Amyloid Beta and Cardiovascular Disease
Intriguing Questions Indeed*

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Cardiovascular disease (CVD) and Alzheimer disease (AD) are 2 major causes of morbidity and mortality and represent formidable medical and societal challenges. The classical pathological signature of AD is the deposition of amyloid-rich plaques in the brain. Amyloid-beta (Abeta) is a key constituent of these plaques, and its deposition in the brain has been strongly implicated in the pathogenesis of AD. Likewise, Abeta deposition in the wall of cerebral microvessels is pathognomonic of cerebral amyloid angiopathy. To date, research into the potential role of Abeta proteins in the pathogenesis of disease has focused almost exclusively on the brain and its associated vasculature. This is despite the fact that substantial amounts of Abeta proteins are produced in the peripheral circulation and are present in platelets, as well as atherosclerotic plaques (1). This raises the question as to the role, if any, of Abeta proteins in the pathogenesis of CVD.

In this issue of the Journal, Stamatelopoulos et al. (2) reported intriguing data from retrospective cohort studies, showing that circulating levels of Abeta40 were predictive of cardiovascular mortality in patients with established coronary heart disease (CHD) and were predictive of the progression of vascular disease (2). Moreover, these associations appeared robust after adjustment for potential confounding influences on both Abeta40 levels and cardiovascular risk, such as age and renal function, and had incremental predictive value for cardiovascular mortality over and above that obtained from the assessment of conventional cardiovascular risk factors alone. They concluded that circulating levels of Abeta40 may help predict which patients with established CHD are at higher risk of cardiovascular mortality and thus may benefit from more intensive conventional CVD risk reduction strategies. They also suggested that these findings may point to novel pathways for CVD development that involve Abeta40, which may point to a novel target for CVD prevention.

Although their study is preliminary and too small to be considered definitive, their hypothesis is certainly worth closer attention. That said, it should be acknowledged that the association between circulating Abeta40 and mortality in patients with CHD could simply reflect imperfect correction for factors that elevate Abeta40 levels, such as impaired renal function, which is itself a potent risk factor for cardiovascular morbidity and mortality. In other words, the mortality associations with Abeta40 levels could simply be indicative of another factor that is influencing both cardiovascular risk and Abeta40 and that Abeta40 is not directly contributing to the CVD risk per se. An alternative view is that they have identified a heretofore unrecognized causal link between Abeta40 and the pathogenesis of CVD that would represent an important finding.

The biology of Abeta proteins is complex, and the normal physiological functions of Abeta proteins are poorly understood. It is notable, however, that Abeta proteins are highly conserved between species, suggesting an important function. It has been proposed that Abeta proteins, in both normal and pathological settings, play a role in modulating inflammatory responses and may have a role in natural antimicrobial defenses (3,4). Abeta proteins are generated from the amyloid protein precursor (APP), a trans-membrane glycoprotein.
that is sequentially processed by beta- and gamma-secretases to release Abeta proteins. These Abeta proteins are hydrophobic monomers, consisting of 39 to 42 amino acids, the most common of which are Abeta40 and Abeta42 (5). Abeta proteins circulate in the plasma and cerebrospinal fluid, Abeta40 being the most abundant. The longer form, Abeta42, is most abundant in the classic cerebral plaques of AD, whereas Abeta40 is the more abundant form in the vascular wall and in platelets. The dynamics and regulation of Abeta protein production and degradation/clearance are also poorly understood. Platelets are thought to be the major source of circulating Abeta proteins. Platelets contain both APP and Abeta40 in their alpha-granules and represent >90% of circulating APP and Abeta (6). The production of Abeta proteins is influenced by cholesterol levels and in particular the cholesterol content of cell membranes. In cell culture, increased cholesterol levels promote the production of Abeta proteins from APP, whereas decreased cholesterol levels decrease the production of Abeta (5). Statins have also been shown to reduce Abeta protein production in cultured cells by promoting a favorable shift in APP processing away from Abeta production, associated with decreased beta- and gamma-secretase-mediated APP proteolysis. The circulating level of Abeta proteins is also influenced by their clearance, and they are actively degraded by a range of proteases, including endothermin-converting enzyme, insulin-degrading enzyme, plasmin, angiotensin-converting enzyme, and especially neprilysin. This latter protease is notable because of the emergence of neprilysin inhibitors as a therapeutic option for heart failure. Finally, Abeta clearance also follows a circadian rhythm, with the greatest clearance of Abeta occurring during sleep, suggesting that plasma levels will be inversely related to sleep duration.

