. Unfortunately, it will take several years from now to establish the role of this potential new approach for the prevention of recurrent IgAN.

References