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● ● ● LYMPHOID NEOPLASIA

Comment on Salaverria et al, page 1394

Cyclin D1-negative mantle cell lymphoma

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In this issue of *Blood*, Salaverria et al report that more than half of Cyclin D1- (CCND1) negative SOX11-positive mantle cell lymphoma (MCL) had *CCND2* gene rearrangement predominantly with immunoglobulin (*IG*) light chain genes.¹

Monomorphic small to medium sized lymphoid cells with CD5+, CD10-, CD23- phenotype		
Most common MCL(80-90%)	Indolent MCL	} CCND1 +
CCND1 + CCND2 - SOX11 +	CCND1 + CCND2 - SOX11 -	
CCND2+ MCL*	CCND1- Indolent MCL****	} CCND1 -
CCND1 - CCND2 +** SOX11 +	CCND1 - CCND2 + SOX11 -	
CCND1- CCND2- MCL***	CCND1- Indolent MCL****	
CCND1 - CCND2 - SOX11 +	CCND1 - CCND2 - SOX11 -	
<div style="display: flex; justify-content: space-around;"> Aggressive course Indolent course </div>		

MCL is characterized by monomorphic small to medium-sized lymphoid cells with CD5+, CD10-, CD23- phenotype.² *CCND1* rearrangement and/or CCND1 immunostaining is a hallmark of diagnosis. However, it has been known that CCND1-negative MCL with a poor clinical outcome exists. Recently, SOX11 has been shown to be a good marker to identify such cases with poor outcome,⁵ although a controversy has been raised.⁷ Salaverria et al revealed that *CCND2* gene rearrangement is frequently found (22 of 40 CCND1-negative MCL cases, 55%) and is a molecular basis for CCND1-negative SOX11-positive MCL (yellow box).¹ Further study on molecular mechanisms of CCND1-negative CCND2-negative SOX11-positive MCL with a poor clinical outcome (orange box) to provide appropriate therapy is needed. *More than half (22/40) of the CCND1-negative SOX11-positive MCL show *CCND2* gene rearrangement. **Translocation of *CCND2* takes place predominantly with *IG* light chain genes (15/22). ***Among CCND1-negative SOX11-positive MCL cases, 18 of 40 did not show *CCND2* translocation. Because controversy exists on SOX11 staining with regard to clinical outcome, further study including identification of other diagnostic markers and molecular basis is warranted. ****CCND1-negative indolent MCL has not been well recognized and would be rare, but its understanding is important for selecting appropriate therapy and for differential diagnosis from the other types of lymphoma.

Mantle cell lymphoma (MCL) is a B-cell neoplasm composed of monomorphic small to medium-sized lymphoid cells.

CCND1 translocation and CCND1 nuclear expression are used for diagnostic purposes and distinguish MCL from other types of lymphomas.²

Since the introduction of anti-CCND1 monoclonal antibody for immunostaining, it has been used to delineate MCL from the other types of lymphoma. CCND1-positive MCL has a poor prognosis. However, CCND1-negative MCL has remained controversial due to its variable clinicopathologic features.^{3,4}

Recent study on indolent CCND1-positive MCL with the most common poor prognosis

type MCL revealed that SOX11 is a good marker to distinguish the latter from the former.⁵

SOX11 is a neural transcription factor involved in central nervous system development and is over-expressed in gliomas compared with normal brain tissue, suggesting a role in malignant transformation. Immunostaining of SOX11 at nuclei in MCL was reported⁶ but the prognostic significance of this finding remains unclear.⁷ This point must be further clarified to establish appropriate therapies for each MCL subtype.

The molecular pathogenesis of CCND1-negative MCL with a poor clinical outcome has not been defined, but it was shown that

more than one-half of such cases (22/40) had *CCND2* translocation, most likely resulting in deregulation of CCND2 expression (see figure).¹ Indeed, a preceding report of CCND1-negative MCL cases with *CCND2* translocation has shown CCND2 overexpression in nuclei.⁸ Cyclin-D families (D1, D2, D3) are differentially expressed in various hematopoietic malignancies and are believed to play roles in malignancies.⁹ Therefore, it is possible that CCND3 plays a role in lymphoma development for CCND1-negative MCL, but Salaverria et al revealed no *CCND3* rearrangement, suggesting mechanisms other than cyclin-D family pathways exist.¹

The cases without *CCND2* gene rearrangement (18/40) had a poor clinical outcome and are positive for SOX11 expression. This may indicate that the pathways involving SOX11 play a role in lymphoma development of CCND1- and D2-negative MCL. Exploration of both CCND1- and D2-negative SOX11-positive MCL (see figure) would lead to a clue underlying molecular mechanisms of MCL development including the most typical MCL.

It should be also noted that *CCND2* predominantly translocates to *IG* light chain genes (*IGK@* or *IGL@*; 15/22, 68%), and only 3 cases show *IG* heavy chain (*IGH@*) gene translocation. The remaining 4 of 22 cases are undisclosed.¹ *IG* gene translocation with *CCND1*, *BCL2*, or *BCL6* is a valuable diagnostic marker, but involvement of *IGH@* gene is more frequent than the cases reported by Salaverria et al.

