

REFERENCES

1. Stonestrom AJ, Hsu SC, Jahn KS, et al. Functions of BET proteins in erythroid gene expression. *Blood*. 2015;125(18):2825-2834.
2. Kouzarides T. Histone acetylases and deacetylases in cell proliferation. *Curr Opin Genet Dev*. 1999;9(1):40-48.
3. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. *Cell*. 2012;150(1):12-27.
4. Filippakopoulos P, Knapp S. The bromodomain interaction module. *FEBS Lett*. 2012;586(17):2692-2704.
5. Muller S, Filippakopoulos P, Knapp S. Bromodomains as therapeutic targets. *Expert Rev Mol Med*. 2011;13:e29.
6. Belkina AC, Denis GV. BET domain co-regulators in obesity, inflammation and cancer. *Nat Rev Cancer*. 2012;12(7):465-477.

7. Filippakopoulos P, Knapp S. Targeting bromodomains: epigenetic readers of lysine acetylation. *Nat Rev Drug Discov*. 2014;13(5):337-356.
8. Lamonica JM, Deng W, Kadauke S, et al. Bromodomain protein Brd3 associates with acetylated GATA1 to promote its chromatin occupancy at erythroid target genes. *Proc Natl Acad Sci U.S.A.* 2011;108(22):E159-E168.
9. Weiss MJ, Yu C, Orkin SH. Erythroid-cell-specific properties of transcription factor GATA-1 revealed by phenotypic rescue of a gene-targeted cell line. *Mol Cell Biol*. 1997;17(3):1642-1651.
10. Hnisz D, Abraham BJ, Lee TI, et al. Super-enhancers in the control of cell identity and disease. *Cell*. 2013;155(4):934-947.

© 2015 by The American Society of Hematology

● ● ● THROMBOSIS AND HEMOSTASIS

Comment on Tanimura et al, page 2835

HLA class II meets β_2 -glycoprotein I

Perumal Thiagarajan BAYLOR COLLEGE OF MEDICINE

In this issue of *Blood*, Tanimura et al describe an interaction between certain human leukocyte antigen (HLA) class II alleles and misfolded β_2 -glycoprotein I (β_2 GPI). This complex is expressed on the surface of HLA class II-expressing placental endothelial cells, and it is a target for the autoantibodies against β_2 GPI seen in patients with antiphospholipid syndrome (APS), providing a mechanistic basis for pregnancy-related morbidity in these patients.¹

In antigen-presenting cells, HLA class II molecules present peptide antigens derived from extracellular proteins by the endocytic pathway to the CD4 T cells via the peptide-binding groove.² Following their assembly in the endoplasmic reticulum with an invariant chain (Ii), the Ii/HLA class II complexes are transported to a late endosomal compartment called the major histocompatibility complex (MHC) class II compartment. Here, Ii is proteolytically processed and removed, allowing peptide loading to the antigen-binding groove in the HLA class II complex. The HLA class II complex is then transported to the plasma membrane to present the peptide cargo to CD4 T cells.

In previous publications, these authors have shown that the HLA class II molecules can also transport certain intact misfolded proteins such as the immunoglobulin G heavy chain from the endosomal compartment to the cell surface.^{3,4} Compared with HLA class I molecules, the peptide-binding groove of HLA class II molecules is open, and it can accommodate longer peptides. By using 293T cells transfected with complementary

DNAs for β_2 GPI and HLA class II complex, the authors showed that misfolded β_2 GPI was bound to HLA class II molecules inside the cell. This interaction presumably occurs in the endosomal compartment, and the complex is transported to the cell surface. The binding of the β_2 GPI/HLA class II complex depends on the HLA-DR alleles. Certain APS-susceptible alleles such HLA-DR7 and HLA-DR4 bound to β_2 GPI more effectively than other alleles. Although these studies were performed in transfected 293T cells with forced expression, the authors demonstrated the association of β_2 GPI/HLA class II complex on endothelial cells in the placenta of patients with APS but not in the placenta of patients without APS. HLA class II-bound misfolded β_2 GPI is not only a target of antibody-induced injury but is also a potent inducer of antigen-specific B cells and may play a role in the persistence of these antibodies in APS patients.

These novel findings raise several interesting questions, which have a direct bearing on the mechanism of the procoagulant state associated with APS. Endothelial cells, the most extensively studied target, express

class II antigens only after stimulation. This raises the question of whether only inflamed endothelial cells are the targets of the antiphospholipid antibodies. However, most patients with APS do not have evidence of vasculitis or other inflammatory conditions. Macrophages, the professional antigen-presenting cells, express HLA class II molecules and internalize β_2 GPI/phosphatidylserine-containing vesicles and platelet microparticles,⁵ and they can potentially express this epitope on their surface. In monocytes, antiphospholipid antibodies induce tissue factor, the major initiator of the coagulation system.⁶ Furthermore, the HLA class II molecules can transmit outside-in signals by triggering multiple pathways,⁷ and several signal transduction cascades have been shown in endothelial activation by β_2 GPI-dependent antiphospholipid antibodies.⁸

Despite a large number of studies on this subject, the precise mechanism of the procoagulant state in APS is still elusive.⁹ The Tanimura et al study provides yet another potential cell surface receptor for β_2 GPI that may be involved in the induction of the procoagulant state.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Tanimura K, Jin H, Suenaga T, et al. β_2 -Glycoprotein I/HLA class II complexes are novel autoantigens in antiphospholipid syndrome. *Blood*. 2015;125(18):2835-2844.
2. Neefjes J, Jongstra ML, Paul P, Bakke O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. *Nat Rev Immunol*. 2011;11(12):823-836.
3. Jiang Y, Arase N, Kohyama M, et al. Transport of misfolded endoplasmic reticulum proteins to the cell surface by MHC class II molecules. *Int Immunol*. 2013;25(4):235-246.
4. Jin H, Arase N, Hirayasu K, et al. Autoantibodies to IgG/HLA class II complexes are associated with rheumatoid arthritis susceptibility. *Proc Natl Acad Sci U.S.A.* 2014;111(10):3787-3792.
5. Thiagarajan P, Le A, Benedict CR. Beta(2)-glycoprotein I promotes the binding of anionic phospholipid vesicles by macrophages. *Arterioscler Thromb Vasc Biol*. 1999;19(11):2807-2811.
6. Kornberg A, Blank M, Kaufman S, Shoenfeld Y. Induction of tissue factor-like activity in monocytes by anti-cardiolipin antibodies. *J Immunol*. 1994;153(3):1328-1332.
7. Al-Daccak R, Mooney N, Charron D. MHC class II signaling in antigen-presenting cells. *Curr Opin Immunol*. 2004;16(1):108-113.
8. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol*. 2011;7(6):330-339.
9. Chaturvedi S, McCrae KR. Recent advances in the antiphospholipid antibody syndrome. *Curr Opin Hematol*. 2014;21(5):371-379.

© 2015 by The American Society of Hematology



blood[®]

2015 125: 2741

doi:10.1182/blood-2015-03-633644

HLA class II meets β_2 -glycoprotein I

Perumal Thiagarajan

Updated information and services can be found at:
<http://www.bloodjournal.org/content/125/18/2741.full.html>

Articles on similar topics can be found in the following Blood collections
[Free Research Articles](#) (4867 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
<http://www.bloodjournal.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:
<http://www.bloodjournal.org/site/subscriptions/index.xhtml>