Comment on Vietzen et al, page 1560

Genetic susceptibility to EBV-related disease

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More than 90% of the general population show evidences of past infection of Epstein-Barr virus (EBV). So why do only a few of us experience EBV-related disease? In this issue of *Blood*, Vietzen et al address this question in the context of EBV-associated infectious mononucleosis (IM or glandular fever) and EBV-associated posttransplant lymphoproliferative disorders (EBV$^+$ PTLDs).[1]

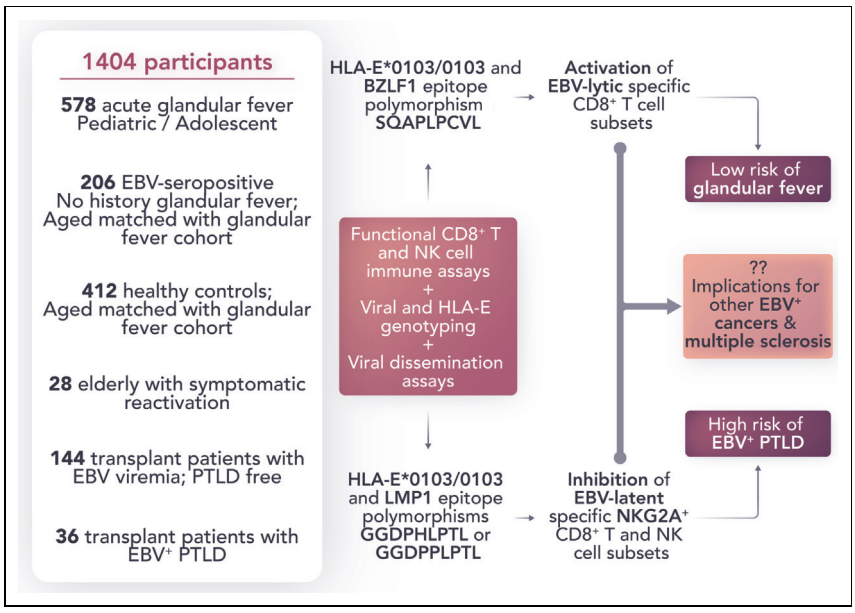
For individual cases, functional CD8$^+$ T-cell and natural killer (NK) cell assays can identify novel disorders with EBV involvement, thereby establishing the correct diagnosis and treatment.[2,3] At a population level, polymorphisms in the classical HLA class I molecule HLA-A are associated with an increased risk of developing IM and EBV-associated classical Hodgkin lymphoma (EBV$^+$ cHL).[4,5] Mechanistic studies suggest that the association is due to the impact of classical HLA class I molecules on the established hierarchy of CD8$^+$ T-cell responses against EBV latency II protein LMP1, and that polymorphisms in EBV latency genes influence the potency of CD8$^+$ T-cell responses in EBV$^+$ PTLD.[6,7]

HLA-E is a minimally polymorphic nonclassical HLA class I molecule that is highly conserved in European populations and is essentially restricted to only 2 alleles (E*01:01. and E*01:03) that appear to be evenly distributed. The alleles differ by a single amino acid that modifies the molecular function and level of cell-surface expression. Notably, HLA-E expression is retained in EBV$^+$ PTLD– and EBV$^+$ AIDS–related lymphomas.[8] There are several lines of evidence suggesting that HLA-E may be involved in the pathogenesis of EBV-related diseases. HLA-E*01:01 is a protective genetic factor in EBV$^+$ cHL that is independent of the HLA-A allele status. It is also known that there are expanded populations of CD8^{bright} T cells that recognize HLA-E in the context of the EBV-lytic protein BZLF1 in patients with the EBV-related disease, multiple sclerosis (MS).[9]

