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EDITORIAL REVIEW

For further investigations in IgA nephropathy the approach from phenotype to genotype is welcome

F. P. SCHENA *Division of Nephrology, Department of Emergency and Organ Transplantation, University of Bari, Policlinico, Bari, Italy*

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IgA nephropathy (IgAN) is a worldwide disease with unknown aetiology and pathogenesis. There is an increasing body of evidence suggesting that IgAN is characterized by (i) high serum levels of IgA, mainly polymeric IgA1, in more than 50% of patients; (ii) increased numbers of IgA-bearing B lymphocytes and activated Tα helper cells; (iii) overexpression of TGFβ and IL-4 mRNA in CD4 + cells and (iv) increased deposition of IgA in the mesangium. Four systems, namely mucosa, bone marrow, blood and kidney are involved in the disease. During the past 10 years, Feehally's group have contributed to our understanding of the important role that the mucosa and bone marrow play in IgAN. In this issue of *Clinical and Experimental Immunology*, Feehally's group [1] describe the occurrence of a deficiency in $\gamma\delta$T cells expressing Vγ3 and Vδ3 in the bone marrow of IgAN patients. In a previous paper, they reported the same deficiency in the duodenal mucosa [2]. Since $\gamma\delta$T cells are regulators of the IgA immune response, these results may provide additional information on the pathogenesis of the disease.

Mesangial IgA deposits in the glomeruli are represented mainly by polymeric IgA. For this reason, the deposits were assumed to be of mucosal origin, but now there is good evidence that the bone marrow is the likely source of the deposited polymeric IgA1 [3], and systemic overproduction of pIgA is present in IgAN patients and enhanced by vaccine stimulation [4,5].

IgA production is T cell dependent since an increased number of activated Tα helper cells (both Th1 and Th2) occurs in IgAN patients [6]. Recent studies have reported a high number of circulating $\gamma\delta$T cells in these patients which increased after systemic antigen challenge [7,8]. The proportion of $\gamma\delta$T cells significantly correlated with serum IgA levels as well as with the proportion of surface IgA positive B cells. Since these cells are precursors of IgA-secreting plasma cells, it is evident that $\gamma\delta$T cells could participate in the switching to IgA production in naive B cells. Toyabe *et al*. [7] demonstrated that the removal of $\gamma\delta$T cells from the peripheral blood mononuclear cells of IgAN patients diminished the induction of IgA-bearing B cells and IgA synthesis. These $\gamma\delta$T cells are represented by different subpopulations distinguished by their restricted TcR V region [9]. There are four Vγ families (Vγ1–4) and six Vδ families (Vδ1–6) which are modulated by specific genes. In fact, during gene rearrangement, each $\gamma\delta$T cell selects one Vγ and one Vδ segment to make up its unique $\gamma\delta$ TcR. Peripheral blood $\gamma\delta$T cells use the Vγ2 and Vδ2 region, while Vγ1, Vδ1 and Vδ3 T cells are dominant in the mucosa. Analysis of the repertoire of the variable region of mucosal and bone marrow $\gamma\delta$ T cells shows a decrease in Vγ3 and Vδ3 gene expression in IgAN patients, thus suggesting that this defect may explain the breakdown of oral tolerance in these patients, which manifests itself as an aberrant mucosal and systemic antibody response to antigens [1,2]. Other abnormalities of the cellular immune system have been found in IgAN patients, namely (i) increased numbers of Tα4 cells, which have the capacity to induce the switch from IgM to IgA synthesis, as do $\gamma\delta$ T cells [10], and (ii) increased expression of CD40L on IgAN–specific T cells [11] which binds CD40 on B lymphocytes, thus inducing cytokine production which modulates isotype switching. In addition, increased production of transforming growth factor β, which induces the IgA isotype switch, and IL-5, which promotes differentiation of IgA-bearing β lymphocytes, has been observed in IgAN patients and relatives [12]. These data clearly show that different susceptibility genes operate in IgAN patients.

