Proinflammatory Vascular Calcification

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Vascular calcification occurs as part of atherosclerosis. It is caused by the deposition of basic calcium phosphate (BCP) crystals in what appears to be a highly regulated process resembling bone formation.\textsuperscript{1–4} Vascular calcification occurs in several forms,\textsuperscript{1–4} including small crystal deposits in the neointima and large calcified areas in more advanced atherosclerotic plaques, which frequently take on the appearance of ectopic bone. Media sclerosis (Mönckeberg disease) is a form of calcification associated with the elastic lamellae and is distinct from atherosclerotic calcification.\textsuperscript{1,3,4} It is common in diabetes mellitus and renal failure and is often seen in combination with atherosclerosis. Studies on the mechanism of vascular calcification have in most cases focused on similarities to bone formation\textsuperscript{1–3}; however, there are likely to be unique characteristics in the regulation of each type of calcification.\textsuperscript{4} Furthermore, the potential relationship between the different types of calcification is poorly understood.

The role of vascular calcification in atherosclerosis remains under discussion.\textsuperscript{1,4} Even though it is accepted as a marker for the atherosclerotic plaque burden in coronaries and has been associated with an increased risk for cardiovascular morbidity and mortality,\textsuperscript{1–5} its activity in the disease process has been questioned. On the one hand, it may limit plaque growth and represent a response to injury similar to fibrosis with no active contribution to the progression of atherosclerosis\textsuperscript{1–4}; on the other hand, it may actively impact the surrounding tissue and plaque stability.\textsuperscript{5}

Evidence from studies on degenerative arthritis, a field that also involves deposition of BCP crystals, suggests that BCP crystals activate synovial fibroblasts, inducing cellular proliferation and secretion of matrix metalloproteinases through a variety of signaling pathways. This activation may explain the close correlation that has been found between BCP crystals and the extent of joint destruction.\textsuperscript{6,7}

In a study published in this issue of \textit{Circulation Research}, Nadra et al\textsuperscript{a} applied the rheumatological perspective on BCP crystal deposition to the vascular wall. It has previously been recognized that inflammatory macrophages colocalized with BCP deposits in early atherosclerotic lesions\textsuperscript{9,10} but their data provide a new functional link between BCP crystals and proinflammatory macrophages. Human macrophages internalized BCP crystals into vacuoles in vitro, which triggered a proinflammatory response in the macrophages, including secretion of the inflammatory cytokines tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-1, and IL-8. The cytokines were secreted in sufficient quantities to activate cultured endothelial cells and to promote capture of flowing leukocytes under shear flow. TNF-\(\alpha\) is of particular interest in vascular calcification because it has been found to promote osteogenic differentiation and calcification of vascular cells.\textsuperscript{11,12} It may potentially lead to a positive feed-back loop, further stimulating macrophage activation and calcification.

The investigators identified protein kinase C (PKC)\(\alpha\) as a key regulator of BCP-induced TNF-\(\alpha\) release. This isoenzyme is active in the formation of phagolysosomes in macrophages after exposure to microorganisms and other stimuli.\textsuperscript{13,14} The BCP crystals caused a rapid translocation of PKC\(\alpha\) to the plasma membrane and then to vacuoles. Both the extracellular-signal-regulated kinase (ERK)1/2 and C-jun N-terminal kinase (JNK) kinase pathways were involved in the TNF-\(\alpha\) release, but only ERK1/2 was dependent on PKC activation. The PKC\(\alpha\) activation appears to be cell specific in that BCP crystal--induced activation of ERK1/2 in fibroblasts has been found to depend on PKC\(\mu\) rather than a calcium-dependent PKC.\textsuperscript{15,16} Other studies in human macrophages have suggested that secretion of pro- versus antiinflammatory cytokines depends on whether a conventional PKC (\(\alpha\) or \(\beta\)) versus the atypical PKC\(\gamma\) is activated. It is possible that a therapeutic blockade of PKC blocks proinflammatory cytokines but also causes a switch to antiinflammatory cytokine production.

Numerous studies examining atherosclerotic lesions in humans and animal models have established a central role for macrophages in disease progression.\textsuperscript{17,18} Thus, the novel results of Nadra et al place BCP crystal deposition at the very heart of atherosclerosis. Vascular calcification becomes an active participant in plaque development, possibly promoting plaque instability through its action on macrophages. The investigators point out that their study focuses on small deposits of BCP (<1 \(\mu\)m), and that their model may be most relevant to intimal calcification. However, they mention in their discussion a preliminary inverse relationship between the BCP crystal size and the macrophage activating potential. If such a relationship were confirmed, it might indicate that all calcification is not created equal and that there are certain stages of crystal deposition that may be more atherogenic. It might suggest that the areas of large calcium depositions, although bulky and a potential problem during interventional procedures,\textsuperscript{18} are overall less of a problem than small deposits that intensify vascular inflammation. Another possibility is that larger calcium deposits trigger a different response in...
monocytic cells such as differentiation along the osteoclast lineage.  

The results of Nadra et al also introduce the question of whether we are detecting the most pertinent areas of vascular calcification when referring patients for so-called coronary calcium scans. Even though a calcium scan may be sufficient to detect significant coronary artery disease, it is likely to miss potentially proinflammatory crystals, which would be under the detection limit of electron beam computed tomography. Such deposits may trigger macrophage activation and place the patient in a higher risk category for acute coronary events due to intensification of inflammation.

The finding that small crystal deposits are inflammatory may help explain why renal failure is associated with increases in cardiovascular morbidity and mortality. Disturbances in calcium and phosphate metabolism increase the propensity for crystal deposition in soft tissue and, if it occurs in the vascular wall, may enhance the inflammatory response and plaque progression.

The proinflammatory effects of small calcium deposits imply that the optimal time for intervention in the treatment of vascular calcification is before crystal deposition, similar to targeting hypercholesterolemia before significant plaque formation. The recognition that vascular calcification has similarities to degenerative arthritis suggests the possibility of developing therapies that target both diseases, and for each field to draw on the expertise of the other field.

In summary, the data of Nadra et al suggest that at least certain forms of BCP crystals play an active role in vascular inflammation and the progression of atherosclerosis. This connection has not been recognized or studied until now, and it significantly broadens our understanding of vascular calcification and likely will provide new targets for prevention and treatment.

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References

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