Bone marrow transplantation rescues Alport mice*

Jürgen Floege¹, Uta Kunter¹, Manfred Weber² and Oliver Gross³

¹Department of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, ²Medical Clinic I, Cologne General Hospital, Cologne and ³Department of Nephrology and Rheumatology, University of Göttingen, Göttingen, Germany

Keywords: Alport’s syndrome; basement membrane; bone marrow transplantation

In the 9 May 2006 issue of Proc Natl Acad Sci USA, Sugimoto and colleagues [1] described fascinating data on a potential approach to treat Alport’s syndrome, a rare genetic disease leading to renal failure, which so far could not be cured. The work was highly publicized and discussed in both scientific journals and the lay press.

Alport’s syndrome derives from a mutation of either the α3, α4 or α5 chain of type IV collagen, i.e. collagen types that constitute basement membranes in the renal glomerulus, the ear and the eye. Mice that are genetically deficient of the α3(IV)-chain (‘Alport mice’) develop a renal phenotype very similar to that of Alport patients (Figure 1), i.e. proteinuria, glomerulonephritis and subsequent tubulointerstitial fibrosis starting at 8 weeks of age and leading to death due to renal failure at 20–23 weeks. In the study by Sugimoto et al. [1], 8 week-old Alport mice were lethally irradiated and then received an allogenic unfractio- nated bone marrow transplant from either LacZ mice, i.e. mice with a normal collagen production plus expression of the LacZ marker in all cells, or from another Alport mouse. Whereas the latter had no effect on the phenotype, the allogeneic bone marrow led to markedly reduced proteinuria upon follow-up, and improved renal function as well as renal histology. LacZ-positive cells constituted about 10% of the glomerular cells and were found in podocyte and mesangial cell locations. The glomerular staining pattern for the α3- and α5(IV) chains was partially restored. If these data can be confirmed and extended by showing that the treatment delays death from renal failure in Alport mice (see subsequently), there would be several major implications of this study.

Clinical manifestations of Alport syndrome can be retarded by bone marrow-derived cells

Clinically, there is at present little therapy to offer patients affected with Alport’s syndrome. Experimentally the administration of ACE inhibitors doubles the interval until renal failure develops in Alport mice [2] (Figure 2), but these data have yet to be confirmed in humans. The work by Sugimoto et al. [1] provides new hope for treating Alport’s disease by replacing the cells generating abnormal collagens with podocytes and mesangial cells capable of producing intact type IV collagen. This observation could be a milestone in the future therapy of Alport’s syndrome. However, more experimental data are required before one can envision bone marrow transplantation or stem cell therapy in children with a disease that still can be ‘treated’ otherwise, i.e. by renal replacement therapy. Thus, in the study of Sugimoto et al. [1] a very pronounced difference in serum blood urea nitrogen (BUN) was noted at week 21 in Alport mice with and without a bone marrow transplant. However, the hardest end point, i.e. death from renal failure, was not tested. This issue appears important to stress, since a similar study of ours in Alport mice, in which they received bone marrow-derived mesenchymal stem cells (MSCs), also led to improved renal histology but failed to delay death from renal failure [3].

Bone marrow-derived (stem?) cells can contribute to glomerular healing

The potential of bone marrow-derived MSC for renal repair has been shown in rodent models of acute renal failure, where the course was improved by intravenous or intraarterial MSC injection [4–6]. In addition, we recently reported that rat MSC injected into a renal artery can accelerate recovery from mesangiolyci....
damage and prevent transient acute renal failure in rat mesangioproliferative glomerulonephritis [7]. In these studies, we and others [4–7] consistently failed to detect any evidence of transdifferentiation of MSC into glomerular or tubular cells. Rather, MSC appeared to secrete high concentrations of growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) which might have helped to restitute glomerular and tubular morphology [7,8]. The remarkable feature of the study of Sugimoto et al. [1] is therefore the evidence suggesting true differentiation of bone marrow-derived cells into resident glomerular cell phenotypes. Whether the above observations imply that other bone marrow-derived cell types than MSC contributed to the effects in the Alport mice remains to be determined.

**Bone marrow-derived (stem?) cells differentiate into glomerular cells**

The presence of bone marrow-derived cells in the mesangium is a well-known phenomenon. In fact, in a normal mesangium, ~10% of the cells are bone marrow-derived monocytes/macrophages. There is little evidence that these cells play a role in producing the mesangial matrix, since they do not synthesize type IV collagen. The new and exciting aspect of the present study is the finding of bone marrow-derived cells in mesangial, and in particular podocyte locations, including their synthesis of ‘correct’ collagen in these locations. Podocytes are considered the Achilles heel of the glomerulus, since they are virtually unable to divide and to replace lost cells [9]. Loss of podocytes is observed in various progressive glomerular diseases and is considered the initiating event in the formation of a focal segmental glomerulosclerosis [9] and in secondary tubulointerstitial damage [10]. Thus, if confirmed in other situations, a mechanism whereby bone marrow cells can replace podocytes would be of major and general clinical relevance to progressive glomerular diseases.

**Conflict of interest statement.** None declared.

**References**


Received for publication: 24.5.06
Accepted in revised form: 26.5.06