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IgE Stimulates Human and Mouse Arterial Cell Apoptosis and Cytokine Expression and Promotes Atherogenesis in *ApoE*^{-/-} Mice
Wang et al

J Clin Invest. 2011;121:3564-3577.

A new report in the *Journal of Clinical Investigation* adds to the ever-increasing evidence that immunological mechanisms play an important role in atherogenesis. These new observations suggest involvement of IgE and its FcεR1α receptor in the promotion of atherosclerosis, and specifically in plaque instability and clinical events.

Evidence continues to accumulate supporting an important role for immunological mechanisms in all phases of atherosclerosis.¹⁻³ Previous studies have supported an important modulating role for disease-specific IgG and IgM and for Fcγ receptors in modulating atherogenesis.⁴⁻⁹ In a recent report, Wang et al contribute to this growing body of literature by presenting novel observations supporting a proatherogenic role for IgE and its high-affinity receptor FcεR1α.¹⁰ The authors compared the extent of atherosclerosis in wild-type *apoE*^{-/-} mice fed a Western diet with *apoE*^{-/-}/ *FcεR1α*^{-/-} mice and observed a profound reduction in lesion formation. Although nearly all the cell types known to be involved in atherogenesis express FcεR1α receptors in vivo, the authors focused primarily on the potential role of this receptor in macrophage biology and demonstrated that IgE mediates a variety of proinflammatory effects in macrophages, such as release of interleukin-6 and monocyte chemoattractant protein-1, as well as proteases such as cathepsins. In addition, it promotes apoptosis. In large part, these effects (particularly the induction of apoptosis) were mediated by aggregated IgE, as would occur when cross-linked by antigen, and also by an obligatory interaction of FcεR1α with Toll-like receptor 4. In particular, these observations suggest the possibility that IgE and its FcεR1α receptor on macrophages may be involved in late phases of atherosclerosis, promoting plaque instability

and clinical events. The potential relevance of these findings to human disease was supported by the finding of elevated IgE levels in patients with various manifestations of cardiovascular disease (CVD), in particular in those with unstable angina and acute coronary events.

A potential role for IgE in CVD has been previously suggested by studies strongly linking mast cells to atherogenesis and aneurysm formation.¹¹⁻¹⁴ By demonstrating the potential for IgE to participate in macrophage activation and promotion of apoptosis, these studies suggest yet another cell type that might become atherogenic by interaction with IgE, particularly IgE cross-linked by antigen. The demonstration that FcεR1α receptors must interact with Toll-like receptor 4 to produce such effects adds to the growing evidence that individual innate immune receptors effect many of their biological actions by combinatorial activity with other innate receptors, as also exemplified by the interactions of CD36 and Toll-like receptor 2 to mediate macrophage apoptosis.¹⁵ Such combinatorial groupings undoubtedly increase the specificity of response of a given innate receptor, perhaps providing individualized responses in different cell types or under different conditions. Likely, the proatherogenic activity of IgE in humans is more complex. In contrast to the data described by Wang et al,¹⁰ IgE binding to FcεR1α was previously reported to actually promote the survival of human monocytes,¹⁶ and in another report, it was reported to induce proinflammatory effects through the low affinity IgE receptor (CD23), including the release of interleukin-6 and thromboxane B₂ in human B lymphocytes.¹⁷ Nevertheless, these studies suggest novel ways by which IgE may contribute to inflammation and destabilization of the advanced plaque and thus could be relevant to clinical disease.

In the article by Wang et al, the authors describe epidemiological studies in which IgE levels were found to be higher in subjects with CVD and, in particular, subjects experiencing unstable angina and acute coronary events.¹⁰ It is not clear at what time in relation to acute events these levels were measured, nor were control patients with other acute illness sampled. Because the prevalence of known CVD risk factors was very high in the CVD patients studied, it is not possible to determine whether the elevated IgE levels are disease associated or possibly disease causing. Furthermore, the levels of IgE measured in the patients were 150- to 300-fold lower than the concentrations of IgE used in the experimental studies in vitro, raising important questions as to the relevance to human disease of the effects studied in cell culture. Aside from the usual arguments that the localized concentrations at the surface of a macrophage in vivo may be quite different than levels in plasma, it is also possible that simultaneous activation of Toll-like receptor 4 might lead to synergistic effects. For example, one could imagine that in a setting of "metabolic endotoxemia" (in which low but ele-

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Commentaries serve as a forum in which experts highlight and discuss articles (published elsewhere) that the editors of *Circulation Research* feel are of particular significance to cardiovascular medicine.

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vated lipopolysaccharide levels occur in some human patients, such as those with diabetes and metabolic syndrome), these ordinarily subthreshold levels of lipopolysaccharide would synergize with similarly low but elevated levels of IgE to mediate some of the described proinflammatory effects. A similar situation has been proposed for the interaction of lipopolysaccharide and minimally modified LDL with macrophages.¹⁸ In addition, aside from conditions in which there are generalized increases in IgE levels, such as parasitic infections and hyper-IgE syndromes, elevated IgE levels usually reflect allergic-type immune responses. It would be of great interest to know whether the increased IgE levels were polyclonal or reflected any disease-specific antigens, such as those to oxidation-specific epitopes characterized for IgG and IgM isotypes in humans and murine models of atherosclerosis.^{4,19} Future studies should identify whether the increases in IgE in cholesterol or Western-diet-fed *apoE*^{-/-} mice are associated with a polyclonal IgE response or also contain IgE against disease-specific antigens.

The report by Wang et al¹⁰ and other reports describing the potential importance of mast cells to CVD have provided a compelling case to study the role of IgE in inflammatory conditions such as atherosclerosis. It adds to the growing evidence of the importance of immune function in atherogenesis and in particular of the role that immunoglobulins play, both through antigen-specific interactions and antigen-independent regulatory roles.

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