

inside blood

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PLATELETS & THROMBOPOIESIS

Comment on Zhang et al, page 4086

Molecular mimicry and immune thrombocytopenia

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In this issue of *Blood*, Zhang and colleagues show evidence that many thrombocytopenic patients infected with HCV have autoantibodies specific for a defined peptide sequence in platelet membrane glycoprotein IIIa. These autoantibodies appear to be the result of an immune response mounted against one or more peptides present in the HCV core envelope protein 1.

Immune thrombocytopenia is a common complication of infection with the human immunodeficiency (HIV)¹ and hepatitis C (HCV)² viruses. In previous works, the authors showed that many patients with HIV-associated thrombocytopenia have autoantibodies that recognize a restricted peptide sequence (GPIIIa49-66) in platelet membrane glycoprotein IIIa (GPIIIa) and can be recovered from patient plasma in the form of immune complexes consisting of autoantibody and platelet fragments.³ A unique feature of these antibodies is their ability to induce reac-

tive oxygen species through activation of 12-lipoxygenase and NADPH oxidase, leading to complement-independent platelet fragmentation.⁴

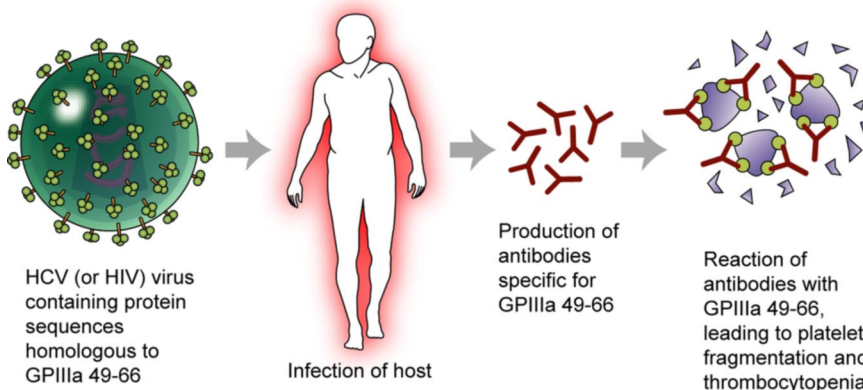
In the new work, Zhang et al used a GP49-66-specific antibody to screen a phage-expression peptide library in order to identify peptides that mimic the antibody binding site and might share homology with HCV proteins.⁵ It was found that sera from patients coinfecting with HCV and HIV reacted with 4 peptides present in nonconserved regions of the HCV core envelope 1 protein. Antibodies

raised against one of these peptides (PHC09) caused severe thrombocytopenia when injected into wild-type mice whose GPIIIa is more than 80% identical to that of humans. Moreover, patient IgG eluted from the PHC09 peptide caused oxidative fragmentation of human platelets comparable to that induced by antibodies from patients infected with HIV. Immunization of wild-type mice with HCV core envelope protein 1 had no effect on platelet count. However, NZB/W F1 mice, a strain in which immune surveillance is defective, produced antibodies specific for PHC09 and became thrombocytopenic. The titer of PHC09-specific antibody in patients coinfecting with HCV and HIV correlated with both the incidence of thrombocytopenia and its severity.

The authors conclude that humans and immunodeficient mice immunized with HCV core envelope protein 1 often produce antibodies that recognize GPIIIa49-66 through molecular mimicry and are capable of causing clinically significant thrombocytopenia.

These remarkable observations provide further evidence for the role of molecular mimicry in the pathogenesis of autoimmune thrombocytopenia in patients infected with HCV. The new observations complement similar findings made previously in patients with HIV-associated immune thrombocytopenia^{3,4} and may have implications for various autoimmune conditions described in patients infected with HCV,⁶ other viruses,⁷ and bacteria.^{8,9}

It seems extraordinary that that both HCV (a member of the flavivirus family) and HIV-1 (a retrovirus) each contain structural elements that mimic peptide sequences in the same region of GPIIIa and that both induce GPIIIa-specific antibodies capable of causing thrombocytopenia. As the authors note, mimicry of host proteins is one mechanism by which viruses escape host surveillance. Location of the epitopes identified in this study in nonconserved regions of the 2 viruses is consistent



HCV (and HIV) contain proteins with peptide sequences homologous to GPIIIa49-66. Infection with either (or both) of these viruses leads to presentation of these peptides to the host immune system and production of antibodies specific for GPIIIa49-66 by some individuals. The antibodies react with GPIIIa on autologous platelets, leading to platelet fragmentation and thrombocytopenia. Defective immune surveillance associated with HIV infection may explain breakage of immune tolerance to the autologous peptides. Professional illustration by Kenneth X. Probst.

with the possibility that they evolved as part of this process.

