Platelets in Atherosclerosis

A New Role for β-Amyloid Peptide Beyond Alzheimer’s Disease

Alain Tedgui, Ziad Mallat

By the mid-1970s, Russell Ross had developed his popular “response to injury” hypothesis of atherogenesis, which postulated that the lesions of atherosclerosis arise as a result of focal injury to arterial endothelium, followed by adherence, aggregation, and release of platelets. During the release reaction, platelet-derived growth factor (PDGF) is secreted from the platelets and promotes the proliferative response of smooth muscle cells considered at that time to be the main promoter of atherosclerotic lesion formation. It has since been clearly demonstrated that smooth muscle cell proliferation is a repair process allowing plaque formation. It has since been clearly demonstrated that smooth muscle cell proliferation is a repair process allowing plaque formation. Yet, they actively participate in the severe clinical manifestations of atherosclerosis, including sudden death, myocardial infarction, and stroke, which mainly result from atherosclerotic plaque disruption leading to thrombus formation.

In this issue of Circulation Research, De Meyer et al provide novel insight into the possible role of platelets in plaque inflammation. By using immunohistochemical analysis, this group demonstrates for the first time that both amyloid precursor protein (APP) and β-amyloid peptide (Aβ) are present in advanced human carotid plaques. Up to this time, Aβ accumulation in brain tissue has been considered the hallmark of Alzheimer’s disease (AD), a progressive neurodegenerative disease that is prevalent among the elderly. The 42 amino acid form of Aβ (Aβ42) plays a pivotal role in neurotoxicity and mononuclear phagocyte activation in AD. Aβ42 stimulates the production of superoxide anions and tumor necrosis factor-α (TNF-α) by macrophages, and it has been recently shown that FPRL1, a G protein–coupled receptor, mediates the activating effect of Aβ42 on mononuclear phagocytes (monocytes and microglia).

De Meyer et al report Aβ-immunoreactive macrophages preferentially localized in the vicinity of neovascularization in advanced human atherosclerotic plaques. These Aβ-positive macrophages express both inducible nitric oxide synthase (iNOS) and COX-2 and often exhibit colocalization with platelets. De Meyer et al suggest that platelets that enter the plaque from neovessels are phagocytized, and APP contained in platelets is cleaved to form Aβ (Figure). In vitro studies using coincubation of platelets (not activated or activated with thrombin) and macrophages allow the authors to establish a link between platelet phagocytosis and macrophage activation via proteolytic processing of APP and generation of Aβ. Their findings support the hypothesis that after platelet phagocytosis by macrophages, proteolytic processing of platelet-derived APP leads to Aβ generation resulting in macrophage activation. However, recent studies have reported that APP and Aβ can be released by platelets after activation with thrombin, collagen, or arachidonic acid. The generated APP can bind to, and may be internalized by, class A scavenger receptors. Platelets that enter the atherosclerotic plaque through neovessels may therefore not necessarily be phagocytized by macrophages to release Aβ. Interaction with plaque collagen might be sufficient to induce APP and Aβ release (Figure). The observation that a rim of CD9-positive platelets often surrounds macrophages that express iNOS supports this view.

A role for platelet phagocytosis in foam cell formation was evoked by Chandler et al as early as 1961 when these authors proposed that phagocytized platelets could be a source of lipids. De Meyer et al confirm that in vitro platelet phagocytosis by J774 macrophages results in the formation of lipid-laden macrophages. They also demonstrate induction of iNOS after platelet phagocytosis in murine J774 and human THP1 macrophages primed with interferon-γ (IFN-γ). The induction of iNOS and production of nitrite by human IFN-γ-stimulated macrophages after platelet phagocytosis is particularly interesting because all previous in vitro attempts to induce iNOS in human macrophages by using various cocktails of proinflammatory cytokines have failed. However, iNOS expression in macrophages can be found in human atherosclerotic plaques.

An important issue that remains unresolved in the study presented by De Meyer et al concerns the mechanisms by which platelets are recognized and phagocytized by macrophages. In vitro experiments were done in the absence of plasma, which reasonably reflects the environment within the human atherosclerotic plaque. Under these conditions, it can be hypothesized that platelets undergo an apoptosis-like process. Brown et al have reported evidence of accelerated programmed cell death when platelets are cultured in the plasma.
Platelets entering the plaque from neovessels might undergo a death process and be phagocytosed via CD36, class A scavenger receptor (SRA), and/or phosphatidylserine receptor (PSR). They can also be activated by collagen and release APP. Intra-cellular APP is cleaved by β-secretase to form Aβ, which can activate macrophages via the G protein-coupled receptor FPRL1. Binding of “dead” platelets to PSR can induce the secretion of the antiinflammatory cytokines IL-10 and TGF-β, which might downregulate iNOS and COX-2 expression triggered by Aβ.

In summary, the important work by De Meyer et al now provides evidence that platelets might participate in plaque inflammation in addition to proinflammatory cytokines, oxidized LDL, and reactive oxygen species. The proinflammatory effect of platelets is not related to thrombus formation and involves Aβ. Up to this time, this peptide was confined to brain. The work of De Meyer et al sheds light on a novel role for Aβ in atherosclerosis.

**References**


**Key Words:** platelets ■ macrophages ■ β-amyloid peptide ■ inflammation
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