Is Epstein-Barr Virus Involved in Primary IgA Nephropathy?

P.M.		André ^a
P.		Le Pogamp ^a
R.		Griffais ^b
D.		Chevet ^a
M.P.		Ramée ^a

^aUniversity Hospital, Rennes; ^bDepartment of Virology, Institut Pasteur, Paris, France

P.M. André, Laboratoire de Bactériologie-Virologie, Faculté de Médecine, Avenue de Pr. Léon Bernard, F-35 043 Rennes Cedex (France)

Dear Sir,

A number of elements suggest a correlation of Epstein-Barr virus (EBV) with primary IgA glomerulopathy (IgAN) where mesangial deposits are mainly polymeric IgA1. (1) In industrialized countries, the age at which nephropathy occurs coincides with the age of EBV sero-conversion. (2) The disease is clinically associated with viral-looking infectious episodes of the upper respiratory tract. EBV has a tropism for pharyngeal cells which are an in vivo replication and reactivation site [1]. (3) EBV in vitro infection of circulating lymphocytes preferentially stimulates, among IgA, the synthesis of the IgA1 isotype at a similar rate to IgG synthesis [2, 3]. Similarly, an increased proportion of polymeric IgA1-producing cells was observed in the tonsils of IgAN-affected subjects [4]. (4) The IgA antibody anti-viral capsid antigen (VCA) response is higher in patients affected by IgAN at the early stage of the disease [5]. (5) IgA eluted from mesangium binds to a nuclear antigen of tonsillar cells [6]. Conventional in situ virus investigation did not yield any positive results. Conversely, EBV induces the synthesis of nuclear-located antigens, EBV nuclear-associated antigens (EBNA), even in a latent state [7].

These facts led us to investigate immune response to EBV and in particular monospecific responses to EBNA1 and EBNA2. If EBNA1 is expressed in any EBV-infected cell, EBNA2 is only expressed at some stages of the in vivo infection by EBV and is associated with the B-cell transformation process [7]. The study was conducted on 27 IgAN-affected patients and on 43 healthy controls of identical age from the same geographical area. Antibody titration was performed by indirect immunofluorescence for anti-early antigen (EA) antibodies and VCA, and by anti-complement immunofluorescence for anti-EBNA.

320 - .
 160 - .
 80 - .
 40 - .
 20 - .
 10 - .
 »: - .

IgAN Controls

Fig. 1. Comparison of the reciprocal titer of anti-EBNA2 antibodies. The solid bars stand for the geometric means and the standard deviations. Dots under and on the hatched line are considered as negative sera.

EBNA1 and 2 were detected on rodent fibroblastic lines transfected by restriction fragments of the EBV genome coding for EBNA1 and EBNA2 [8].

While no significant difference was observed for anti-VCA and anti-EBNA1 antibodies (2 out of 27 patients and 1 out of 43 controls had no anti-EBV antibody), a larger proportion of patients had a > 20 titer of anti-EBNA2 antibodies (44.4 versus 13.9%; $p < 0.01$); titer of these antibodies was higher in patients, $p < 0.001$ (fig. 1). Anti-EA titers were also significantly higher, $p < 0.05$, even if the proportion of patients with antibodies (30 versus 18.6%; $p < 0.2$) was not significant.

186

André/LePogamp/Griffais/Chevet/Ramée

These results are consistent with an anomaly of immune response to EBV in IgAN-affected patients. Persistence of anti-EBNA2 response had already been recorded in patients with rheumatoid arthritis or AIDS, whose response is associated with more frequent EBV reactivation consecutive to an inappropriate immune control of the infection [9, 10]. EBV reactivations could induce a polyclonal stimulation with an increase in IgA synthesis. This hypothesis would implicate the virus as one of the IgAN etiological factors (or a co-factor).

References

Wolf H, Haus M, Wilmes E: Persistence of Epstein-Barr virus in the parotid gland. *J Virol* 1984;51:795–798.

Chan MA, Stein LD, Dosch HM, et al: Heterogeneity of EBV-transformable human B lymphocyte populations. *J Immunol* 1986;136:106–112.

Conley ME, Chan MA, Sigal NH: In vitro regulation of IgA subclass production. III. Selective transformation of IgA1 producing cells by Epstein-Barr virus. *J Immunol* 1987; 138: 1403–1407.

Nagy J, Brandtzaeg P: Tonsillar distribution of IgA and IgG immunocytes and production of IgA subclasses and J chain in tonsillitis vary with the presence or absence of IgA nephropathy. *Scand J Immunol* 1988;27:393–399.

Uj M, Szűcs G, Nagy J, et al: Antibodies to viruses of the herpes group in glomerulonephritis of membranous, membranoproliferative and IgA types. *Int Urol Nephrol* 1988;20:201–209.

Tomino Y, Sakai H, Endoh M, et al: Cross-reactivity of IgA antibodies between renal mesangial areas and nuclei of tonsillar cells in patients with IgA nephropathy. *Clin Exp Immunol* 1983;51:605–610.

Dillner J, Kallin B: The Epstein-Barr virus proteins. *Adv Cancer Res* 1988;50:95–158.

Polack A, Hartl G, Zimmer U, et al: A complete set of overlapping cosmid clones of M-ABA virus derived from nasopharyngeal carcinoma and its similarity to other Epstein-Barr virus isolates. *Gene* 1984;27:279–288.

Seigneurin JM, Lavoué MF, Genoulaz O, et al: Antibody response against the Epstein-Barr virus-coded nuclear antigen 2(EBNA2) in different groups of individuals. *Int J Cancer* 1987;40:349–353.

10 Fox R: Epstein-Barr virus and human autoimmune diseases: possibilities and pitfalls. *J Virol Methods* 1988;21:19–27.