Non-*Ig* translocation of *CCND2* is also noted,¹ although approximately 40% cases with *BCL6* translocation have been shown to possess non-*IG* gene translocation.¹⁰

High frequency of *IG* light chain gene translocation may indicate that the translocation takes place in a different stage of B-cell differentiation compared with the stages where *CCND1*, *BCL2* or *BCL6* translocation occurs. Alternatively, genomic and/or epigenomic configurations unique to CCND1-negative MCL may cause different environments for chromosome translocations.

CCND1-negative MCL is rare, but identification of *CCND2* gene rearrangement in such cases provides a very robust marker indicating the need for intensive therapy. This report by Salaverria and colleagues surely opens a gate to better understanding the whole picture of molecular mechanisms of MCL development.

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

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approximately 25% to 30% of young patients with severe hemophilia A. They preclude treatment with FVIII products by neutralizing FVIII activity. Although immune tolerance therapy and alternative hemostatic treatments that bypass FVIII are available, it is generally more difficult to prevent bleeding and arthropathy. As a matter of fact, hemophilia patients with inhibitors are jolted back to an era when hemophilia was associated with severe impairments in daily life.

So, why is it that a minority of patients develops inhibitors and that the majority of patients is seemingly tolerant to the foreign FVIII protein? What we know is that inhibitor development is caused by an intricate interplay of both genetic and environmental factors (see figure).^{4,5} Astermark and colleagues have demonstrated that the *F8* genotype and other markers in immune response genes are major players in the field.⁶ These genetic markers of inhibitor development include HLA class II alleles and several single nucleotide polymorphisms (SNPs) in immune response genes.⁷⁻⁹

Still, further insight into the etiology of inhibitor development is urgently needed. If it is possible to predict a specific patient's individual risk of developing inhibitors, individualized treatment regimens or modification of immunologic factors in high-risk patients could possibly prevent inhibitors. Moreover, identification of immunologic pathways to inhibitor development may provide novel therapeutic targets to prevent inhibitors. So, how to push forward in the quest toward the prediction and prevention of inhibitor development?

In the current study, Astermark et al endeavored to unravel the genetic susceptibility for inhibitor development. This enormous challenge required a substantial number of patients. The authors joined hemophilia researchers worldwide and succeeded in studying 833 patients by combining cohorts from 3 different studies. An evaluation of 13 331 SNPs in primarily immune response and immune modifier genes yielded 53 SNPs that predicted inhibitor status in all cohorts. Of these, 13 markers were statistically significantly associated with inhibitor development in the combined cohort (meta *P* values < .001). In addition, 8 of the 53 SNPs were significant predictors among the discordant brother pairs. The identified genetic markers are known to be involved in various B and

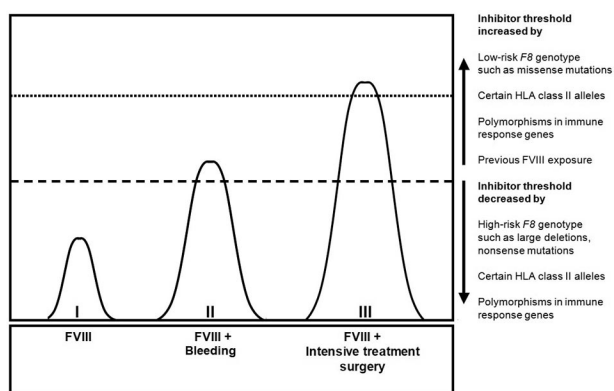
● ● ● THROMBOSIS & HEMOSTASIS

Comment on Astermark et al, page 1446

Unraveling the genetics of inhibitors in hemophilia

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In this issue of *Blood*, Astermark et al have identified novel genetic markers of inhibitory antibody formation in hemophilia patients that may ultimately lead to prediction and even prevention of this severe complication of hemophilia treatment.¹



The combined action of genetic and environmental determinants on the risk of inhibitor development.¹⁰

Hemophilia treatment has improved dramatically over the past decades. Before the 1960s, hemophilia was a crippling disease as the bleeding tendency led to irreversible arthropathy and increased mortality.² Improvements in concentration and purification techniques gave patients in the Western world access to clotting factor concentrates, warding off the sequelae of repeated joint bleeds. These advances were overshadowed by the viral infections that occurred in the 1980s, when

many hemophilia patients tragically became infected with HIV and the hepatitis C virus.³ Nowadays, major advances in safety of clotting factor products and institution of regular prophylactic clotting factor infusions have made a normal life with hemophilia possible.

Unfortunately, these achievements of modern hemophilia care are off the map for patients that develop inhibitory antibodies to factor VIII (FVIII). These so-called inhibitors form a severe complication of FVIII therapy in