
EDITORIAL

IgA nephropathy: A stem cell disease?

Despite intensive investigation by several groups, a widely accepted hypothesis for the pathogenesis of immunoglobulin A (IgA) nephropathy has not yet emerged. Most data available so far are consistent with the possibility that immunological dysfunction plays an important role [1]. Thirty-five to 50% of patients with IgA nephropathy have elevated serum IgA levels, especially of the IgA1 subclass derived from bone marrow. This circulating IgA is partly macromolecular, and the deposited IgA in the mesangium can be eluted from the glomeruli as polymeric IgA1. Whether in IgA nephropathy the circulating IgA1 is bound to antigens in the form of immune complexes is still a controversial issue. No single major infectious pathogen has been identified as a potential source of antigen, in spite of the well-known recurrence of acute disease after infectious episodes at the mucosal level. The failure to identify specific antigens has led increasingly to the view that polymeric IgA may be antigen-independent, and that the circulating polymeric IgA is low-affinity, “natural” antibodies, generated by polyclonal B-cell activation. Actually, peripheral blood B-cells from patients with IgA nephropathy have exhibited abnormally high rates of IgA secretion either in the absence of stimuli or, more consistently, upon mitogen stimulation [2]. Several studies have also reported increased fractions of peripheral blood B-cells expressing surface IgA. However, it is unlikely that the excess amount of circulating IgA is the sole cause of IgA renal deposition, as indicated by the rare occurrence of IgA-associated glomerular damage in acquired immune deficiency syndrome patients, despite very high levels of circulating IgA. The recent observation that circulating IgA from patients with IgA nephropathy exhibits abnormal glycosylation (a reduced galactosylation of O-linked glycans) suggests that mesangial deposition of IgA in this disease might rather be due to intrinsic alterations of IgA1 [3].

Indeed, reduced galactosylation modifies the conformational stability of the IgA1 molecule and consequently the interaction of the IgA1 molecule with receptors and tissue proteins that may favor a reduced clearance and increased deposition in the mesangium.

Investigators searching for an upstream immunologic abnormality have suggested that abnormal T-lymphocyte function drives the increased IgA production by B cells. Specifically, the number of T helper (Tc4) lymphocytes, which are endowed with the capacity to switch B cells from IgM to IgA synthesis, is increased in patients with IgA nephropathy. In further support of a role for Tc4 cells, increased frequency of the Sda1 allele, the portion of the gene that mediates the switch from IgM to IgA, has been shown in patients with IgA nephropathy [1]. Investigation into the pathogenesis of IgA nephropathy has been flawed by the difficulty in developing a suitable animal model. The study presented in this issue of Kidney International by Imasawa and co-workers [4] is based on the experimental model of high IgA producer (HIGA) ddY mice, which spontaneously develop mesangial IgA deposition by approximately 25 weeks of age. While not too much emphasis may be given to the HIGA mice as a model of human IgA nephropathy, in that no chronic renal impairment is demonstrated, this murine model provides a useful tool to examine mechanisms of the formation and possible significance of IgA deposits. The authors hypothesized that the pathogenic agent of IgA nephropathy lies in bone marrow cells, based on two earlier observations: 1) bone marrow cells (BMCs) from IgA nephropathy-prone ddY mice transplanted into normal B6 mice increased the deposition of serum macromolecular IgA and glomerular IgA in the recipients [5]; 2) in a patient with IgA nephropathy and chronic myeloblastic leukemia, allogeneic bone marrow transplantation (BMT) not only cured the leukemia but also eliminated the mesangial IgA deposits. In the present study, the authors document that HIGA mice transplanted at around 25 weeks of age with allogeneic BMCs from normal B6 mice develop less mesangial IgA and complement C3 deposition and less severe glomerulonephritis than the HIGA—HIGA mice. These B6—HIGA mice also excreted less urinary albumin than the HIGA—HIGA mice. Serum IgA levels, particularly macromolecular IgA, were lower than in HIGA—HIGA mice. These data suggest the exciting and provocative hypothesis that allogeneic BMT might be a tool for treating IgA nephropathy. However, major issues remain to be addressed. For example, which types of cells and what factors are defective at the stem cell level and play an important role in increasing serum level of macromolecular IgA?