HLA-E has a role in both the innate and adaptive immune responses through its recognition by the T-cell receptor and the NK cell inhibitory CD94/NKG2A receptor, respectively. The CD94/NKG2A receptor is predominantly expressed in CD56^{bright} NK cells (relative to CD56^{dim} NK cells) and is expressed on a subset of activated CD8$^+$ T cells. A restricted set of distinct EBV-encoded BZLF1 or LMP-1–derived peptides are presented by HLA-E, and specific LMP1 polymorphisms preferentially bind to HLA-E via NKG2A to block NK cell effector function.[10]

Vietzen et al postulated that variations in CD94/NKG2A–HLA-E interactions on T- and NK cell subsets might have functional relevance in EBV control. In an elegant study, they combined genetic association approaches with EBV dissemination and functional immune (CD8$^+$ T- and NK) cell subset assays (see figure). The authors demonstrated that HLA-E–restricted immune responses and EBV epitope polymorphisms have a substantial impact on mediating susceptibility and protection from IM and EBV$^+$ PTLD. Not only is their investigation notable for its scale (1404 participants; including those with IM, age-matched asymptomatic EBV carriers, elderly patients with symptomatic reactivation, transplant, and PTLD), but it is also distinguished by providing an immuno-mechanistic basis to back up their genetic association observations.

Collectively, the work of Vietzen et al shows that the development of IM depends on the host HLA-E allele and HLA-E–restricted CD8$^+$ T-cell responses. The risk for PTLD is associated with the HLA-E/LMP-1/NKG2A axis and depends on specific EBV and host genetic variations involved in this pathway. They build upon previous foundational studies to provide new insight into the immunopathogenesis of IM and EBV$^+$ PTLD. Further studies will be required to determine whether similar mechanisms that affect viral dissemination are applicable to other EBV malignancies and related diseases, including MS. Understanding the viral and host genetic basis of susceptibility to EBV-related disease may contribute to the development of



Role of host and viral genotype on susceptibility to IM and EBV$^+$ PTLD. The development of IM depends on the host HLA-E allele and HLA-E–restricted CD8$^+$ T-cell response. EBV$^+$ PTLD are associated with the HLA-E/LMP-1/NKG2A axis and depend on specific EBV and host genetic variations involved in this pathway. Professional illustration by Somersault18:24.

preventive vaccines and immunotherapy treatments.

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REFERENCES

1. Vietzen H, Furlano PL, Cornelissen JJ, et al. HLA-E-restricted immune responses are crucial for the control of EBV infections and the prevention of PTLD. *Blood*. 2023; 141(13):1560-1573.
2. Nourse JP, Jones K, Dua U, et al. Fulminant infectious mononucleosis and recurrent Epstein-Barr virus reactivation in an adolescent. *Clin Infect Dis*. 2010;50(6): e34-e37.
3. Opat S, Hearps AC, Thia K, et al. Adaptive reprogramming of NK cells in X-linked lymphoproliferative syndrome. *Blood*. 2018; 131(6):699-702.
4. Diepstra A, Niens M, Vellenga E, et al. Association with HLA class I in Epstein-Barr-virus-positive and with HLA class III in Epstein-Barr-virus-negative Hodgkin's lymphoma. *Lancet*. 2005;365(9478): 2216-2224.
5. McAulay KA, Higgins CD, Macsween KF, et al. HLA class I polymorphisms are associated with development of infectious mononucleosis upon primary EBV infection. *J Clin Invest*. 2007;117(10):3042-3048.
6. Jones K, Nourse JP, Morrison L, et al. Expansion of EBNA1-specific effector T cells in posttransplantation lymphoproliferative disorders. *Blood*. 2010;116(13):2245-2252.
7. Jones K, Wockner L, Brennan RM, et al. The impact of HLA class I and EBV latency-II antigen-specific CD8(+) T cells on the pathogenesis of EBV(+) Hodgkin lymphoma. *Clin Exp Immunol*. 2016;183(2): 206-220.
8. Gandhi MK, Hoang T, Law SC, et al. EBV-associated primary CNS lymphoma occurring after immunosuppression is a distinct immunobiological entity. *Blood*. 2021;137(11):1468-1477.
9. Jorgensen PB, Livbjerg AH, Hansen HJ, Petersen T, Hollsberg P. Epstein-Barr virus peptide presented by HLA-E is predominantly recognized by CD8(bright) cells in multiple sclerosis patients. *PLoS One*. 2012;7(9):e46120.
10. Mbiribindi B, Pena JK, Arvedson MP, et al. Epstein-Barr virus peptides derived from latent cycle proteins alter NKG2A + NK cell effector function. *Sci Rep*. 2020;10(1):19973.

