Interleukin-1β Is a Key Biomarker and Mediator of Inflammatory Vascular Calcification

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Atherosclerotic plaque calcification is a frequent and severe complication of atherosclerosis with significant clinical consequences. The causes of vascular calcification are multifactorial and include impaired phosphate metabolism, increased inflammation with consequent oxidative stress, alterations in systemic metabolic factors (hyperglycemia and hyperlipidemia), and alterations in tissue mechanical stress. Cytokines released by inflammatory cells induce smooth muscle cell (SMC) apoptosis or SMC transdifferentiation to osteochondrogenic phenotypes, both of which contribute to mineral deposition in the plaque. The calcium released in apoptotic bodies forms a nidus of microcalcification, prompting cycles of inflammation, thus making the plaque more susceptible to rupture. By contrast at later times in plaque progression, fusion of microcalcifications to form macrocalcification might actually convey protection against plaque rupture. Inflammatory cytokines can also stimulate the expression of osteogenic transcription factors by SMCs leading to phenotypic transition. Tumor necrosis factor-α (TNF-α), released primarily by macrophages, has been established as a key cytokine; in addition to promoting apoptosis and accumulation of apoptotic bodies, TNF-α is also an activator of osteogenic programming in SMCs via the BMP-2 (bone morphogenetic protein 2), Msx2 (msh homeobox 2), Wnt signaling cascade. Interleukin 1β (IL-1β) is another inflammatory cytokine reported to influence vascular calcification; however, the mechanisms involved are not completely clear and may be different from TNF-α.

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In this issue of ATVB, Ceneri et al have published an article that sheds light on the role IL-1β in plaque calcification. They demonstrate the impact of IL-1β on atherosclerotic calcification and propose Rac2 as a key signaling molecule that regulates Rac1-mediated IL-1β production by bone-marrow-derived cells of the immune system. Using apolipoprotein E knockout (ApoE−/−) mice fed high-fat diet, they show that advanced plaque calcification is associated with increased IL-1β and decreased Rac2 levels. Their data suggest that Rac2 is an inhibitor of Rac1 and in late stages of atherosclerosis, levels of Rac2 decrease, leading to an increase in IL-1β expression in advanced lesions. They have generated mice with systemic deletion of the gene for Rac2 crossed with ApoE−/− mice and use these to show that calcification is driven by hematopoietic cells that produce IL-1β. Furthermore, to determine the cellular population involved in the increased calcification, Ceneri et al performed reciprocal bone marrow transplant studies. They demonstrate that transplantation of Rac2−/−ApoE−/− bone marrow cells into Rac2+/−ApoE−/− mice led to an increase in vascular calcification and also to increased serum levels of IL-1β. However, it is important to note that recent studies using lineage tracing have shown that many cells in mouse atherosclerotic plaques that stain positive for macrophage markers are in fact SMC derived. In the article by Ceneri et al, immuno- nostaining shows that the majority of the CD68-positive cells in the plaque also express Rac2 and IL-1β, suggesting that the SMC-derived plaque macrophages may produce endogenous IL-1β. The authors go on to show that treatment with an IL1 receptor antagonist (anakinra) reduced calcification. However, it is important to note that this treatment modality may not have been as specific as using a monoclonal antibody against IL-1β.

Anakinra treatment may have secondary effects on cytokine production, as it also caused a reduction in serum IL-1β levels via an unknown mechanism. Furthermore, another study has shown that anakinra might also reduce TNF-α production.

Finally, in a retrospective small clinical trial of patients with coronary artery disease, the authors show that Rac2 is decreased whereas IL-1β is increased in calcified coronary arteries. High coronary calcium burden was positively correlated with serum levels of IL-1β, and the incidence of sudden cardiac death was increased in these patients. These results are promising, suggesting that IL-1β may be useful as a biomarker and predictor of calcification risk and cardiovascular end points in patients with coronary artery disease. This article shows evidence of such an interaction, but the true impact of IL-1β on calcification risk and cardiovascular end points requires further study. The plaques shown in the mouse studies and the clinical study exhibit advanced calcification. Further studies will be required to distinguish whether IL-1β levels correlate with inflammatory and unstable plaque calcification, or with more atheroprotective macrocalcification where matrix calcification comprises the bulk volume of the plaque thereby preventing rupture. The small number of patients along with the binary grouping of coronary calcium scores precludes such a determination. The respective roles of IL-1β and TNF-α in promoting calcification also deserve further study. TNF-α plays a significant role in the accumulation of apoptotic bodies that promote initiation of pathological microcalcifications.

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instability. Some studies have suggested that in procalcific conditions, SMCs produce IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β, or might signal to macrophages to increase IL-1β. These interactions between different cells and cytokines during plaque progression require further study so that treatments can be designed to treat all steps of plaque calcification.

In summary, Ceneri et al. have provided important insights into the role of IL-1β in atherosclerotic calcification. For the first time, they have demonstrated a promising prognostic tool using serum IL-1β levels as a biomarker of advanced atherosclerotic plaque calcification. There is an important clinical trial now underway that examines the effect of treatment with a monoclonal antibody against IL-1β (Canakinumab) with results due in 2017. It will be interesting to see whether atherosclerotic plaque calcification is influenced by IL-1β inhibition in patients. Although the authors propose that targeting Rac2 might be a promising avenue for therapeutic strategies, as we enter an era of precision medicine, we need to remember that calcification remains a multifaceted disease with many different players that are involved in early through late stages of plaque development.

Disclosures
None.

References

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