

Correspondence

Reply

To the Editor:

We thank Varner¹ for his interesting correspondence offering a possible mechanism by which atopic subjects may be protected from myocardial infarction (MI). In addition to the group cited by Varner, others have reported that atopic subjects display platelet dysfunction (reviewed in Kasperska-Zajac and Rogala²). We agree that this phenomenon warrants further study and that it may have wide-ranging clinical implications. In our report,³ we found that allergen-specific IgE was inversely related to MI, whereas total IgE and nonspecific IgE were directly related to MI. This led us to posit that IgE per se is unlikely to be protective against MI, and rather that more “proximal” regulators of the T_H2 program (eg, IL-4) may be atheroprotective either directly, or indirectly through suppression of T_H1 signals. Our finding is consistent with an earlier report that total IgE predicts future nonfatal MI in a manner unrelated to allergy.⁴

The positive association of bulk IgE with MI raises some interesting issues. Platelets express both the high-affinity IgE receptor, FcεRI, and FcεRII. When decorated with receptor-bound IgE, platelets can be activated by IgE-specific allergens, and also aggregate in response to IgE crosslinking.² As omalizumab is thought not to interact with cell-bound IgE, IgE crosslinking on platelets presumably does not underlie its recently reported association with thrombosis. At face value, however, the finding that IgE in conjunction with allergen can activate platelets *in vitro* suggests, as is supported by several studies,² that intravascular platelets may actually be activated *in vivo* during high allergen exposure. Whether bleeding time measurements accurately reflect platelet functional/aggregation status throughout the circulation in this scenario is not clear. Moreover, it seems plausible that platelet aggregation in atopic subjects could vary with allergen exposure and disease activity, and perhaps also differ across atopic disorders.

T_H1 inflammation has been broadly implicated in atherosclerosis, but good evidence also suggests that T_H1 signals may modify platelet function specifically. Interestingly, T_H1-biased mice are prone to intravascular thrombosis, including within the coronary arteries,⁵ and the T_H1 cytokine interferon-γ induces platelet proinflammatory functions.⁶ In addition, recent reports indicate that direct contact with T cells activates platelets through CD40L-CD40 interactions, and also that platelet CD40L plays an important role in vascular inflammation and coagulation (reviewed in Danese and Fiocchi⁷). While more work needs to be done, reports such as these clearly suggest that T_H1 signals impact

clotting and also that it may be difficult to cleanly distinguish between contributions of platelets to hemostasis and inflammation. Given that IgE signaling amplifies the T_H2 cascade and omalizumab is thought to interrupt this positive feedback circuit, it is possible that omalizumab may exert complex and indirect effects on platelet function. We agree with Varner that the recent experience with omalizumab may offer new opportunities to advance our understanding of the crosstalk that occurs between platelets and the allergic cascade. New insights into this crosstalk may well lead to novel treatments for patients with cardiovascular and allergic diseases alike.

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