explain the dependence of hypertrophy on PI3K, p21 has roles beyond that of cell-cycle inhibition depending on the cellular stress and environment. One of the original descriptions of p21 was as an inducer of cellular senescence,[18] and p21 deletion was shown to prolong the lifespan of telomerase-deficient cells and mice,[19] a condition associated with shortened lifespan in humans and in mice. Coincidently, p21 but not p16 (another cyclin-dependent inhibitor) was found to be involved in telomere shortening-induced senescence of human cells,[20] and transduction of p21 but not of p16 caused hypertrophy in renal proximal tubule cells.[11] Perhaps the consequences of renal hypertrophy and the fibrotic changes associated with aging are both controlled by the same PI3K/Akt/p21 pathways. These possibilities should be fruitful areas for future investigations.

In summary (Figure 1), both p21 and the PI3K/Akt pathways have been shown to be associated with cellular and organ hypertrophy. The work of Chuang *et al.*[13] reiterates this concept and at the same time shows that these pathways may be mutually interdependent. More work is needed to support these interactions and to elucidate fully the pathway of hypertrophy. At the same time, however, this work has pointed out possible intervention strategies, by PI3K/Akt inhibition, to ameliorate hypertrophy.

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Membranous nephropathy: When and how to treat

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The treatment of idiopathic membranous nephropathy is heavily debated because of wide variation in outcome. A rational treatment strategy is needed to appropriately administer conservative treatment to the low-risk group but immunosuppressive therapy to those with medium or high risk of renal deterioration. Currently, combinations of steroids with alkylating agents are best studied. Newer forms of immunosuppressive treatment are currently under study.

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Idiopathic membranous nephropathy (IMN) is a common cause of the nephrotic syndrome in adult patients. The treatment of patients with IMN has been a regular theme for debate. Today, once the diagnosis is made, symptomatic management for proteinuria and hypertension is mandated in almost all patients. The impact of these treatments alone on the natural history is expected to be positive but is difficult to delineate distinctly. This wide variation in outcome is one of the factors that have led metaanalysis and systematic reviews of this disease to reach varying conclusions about the impact of immunosuppressive treatment on patient and renal survival and on remission rate of proteinuria.

Reports of the natural history of IMN are divergent and thus have set the stage for heavy disputes on the use of immunosuppressive therapy. The spectrum varies from a relatively benign course of 65% spontaneous remission of proteinuria and

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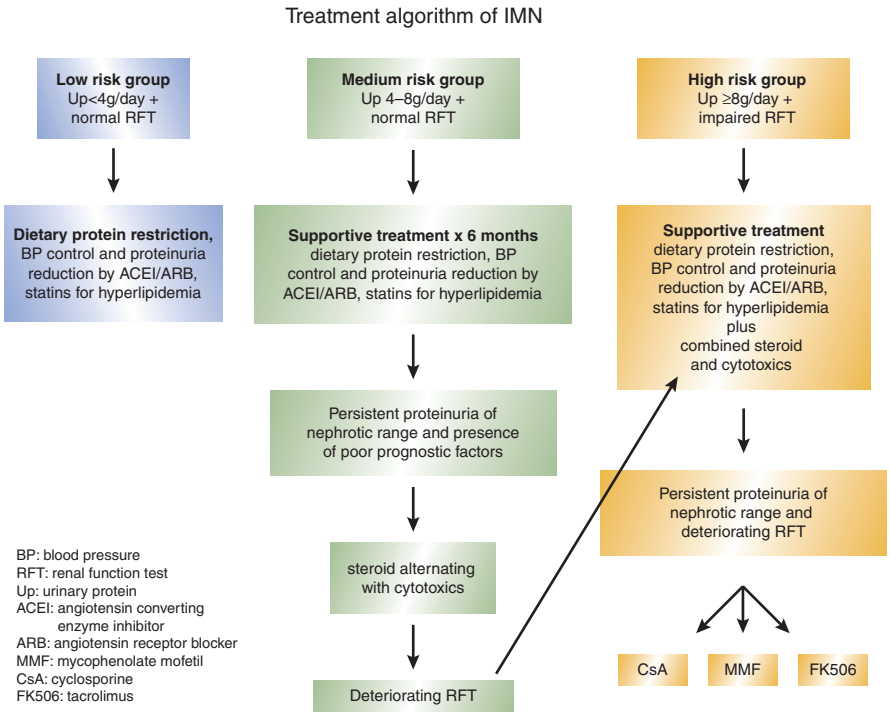