A second and quite unexpected property of antibodies specific for GP49-66 is their ability to induce oxidative platelet fragmentation *in vitro* (and presumably *in vivo*). GPIIb/IIIa is by far the most immunogenic of platelet proteins and a large number of auto-, allo-, and drug-dependent antibodies reactive with this target have been studied. Yet, no others have been shown to evoke this type of platelet response. Peterson et al previously studied a group of IgG antibodies from patients with quinine-induced immune thrombocytopenia that recognize the very peptide sequence (GPIIIa49-66) identified by Zhang et al as a target for HCV and HIV autoantibodies.^{10,11} Yet the quinine-dependent antibodies appear not to be capable of inducing platelet fragmentation. Why the autoantibodies identified by Zhang et al have this unusual property is not fully understood.¹² Further studies of this process at a molecular level could lead to characterization of a new mechanism for immune-mediated cytopenia.

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

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CLINICAL TRIALS

Comment on Adès et al, page 3947

REvelation (del: 5q)

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Nowhere has the notion of personalized medicine been more realized than in oncology therapeutics. Within MDS, the use of lenalidomide for lower-risk patients with the del (5q) cytogenetic abnormality is emblematic of this approach. But is the drug personalized enough to be used in any patient whose cancer expresses del (5q)?

Therapy for myelodysplastic syndromes (MDS) has undergone a revolution of sorts in the past 5 years, with the approval by the US Food and Drug Administration of 3 drugs specifically for this collection of diseases: azacitidine in 2004,¹ lenalidomide in 2005,² and decitabine in 2006.³ Only 1 of these, lenalidomide, is approved for an MDS subgroup: patients with lower-risk (International Prognostic Scoring System [IPSS] scores ≤ 1.0), transfusion-dependent disease who

harbor the del (5q) cytogenetic abnormality. In this narrowly defined group, who comprise approximately 8% to 9% of all MDS patients, lenalidomide is a wonder drug, yielding transfusion independence responses in 67% of patients, complete cytogenetic remissions in 44%, and a duration of transfusion independence lasting a median of 2.2 years.⁴ One question that arises frequently is whether the drug can be used with equal efficacy, and as frontline therapy, for those MDS patients with

higher-risk (IPSS scores ≥ 1.5) disease and a del (5q) abnormality.

In this issue of *Blood*, Adès and colleagues report the results from a phase 2 study, exploring the safety and efficacy of lenalidomide in 29 del (5q) patients with higher risk MDS and 18 del (5q) patients with acute myeloid leukemia (AML) and 20% to 30% myeloblasts.⁵ Among the MDS patients, 6 (21%) achieved a complete remission (CR), 2 (7%) a marrow CR, and 4 (14%) hematologic improvement in erythropoiesis. Among AML patients, 1 (6%) achieved a CR. Median response duration was 6.5 months for all patients, 11.5 months for those with an isolated del (5q) abnormality, and median overall survival was 272 days (~ 9 months). CR was more likely to occur in those with an isolated del (5q) lesion (in 6 of 9 patients, or 67%) compared with those with additional cytogenetic abnormalities ($P < .001$). It was also more likely to occur in those with an initial platelet count greater than 100 000/mm³ (in 6 of 13 patients, or 46%), compared with those with lower platelet counts ($P = .001$). A majority of patients experienced severe neutropenia and/or thrombocytopenia, and 30 patients (64%) required hospitalization during their treatment course.

Compare these results to those presented by Fenaux and colleagues of a phase 3 study of azacitidine versus conventional care in patients with higher-risk MDS (AZA-001) at the American Society of Hematology Annual Meeting 1 year ago.⁶ Median survival in the azacitidine arm was 24.4 months (a full 15 months greater than the present study), though CR rates were similar (17%), and partial remission and hematologic improvements were higher (12% and 49%, respectively). It is unclear whether these advantages translated to AZA-001 patients with the del (5q) abnormality, either in isolation or with additional cytogenetic abnormalities, though a preliminary report suggests that a combination of MDS and AML patients with the del (5q) lesion had a median survival of 9 months, significantly lower than similar patients without this abnormality (15 months, $P = .007$).⁷

Why the inferior responses to single-agent lenalidomide in the study by Adès et al, when presumably therapy is "targeted" more to a distinct, identifiable lesion for which this therapy has demonstrated presumed cytotoxicity (with cytogenetic response rates) in lower-risk disease? We may be witnessing a recapitulation of the FMS-like tyrosine kinase 3 (*flt3*) internal tandem