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LYMPHOID NEOPLASIA

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Highs and lows of t(4;14) in multiple myeloma

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In this issue of *Blood*, Stong et al show that true high-risk t(4;14) multiple myeloma (MM) patients can be identified by using the coordinates of the translocation breakpoints in the *NSD2* gene.[1] The authors provide an elegant and detailed characterization of a single genetic alteration that improves our understanding of disease biology and prediction of clinical outcomes (see figure).

Among the first reports showing the presence of t(4;14) in MM were those published in 1997 by Chesi et al[2] and Richelda et al.[3] One year later, Chesi et al[4] demonstrated that the t(4;14) was an interesting example of an IgH translocation that simultaneously dysregulates 2 genes with oncogenic potential: *FGFR3* and *MMSET*, which is currently named *NSD2*. In 2001, Fonseca et al showed that the t(4;14) was strongly associated with chromosome 13 abnormalities.[5] This finding was confirmed in the comprehensive analysis performed by Stong et al,[1] which further uncovered a constellation of copy number alterations and somatic mutations that were enriched in t(4;14) patients. Most interestingly, *FGFR3* mutations were exclusive to these and absent in non-t(4;14) patients, but such mutations had no impact in survival.[1]

In 2001 and 2003, Rasmussen et al[6] and Keats et al[7] concluded that, in MM, t(4;14) is an adverse prognostic factor irrespective of *FGFR3* expression. Notably, Stong et al[1] confirmed this finding and uncovered that expression of *NSD2* was also unrelated to poor outcome. In 2013, Walker et al[8] performed whole genome sequencing and identified breakpoint locations upstream of the *NSD2* gene or within the coding sequence. Other groups have suggested a potential association between expression of *NSD2* truncated isoforms (resulting from breakpoint locations within the coding sequence) and a poor prognosis, but the study from Stong et al, performed in the largest cohort of 258 t(4;14) newly diagnosed MM patients (153 discovery and 105 independent replication), showed unequivocally that only those with a breakpoint within the *NSD2* gene and downstream of the translation start site (coined as "late disruption"; 31%) have a dismal overall survival.[1] Patients with a breakpoint between the transcription and translation start site ("early disruption"; 23.5%) and upstream ("no disruption"; 45.5%) of the *NSD2* gene displayed progressively longer survival.[1] Importantly, risk stratification according to the 3 breakpoint regions was superior to that achieved with previously identified *NSD2* truncated isoforms.[1] Thus, an *NSD2* breakpoint analysis is the way forward to identify high-risk t(4;14) patients.

The authors have probably generated the largest dataset on t(4;14) MM, which includes whole genome and RNA sequencing data. The latter were used to analyze fusion *NSD2* transcripts, which confirmed in most patients the correlation between the no disruption or early disruption and full-length fusion transcripts, as well as between late disruption and truncated fusion transcripts.[1] Further investigation from this group using data from RNA sequencing will be an important sequel of this article, hopefully identifying novel therapeutic targets for t(4;14) MM. The identification of true high-risk t(4;14) may prove extremely useful for the initial use of targeted therapy for this genetic risk group. The median overall survival of patients with no disruption, early disruption, and late disruption t(4;14) was 75.1, 59.4 and 28.6 months, respectively.[1]

The discovery and independent replication cohorts included patients receiving numerous induction regimens and transplant-based and nontransplant approaches, as well as maintenance of fixed vs continuous duration. Thus, although targeted therapies are eagerly awaited for this and other genetic subgroups, future analyses should address