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EDITORIAL COMMENT

# LL-37: A Direct Link Between Inflammation and Myocardial Infarction

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In this issue of *JACC: Basic to Translational Science*, Dimayuga et al[1] have identified a new biomarker that is associated with greater risk of myocardial infarction (MI), cathelicidin antimicrobial peptide LL-37.[1] LL-37 promotes inflammatory signaling and is expelled during degranulation of activated neutrophils.[2] Dimayuga et al[1] previously reported impairment of T-cell tolerance response to LL-37 in patients with acute coronary syndrome that led to the current studies.[3] Among patients with subclinical atherosclerosis demonstrated by coronary artery calcium (CAC), LL-37 was associated with a greater risk of future MI but not associated with CAC score. These results suggest that LL-37 promoted thrombosis but not atherosclerosis. This type of discordance has been observed previously. Treatment of women aged 50 to 59 years with estrogen in the Women's Health Initiative trial led to a reduction in atherosclerotic burden, demonstrated by a reduction in CAC.[4] By contrast, estrogen plus progestin appeared to increase the risk of MI and death from coronary heart disease during the first year after initiation.[5] Thus, although estrogen may retard the progression of atherosclerosis in selected women, it appears to increase the risk of thrombotic complications, particularly early after initiation. Similarly, LL-37 appears to increase the risk of thrombotic complications without a direct effect on the extent of atherosclerosis.

To determine mechanisms by which LL-37 could promote thrombosis, Dimayuga et al[1] evaluated blood from patients with acute coronary syndrome and found immune complexes—LL-37 complexed with immunoglobulin (Ig) G. A link to thrombosis was shown by demonstrating that LL-37 immune complexes activate platelets by binding to FcγRIIa. FcγRIIa was identified as the low-affinity receptor for the fragment constant (Fc) portion of IgG.[6] Binding of antibodies to FcγRIIa trigger platelet activation and thereby promote thrombosis. Platelet FcγRIIa is involved in heparin-induced thrombocytopenia and thrombosis.[7] The principal cellular target for anti-platelet factor 4/heparin antibodies is the platelet FcγRIIa receptor. Thus, the mechanism by which LL-37 promotes thrombotic complications such as MI is consistent with known interactions between immune complexes and FcγRIIa, which have been associated with thrombosis.

A wide range of platelet expression of FcγRIIa has been reported in patients with MI and stable coronary artery disease.[8] We have found that greater platelet expression of FcγRIIa has been associated with a greater risk of subsequent MI, stroke, and death.[9] Thus, both higher concentrations of LL-37 and greater platelet expression of FcγRIIa might work together to increase the risk of thrombotic complications.

In summary, LL-37 is biomarker associated with greater risk of thrombotic complications such as MI. LL-37 is a direct link between inflammation/immune activation and thrombosis. This biomarker does not appear to promote atherosclerosis. Further evaluation of this biomarker is merited to assess both prognostic and therapeutic implications.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Dr Schneider is a named inventor on patents (US 10,502,737 and US 11,747,335 B2) that propose the use of FcγRIIa for assaying platelet reactivity and treatment selection; and is a founder of Prolocor Inc.

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