Figure 1 | Treatment algorithm for idiopathic membranous nephropathy. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CsA, cyclosporine; FK506, tacrolimus; MMF, mycophenolate mofetil; RFT, renal function test; Up, urinary protein.

an estimated renal survival rate of 88% in untreated patients at 5 years to a poor outcome with corresponding rates of 33% and 60%, respectively, in untreated patients at 10 years. The difference lies in the heterogeneity of the patients. Outcome in non-nephrotic patients with IMN invariably is good, with reported 10-year renal survival rates approximating 100% (reviewed by du Buf-Vereijken *et al.*[1]). In contrast, du Buf-Vereijken and co-workers[1] had found that nearly half the patients with IMN and nephrotic syndrome developed renal failure after exclusion of non-nephrotic patients in their analysis of the natural history. Hence, the identification of parameters that bear poor prognostic outcome is important for selecting patients to receive appropriate immunosuppressive therapy. Apparently, our ability to predict those who are most likely to progress has improved. Male gender, increasing age, nephrotic-range proteinuria, the ratio of IgG to α_1-microglobulin excretion in urine, focal segmental glomerulosclerosis, and impaired renal function at presentation are predicting factors for risk of renal progression in IMN.[2] It is, therefore, logical to adopt a more aggressive approach in immunosuppressive therapy for those patients with medium to high risk, whereas a symptomatic approach is appropriate for those with low risk of renal progression. Obviously, conservative treatment of patients with proteinuria has changed dramatically in the past decade with statins and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The ACEIs or ARBs decrease proteinuria and attenuate renal progression in patients with diabetic and nondiabetic proteinuric renal diseases. However, the beneficial effect of ACEIs or ARBs in improving the long-term prognostic outcome in IMN remains to be proven.

In late 1960s, IMN was considered a slowly progressive disease that was totally unresponsive to steroid treatment. Two subsequent randomized controlled trials (RCTs) unequivocally proved that steroid alone in limited dosage or during a limited period did not prevent deterioration in renal function.[3,4] It is possible that a higher dose of steroid administered for a longer period may be more effective, but the side effects are considerable. A subsequent approach devised to reduce the steroid toxicity was to use the steroid-sparing property of immunosuppressive agents. The best study on the efficacy of combining an alkylating agent and prednisone in patients with IMN undoubtedly is the RCT conducted by Ponticelli and co-workers from Italy.[5] Nephrotic patients with IMN and normal renal function were randomized for treatment with alternating monthly cycles of prednisone and chlorambucil versus no treatment. The duration of treatment was 6 months. A long-term beneficial effect of immunosuppressive therapy was demonstrated when these patients were followed up for more than 10 years. Treatment increased the remission rate (at the end of follow-up, 63% versus 33%) and improved renal survival (92% versus 60%). In the recently published Cochrane metaanalysis,[6] results provided by the study of Ponticelli and co-workers[5] are virtually cancelled out by reports of three other RCTs. However, the sample size and follow-up duration of these RCTs were small and limited. Notably, these studies documented significantly lower proteinuria in treated patients. The efficacy of alkylating agents in patients with IMN is supported by other studies that again are far from conclusive either because of a small sample size or because of the use of historical controls for comparison.[6] More importantly, these studies included only patients with renal impairment representing those with an unfavorable renal prognosis and low likelihood of spontaneous remissions. Hence, one may be tempted to consider immunosuppressive therapy consisting of alkylating agents and prednisone as an acceptable therapy for patients with IMN.