Key words: galactosylation, HIGA mice, bone marrow transplantation, T helper cells, bone marrow cells.

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Since BMCs transplanted into both B6—HIGA and HIGA—HIGA mice were equally exposed to the same environmental factors, the authors hypothesize that immunological differences in the two groups must lie in the BMCs. Although they do not deny a role for antigens in the pathogenesis of IgA nephropathy, they consider the antigen only as a stimulus to activate an abnormal response in dysfunctional BMCs. An alternative explanation could be that in IgA nephropathy-prone mice abnormal self antigens are inefficiently presented within the thymus in such a way that autoreactive T helper clones are generated and stimulate abnormal IgA production by B cells in the periphery. Experiments reported in the last few years [6], designed to investigate the mechanism that maintains tolerance to grafts in mixed mouse allogeneic chimeras, have provided substantial arguments linking BMT-induced donor-specific tolerance and thymic presentation of donor antigens to allogeneic T cells. In these mixed allogeneic chimeras, induction of tolerance was associated with donor antigen-presenting cells in the thymus, and the maintenance of the tolerance state depended on the persistence of donor antigens in the thymus. It is possible to infer that the mechanism(s) responsible for IgA correction by allogeneic BMCs in HIGA mice recognize a similar pattern and that the allogeneic BMT provides antigens in the thymus that effectively prevent generation of aberrant autoreactive T helper cells.

Bone marrow transplantation is now becoming a promising strategy for the treatment of patients with autoimmune diseases. In various animal models for autoimmune diseases, it has been documented that fully allogeneic BMCs, after purging the marrow of destructive T cells, can be used to treat autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, immune thromboocytic purpura, and autoimmune insulinitis [7]. However, the fully allogeneic chimeras—with donor and recipient fully mismatched at the major histocompatibility complex—exhibit immunodeficiencies after total-body irradiation followed by BMT in that they fail to exhibit primary humoral immune response and have a deficient cellular immune response to certain intracellular pathogens [8]. On the other hand, transplanting mixed bone marrow from both allogeneic autoimmune-resistant mice and syngeneic autoimmune-prone mice into lethally irradiated recipients corrects the autoimmune disease in the lupus-prone strain of mice and also avoids the annoying immunodeficiencies produced by allogeneic BMCs [8]. Imasawa and co-workers [4] exclude immunodeficiency in their B6—HIGA allogeneic chimeras, based on data showing that IgG level was comparable and IgM content was superior to those parameters in HIGA—HIGA or unmanipulated HIGA mice. However, more accurate criteria, such as the ability to mount a primary antibody response against cellular antigen, are called for to clarify the issue. In any case, the therapeutic efficacy of mixed allogeneic-syngeneic BMTs on IgA production and IgA-mediated damage in HIGA mice is worth evaluating.

What are the future therapeutic implications of these findings for human autoimmune disease? Patients with a hematological condition such as leukemia and/or aplastic anemia and a concomitant autoimmune disease (mostly rheumatoid arthritis) have been reported to be cured following allogeneic BMTs [9]. There are also a few patients who have been treated in this way for their autoimmune disease alone.

However, the use of allogeneic BMT in non-malignant disorders must be very carefully considered, in view of toxicity and potential morbidity associated with it. New non-myeloablative conditioning regimens, designed to allow the donor’s immune system to take over, are already utilized for malignant and non-malignant hematologic diseases, and may become an attractive option for severe, refractory autoimmune disease. As for the applicability of BMT to treatment of human IgA nephropathy, that cannot be foreseen at this time. Certainly, accurate comparisons with already existing protocols (with angiotensin-converting enzyme inhibitors or steroids and other immunosuppressive agents) currently used for therapeutic management of the disease [10] are mandatory.

**ACKNOWLEDGMENTS**

The authors thank Dr. Norberto Perico for helpful discussions and Mrs. Laura Arioli for help in preparing the manuscript.

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**NOTE ADDED IN PROOF**

In a recent study (Nat Med 5:1018–1025, 1999) Zheng et al documented that knockout mice manifesting deficiency of an anti-inflammatory protein uteroglobin (UG) develop almost all of the pathologic features of human IgA. UG administration prevented glomerular accumulation of exogenous IgA in UG-KO mice. These results provide a role for UG in preventing IgA nephropathy.

**REFERENCES**

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Editorial


