inhibitor of the IRE1
leukemic regression in CLL-bearing TCL1
mouse model with overexpression of the
ER stress response is critical for the growth
with prosurvival function, is increased.
Moreover, the expression of BIP, a chaperone
with prosurvival function, is increased.
Indeed, it has been reported that the
ER stress response is critical for the growth
of human CLL and mouse CLL (in the
mouse model with overexpression of the
TCL1 gene). Based on findings showing
that inhibitors of the ER stress response induce
apoptosis of mouse and human CLL cells in
vitro and suppressed leukemic progression in
mice in vivo, the UPR pathway may be a
powerful novel molecular target for the
treatment of CLL patients. In this context,
an inhibitor of the IRE1α RNase activity has
been developed, which effectively induces
leukemic regression in CLL-bearing TCL1
transgenic mice. Apart from their potential
as a treatment strategy, UPR components
are expected to have value as prognostic or
predictive markers, because higher RNA
expression levels of CHOP and XBP1 were
correlated with more aggressive disease.

On the basis of its profound antitumor activity,
the BTK inhibitor ibrutinib was recently registered in the United States for
previously treated patients with CLL. Interestingly, Krysov et al found that treatment
of CLL cells in vitro with small molecule inhibitors of BTK and spleen tyrosine kinase
reduced the expression of anti-IgM–induced BIP and PERK. It is therefore conceivable that
the successful antitumor activity of ibrutinib is partly based on inhibition of UPR activation.
It will be interesting to investigate whether its in vitro effects on BIP and PERK
expression can be used to monitor or predict response or resistance to ibrutinib.

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

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THROMBOSIS & HEMOSTASIS

Comment on Ma et al, page 3155

Cautious enthusiasm about GWAS findings

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In this issue of Blood, Ma and colleagues report the first agnostic investigation by a genome-wide association study (GWAS) in search of genetic determinants of a variation in plasma plasminogen levels.

Plasminogen is the zymogen of plasmin, a key player in a broad spectrum of biological functions including coagulation, hemostasis, inflammation, and cell migration and adhesion. The significance of GWAS investigation searching for genetic determinants underlying normal variation of plasminogen plasma levels lies in the potential of providing new clues about the biological processes that may contribute to the underlying liability for a wide range of disorders. Better mechanistic understanding is a foundational step prior to novel therapeutic target discoveries and precision medicine applications.

Ma et al add to previous studies of genetic determinants of plasma proteins from the fibrinolytic pathway, plasminogen activator inhibitor 1 and tissue plasminogen activator, with the identification of genetic variants associated with plasminogen protein level variation. Using 2 independent study samples, Ma et al first conducted a GWAS of plasminogen levels in each, followed by a meta-analysis of both study samples combined. The authors then refined their work by conducting additional statistical analyses to better understand the relationship between the most promising genetic variants and their relationship with known nongenetic determinants of plasminogen levels, such as smoking and sex. This GWAS meta-analysis was complemented with a linkage scan analysis, functional exploration, and further genotyping of selected regions.

Ma et al claim 3 salient findings. Reassuring but not surprising was the finding of genetic variations associated with plasminogen levels in PLG (which codes for plasminogen) and LPA, a gene adjacent and highly homologous to PLG that codes for lipoprotein(a). Partly due to its homology with PLG, genetic variations in LPA could impair plasminogen levels. The PLG and LPA association findings were genome-wide significant (ie, accounting for multiple hypothesis testing) in the discovery sample, were then replicated in an independent study sample, and remained highly significant in the meta-analysis. Of greatest interest but
inviting debate are the novel findings about the SIGLEC14 variant associations with plasminogen levels. Although variants of SIGLEC14 were identified in both study samples, they reached genome-wide significance only when both study samples were combined in the meta-analysis, leaving no independent study sample for replication. SIGLEC14 codes for Siglec-14 (sialic acid–binding immunoglobulin-like lectin 14), a member of a family of proteins mainly expressed on white blood cells and engaged in immune and inflammation functions. Given the accumulating evidence for the role of inflammation in thrombotic outcomes, including an initiating mechanism in venous clot formation, these findings are potentially exciting new research avenues. However, in the absence of independent replication, cautious enthusiasm about the interpretation of the SIGLEC14 association results is called for here.

In addition to the stringent statistical significance threshold imposed by the multiple-hypothesis testing framework and the need for independent replication, GWAS association findings are further challenged by their relative ability to pinpoint the causal variants owing to linkage disequilibrium, as well as the potential effect of other genetic or nongenetic factors. Ma et al have approached these challenges by investigating the relationship of identified variants with each other and with known nongenetic determinants of plasminogen levels. These analyses showed that genetic variants of PLG, LPA, and SIGLEC14 were independent determinants of plasma plasminogen levels.

The next step is to demonstrate functional relevance of identified GWAS variants. Ma et al have made an attempt at validating the functional relevance of their PLG findings, exploring a publically available expression quantitative trait locus (eQTL) database, that is, a catalog containing information generated from various tissues about the effect of genetic variants on gene expression levels. None of the identified PLG variants by Ma et al matched eQTLs from the database. Therefore, the functional relevance of the PLG variants, and that of the unexplored LPA and SIGLEC14 variants, remains unknown.

Finally, about the clinical relevance of plasminogen level determinants, plasminogen is the zymogen of the active fibrinolytic enzyme plasmin, and low levels could be expected to result in impaired fibrinolysis and pathological thrombosis. However, evidence suggests that plasminogen deficiency is not a strong thrombotic risk factor when present as a single defect. Although the association with thrombosis is tenuous, type 1 plasminogen deficiency is clearly associated with ligneous conjunctivitis, an inflammatory disorder that manifests itself by fibrin-rich pseudomembranes developing on ocular and extraocular mucosa.

The study by Ma et al reporting the association of PLG and LPA variants with plasma plasminogen levels adds to previous GWAS findings on the fibrinolytic pathway and opens the way for experimental work to establish a specific role for these variants in fibrinolysis. The SIGLEC14 findings await proper replication. Given the innate immune role of Siglec proteins, if replicated and functionally validated, these findings could have a major impact on our understanding of plasma plasminogen level regulation.

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