Because of the side effects and the observation that disease activity may still progress after 6-month therapy of alkylating agents and prednisone, other classes of immunosuppressive agents have been used in the treatment of patients with IMN. These include cyclophosphamide, cyclosporine (CsA), mycophenolate mofetil (MMF), tacrolimus (FK506), and, most recently, the anti-CD20 monoclonal antibody rituximab. Relevant data

from the most important studies are well summarized in a recent review.[1] It should be noted that no randomized trials of sufficient patient number have compared the various classes of agents, and therefore it is difficult to draw hard conclusions. So far, there are no good data to suggest that rituximab is effective in patients at risk for renal progression. Many studies showed the short-term antiproteinuric effect of CsA in patients with IMN. Most investigators agree that the effect is evident within 3 months after the start of therapy, and that continued use of CsA beyond 4 months is not useful in non-responders. It remains unclear whether use of CsA could have long-term benefits. In a small RCT of 18 patients with IMN and renal impairment, Cattran and co-workers[7] observed attenuation of renal deterioration in CsA therapy compared with placebo. However, treatment with CsA did not result in improvement in renal function, and no patient developed complete remission of proteinuria, in contrast to observed effects of alkylating agents. CsA failed to exert long-term benefits in the Cyclosporine in Membranous Nephropathy Study Group, comparing CsA with conservative treatment in patients with IMN and renal function deterioration (R Pisoni *et al.*, *J Am Soc Nephrol* 2000; **11**: 0514A, abstr.). The situation may be different in patients with no renal impairment. The efficacy of CsA was studied in an RCT of patients with IMN and normal renal function yet steroid-resistant (steroid for 8 weeks only).[8] CsA treatment (26 weeks) significantly decreased proteinuria as compared with placebo. However, after the end of treatment, many relapses occurred, and at the end of follow-up, differences in remission rates were not impressive. Furthermore, the potential nephrotoxicity may necessitate dose reduction.

Praga and co-workers[9] (this issue) now report a multicenter study of 48 Spanish patients with IMN to study the therapeutic effect of tacrolimus (FK506). Patients were initially treated by ACEI or ARB for at least 2 months before being randomized to either a treatment or a no-treatment group. A higher incidence of complete recovery and partial recovery was noticed in the treatment group. The relapse rate was 47% by 18 months following the cessation of treatment. FK506 is a calcineurin inhibitor similar to CsA that has intrinsic nephrotoxicity. Caution must be exercised before one is convinced that FK506 is the preferred treatment for IMN. Comparing FK506 with no treatment gives less convincing evidence, as previous studies had documented the superiority of improving symptoms with most forms of immunosuppressive treatment. Comparison between FK506 and corticosteroid/cytotoxic agent treatment is preferred to determine whether FK506 is as good as or better than the present regime. Up to 30% spontaneous remission occurs in IMN patients; though more common in the first 2 years after presentation, it can occur at any time. An observed period of 9 months may arguably still be short. The response rate and relapse rate were no better than with the steroid/cytotoxic agent regime. The relapse rate of corticosteroid/cytotoxic agent treatment is 32%, and that of CsA treatment is 30%–40%, by 2 years. Lastly, the long-term renal survival is not known for this group of patients receiving FK506, as the follow-up period remains short.

The recent reports of use of MMF will also be attractive if steroid/cytotoxic agent treatment fails, as the side effects of MMF are definitely less than those of FK506 or CsA. Experience with MMF in patients with IMN is limited and inconclusive. Miller and co-workers[10] treated 16 patients with IMN of whom the majority were high-risk with evidence of renal failure, using MMF in dosages of 0.5 to 2 g per day for periods between 2 and 10 months. Partial remission of proteinuria was achieved in only two patients. In contrast, a pilot study of Dutch patients with IMN and renal insufficiency using a combination of steroid and MMF (2 g per day) for 1 year achieved a significant decrease in serum creatinine and proteinuria.[1]

Finally, what have we learned, from numerous previous studies and metaanalysis, about how to manage patients with IMN? As a recent review[2] suggests, we should stratify patients into different categories in regard to their risk for progression to chronic renal failure. A treatment algorithm is shown in Figure 1. In only a small proportion of high-risk patients with IMN, a longer duration of combination of corticosteroid and cytotoxic agents should be taken as the treatment standard. When this regime fails or undesirable side effects occur, other immunosuppressive therapy such as CsA, FK506, or MMF may be an alternative.

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