To the editor:

A hypothesis that explains the heterogeneity of drug-induced immune thrombocytopenia

A new hypothesis is presented here to explain recent observations about drug-induced immune thrombocytopenia (DIT). Characterization of quinine-dependent autoantibodies has led to the current paradigm that quinine associates noncovalently with a target platelet receptor and induces formation of a neo-epitope that can elicit specific immune response. It was thought that quinine binds to a favored site on the target receptor or autoantibody, itself becoming a part of the neo-epitope or antibody, and contribute directly to the antibody-epitope association. Both scenarios entail a favored quinine-binding site—with well-defined sequence or structural features—in target receptors. However, it is not clear how this paradigm explains the well-documented heterogeneity in DIT-causing drugs and associated epitopes.

Peterson et al recently showed that while 14 of 16 quinine-dependent anti-GPIIbα autoantibodies bind to hybrid and plexin/semaphorin/integrin (PSI) domains of glycoprotein IIIa (GPIIIa) in a Western blot assay, there is epitope heterogeneity within these domains. They attributed the observed heterogeneity to the diversity of autoantibodies: different antibodies bind to different epitopes that still share the same quinine-binding site. However, the antibody diversity could not explain the lack of a common feature among identified quinine-dependent epitopes in GPIb-IX and GPIIb-IIIα complexes. Alternatively, the epitope heterogeneity could be explained as different quinine-binding sites recognized by different autoantibodies. But the modest size of hybrid and PSI domains makes them unlikely to accommodate multiple high-affinity binding-sites for quinine. If not a high-affinity quinine-binding site, which feature of hybrid and PSI domains may distinguish them from other domains in GPIIIa (eg, βα domain) as the preferred target for quinine-dependent antibody-binding?

In crystal structures of both GPIb-IIIα and integrin αβ, the PSI domain has the highest B-factors, an indicator for dynamic motion and flexibility, suggesting that it may be the most flexible domain in GPIIIa. Generally speaking, all proteins transiently sample denatured or nonnative conformations, even under native conditions. The more flexible a protein domain or region is, the less stable it is, and the more frequently it samples denatured conformations. Therefore, the PSI domain should display denatured conformations more often than the other domains in GPIIIa. A key difference between protein denatured and native conformations is the increased hydrophobic surface area in the former. Most drugs, including quinine, contain significant hydrophobic elements that confer membrane permeability. I propose that quinine may bind to and stabilize denatured or nonnative conformations in platelet receptors, some of which are recognized as foreign and thereby initiate specific immune response.

This hypothesis accommodates the heterogeneity of quinine-dependent neo-epitopes in preferred domains. As denatured conformations are intrinsically heterogeneous, those stabilized by quinine-binding may be stochastic, resulting in the epitope heterogeneity. At the same time, the preferred binding of quinine for hybrid and PSI domains in GPIIIα can be explained by the instability of these domains. The same reasoning can be applied to the preferred binding of quinine for GPIIX rather than GPIbβ: our recent study suggests that the GPIX ectodomain is the least stable among the subunits in GPIb-IX. Quinine may still bind other domains in GPIb-IX or GPIIb-IIIα, even other platelet receptors, to induce neo-epitope formation because these domains also transiently sample denatured conformations, albeit at a lower rate due to their higher stability. Similarly, quinine can also bind and stabilize transiently denatured domains on the surface of leukocytes and endothelial cells to induce autoantibodies against these cells. Finally, this hypothesis is applicable to other drugs and explains their preferential induction of anti-GPIX autoantibodies.

This hypothesis, or whether the quinine-bound hybrid and PSI domains adopt the native or nonnative conformation, can be tested through structural analysis of receptor/quinine/antibody complexes. If this hypothesis is true, structural details of binding of any particular quinine-dependent antibody may not provide an adequate representation. Research efforts should be devoted to understanding factors that influence susceptible domains in sampling denatured or nonnative conformations and influence drugs in binding denatured protein domains.

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

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References

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