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Is EBNA1 the molecular mimicry trigger of Epstein-Barr virus associated systemic lupus erythematosus?

Running title: anti-EBNA1 EBV antibodies and SLE

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Abstract

This letter to the editor raises concerns as to whether anti-EBNA1 Epstein-Barr virus (EBV) antibodies could be the viral triggers of systemic lupus erythematosus (SLE). We grow some concerns and comment on that in view of a recent study speculating that indeed anti-EBNA1 antibodies are the likely primary initiators of SLE-specific autoantibodies via molecular mimicry. In our mind, their data are not as convincing as it would be expected to reach a consensus for a decisive role of EBV in provoking SLE.

(Submitted 27 February 2022; accepted 11 March 2022)

Keywords- Antibody; autoantibody; infection; molecular mimicry; virus

Dear Editor,

The group of JA James and JB Hurley has recently published a paper on the role of antibodies specific for EBNA1 of Epstein-Barr virus (EBV) in provoking autoantibodies specific for systemic lupus erythematosus (SLE) (1). To establish an association between a virus such as EBV and disease-related autoantibodies in not an easy task. Especially for EBV this is even harder, as the great majority of adults are infected with EBV and a connection is practically impossible to be established (2-4). To circumvent that, these authors, as well other groups, have decided in the past to perform virological and immunological assessments in pediatric and young patients with SLE. For example, in. one of their previous studies, these investigators have studied children and young adults and found that practically all (99%) of these young SLE patients had seroconverted against EBV compared to just 70% of the control cohort. Their findings were more prominent, taking into consideration that those differences were found in the seroconversion rates against four other herpes viruses; a finding, which makes their discovery pathophysiologically significant.

If their findings hold true (1), it would be of interest to identify, which is the "antigenic sin" i.e. the original viral antigen that provokes the induction of autoantibodies. According to the Authors this antigen must be EBNA1. This is not the first time that such an expectation has been raised. In their more recent paper, the paper that has attracted our attention, Hurley et al report that that IgG anti-EBNA1 antibodies were present in 99.2% compared to 92.8% of their matched controls (1). This statistically significant difference is according to the investigators an indirect proof that autoantibodies characteristic of SLE largely results from an anti-EBNA1 heteroimmune reaction (1). Such associations were not obtained for other EBV antigens.

That anti-EBNA1 antibody responses could be reliable triggers of SLE-specific autoantibodies (and a risk factor of autoimmunity in immunological terms) has been based on previous data supporting various SLE autoantigens cross-react with EBNA1 heteroimmune antibodies, including those against Sm B/B', Ro and C1q (2-5). Such data have been obtained not only in clinical samples but also in experimental animal models of SLE.

We do not feel that a statistically significant difference between two percentages and in particular that of 99.2% compare to that of 92.8% is highly convincing of the true impact of EBNA1 in the risk of EBV in provoking SLE. It

would be preferable if such differences were noted (even by chance) in sequential series of sera, free of the virus, in individuals who acquired subsequently EBV infection and developed SLE compared to those infected without any disease of this kind. In fact, a recent study has been able to provide such data in young military personnel of the US army (6). Amongst those men, EBV has been found to have a significant impact on the development of subsequent multiple sclerosis and the most frequently found peptides reacting of all were those of EBNA (6). Such data is masking a true impact on understanding the decisive role that EBV and EBNA may have as a priori inducer of autoantibodies and autoimmunity. Others and we have repeatedly noted that EBV is a common denominator of several autoimmune diseases ranging from SLE and multiple sclerosis to autoimmune liver diseases (2-5, 7-11).

CONCLUSIONS

In conclusion, EBV is one of the most prominent triggers of autoantibodies during infection. Whether this virus is also a maker of autoimmune disease would not be easy to document. Nevertheless, serological, immunological, virological and experimental studies investigating this topic will solve once for good this matter.

AUTHORS CONTRIBUTIONS

DPB had the original idea and scripted the original draft. EP, CL, GE and CK have drafted parts of the draft and revised the final version. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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