Recently, recombinant DNA technology has greatly facilitated the search for genetic markers in IgAN and several different polymorphic genes have been investigated using the candidate gene approach [13]. Results from these studies (Table 1) are conflicting, therefore it has been postulated that genetic factors vary among different populations.

I believe that molecular genetic profiling should be undertaken using a different methodology which consists of collecting DNA samples from IgAN patients and family members. This allows a set of expression genetic profiles in familial and sporadic IgAN to be obtained. Recently, Gharavi *et al*. [14] investigated IgAN using genome DNA–wide analysis and they identified a locus on chromosome 6q22–23, which may contain the IgAN1 gene, responsible for the development of the disease. However, in only 58% of studied Italian IgAN families was disease linked with this gene. This means that other genes are responsible for the development of IgAN and probably variable combinations of genes are involved in different areas of the world. For this reason, three familial genetic studies scanning whole genomic DNA for IgAN disease loci are in progress in the USA,

Correspondence: Prof F. P. Schena, Division of Nephrology, Policlinico Piazza G. Cesare 11, 70124, Bari, Italy
E-mail: fp.schena@nephro.uniba.it

Table 1. Association studies in IgA nephropathy

Candidate genes	Polymorphisms	Onset	Progression	No. of points	Population
TCR Cβ	RFLP (Bgl II)	n		40	German
			y	34	Japanese
TCR Cα	RFLP (Taq I)	y	n	53	Chinese
		n		213	Japanese
			y	84	Japanese
ecNOS	ecNOS4 b/a	n	y	68	Japanese
		n	n	115	Korean
		n	n	70	German
NPYY1R	Y/y	n	y	68	Japanese
IL-1ra	VNTR	y	y	111	Chinese
TNFα	-308A/G	n	y	111	Chinese
TNFβ	RFLP (Ncol)	y		77	British
Sμ, Sα	RFLP (Sacl)	n	y	78	Chinese
AGT	M235T		y	168	Canadian
			n	64	American
		n	n	247	Italian
			n	274	French
AT1R	A1166C		n	64	American
			n	168	Canadian
			n	274	French
ACE	I/D		y	53	Japanese
		n	y	48	Japanese
			y	97	Japanese
		n	y	100	Scottish
		n	n	204	German
			y	64	American
			y	168	Canadian
		n	n	70	German
		n	n	247	Italian
			n	274	French
			n	527	Japanese
		n	n	110	German
PAF	G994T	n	y	89	Japanese
UTR	G38A	n	y	110	German
megsin	C2093T	n	n	110	German
α1	α1hs1/2	n	y	104	French

Europe (www.health-tech-net.org/IgAN) and Japan, since IgAN is the most prevalent idiopathic glomerulonephritis. Specific regions, within the 22 pairs of human autosomes, that may carry one or more genes responsible for the development of IgAN will be mapped by linkage analysis.

Data from basic and clinical studies are useful because genes responsible for observed immunological phenotypic abnormalities will be searched in those genomic regions of chromosomes suspected of an association with disease susceptibility. Furthermore, the design for testing whether the candidate gene is involved in the development of IgAN may be either the case control study or the cohort study and can be used to study gene–environment interactions. Since tests of linkage for genes of modest effect may not be so powerful, the investigators may use the transmission/disequilibrium test of Spielman [15] using trios (single affected and nonaffected individuals and their parents). This association test can also be performed for pairs of affected and nonaffected siblings (concordant and discordant sib-pairs). This type of association study seems to be more powerful than linkage studies.

In conclusion, genomic studies and computational advances will lead to an information revolution concerning the pathogenesis of IgAN. A combination of rich cellular data, genomic profiling, and computational predictions may provide a fuller understanding of this disease. In the future, additional data will be available from DNA chips, mass spectrometry of proteins and large-scale scans of protein–protein interactions thereby expanding this knowledge further.

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