Beyond the circulation, Abeta proteins (predominantly Abeta40) have been identified in human atherosclerotic lesions, as well as activated and nonactivated human platelets. In a study of human atherosclerotic plaques from the aortas of elderly people, Abeta40 was 100 times more abundant than Abeta42 (1). The predominant source of Abeta40 in atherosclerotic plaques is thought to derive from the alpha-granules of platelets and/or processing of APP in the vascular wall, notably by endothelial cells or the myocytes of the arterial media. Thus, human atherosclerotic plaques in the peripheral circulation often contain APP, Abeta40, platelets, and activated macrophages (7). Macrophage activation within the atherosclerotic plaque seems to be mediated by processing of platelet-derived APP to Abeta by secretase enzymes within the macrophage (8). Activation of platelets within the plaque also leads to Abeta release. This latter finding is intriguing because the predominant Abeta protein in the platelet and the circulation is Abeta40 and the study of Stamatelopoulos et al. (2) reported an association between circulating Abeta40 levels and cardiovascular mortality in patients with an established atherosclerotic plaque burden (2). Could it be that circulating levels of Abeta40 are at least in part a marker of atherosclerotic plaque burden and/or macrophage activation within the plaque? Is Abeta40 a biomarker of plaque burden or vulnerability?

There are a number of mechanisms whereby the presence of Abeta proteins in the vascular wall in general, or more specifically the atherosclerotic plaque, could contribute to the genesis and evolution of CVD. Cerebral amyloid angiopathy is a good example whereby the deposition of Abeta proteins in the vascular wall of cerebral vessels creates a chronic inflammatory microenvironment, leading to a loss of vascular wall integrity and a propensity to microbleeds and hemorrhage. Prior studies have suggested that exposing human endothelial cells to Abeta40 in vitro induces CD40 expression and interleukin 1-beta and interferon-gamma secretion (9). Although exposing human vascular smooth muscle cells (VSMCs) to Abeta40 did not directly promote an inflammatory response, it did lead to a dedifferentiation of VSMCs from a contractile to a proinflammatory secretory phenotype and preactivated VSMCs to generate an amplified inflammatory response to cytokines (e.g., interleukin 1-beta via pathways thought to involve phosphoinositide 3-kinase and possibly nuclear factor kappaB) (10). Thus, it is possible to envision Abeta40 activation of the endothelial cell and VSMC acting in concert to initiate and amplify an inflammatory response. It is also conceivable that this mechanism could prime the plaque for an enhanced inflammatory response to infectious agents or other stresses, linking acute infection or stress to acute CVD events. Furthermore, Abeta40 has been shown to induce apoptosis of VSMCs and activate matrix metalloproteinase-2 and possibly matrix metalloproteinase-9, all of which could contribute to increased plaque instability (11). Inflammation may also be induced by Abeta binding to the receptor for advanced glycation end products, which activates the Janus kinase/signal transducer and activator of transcription pathway and nuclear factor kappaB signaling (12).

Finally, it is unlikely that Abeta proteins have been preserved through evolution to induce cell injury and more likely that their proinflammatory action is a
defense mechanism that has the potential to become maladaptive. In this regard, there is an emerging view that the normal function of Abeta proteins is as an antimicrobial peptide (AMP) (4). AMPs are a naturally occurring family of peptides with potent, broad-spectrum antibiotic activity that targets Gram-negative and Gram-positive bacteria, mycobacteria, enveloped viruses, fungi, and protozoa, which play a key role in innate immunity. AMPs are also potent immunomodulators that mediate cytokine release and adaptive immune responses (13). The physiochemical and biological properties of Abeta proteins are remarkably similar to those of other members of the AMP family of peptides. Only 1 AMP has been identified in humans, the LL-37 peptide (14), which shows remarkable similarity to Abeta in its propensity to form cytotoxic soluble oligomers. Patients with low levels of LL-37 are at increased risk for serious infections (15), and genetically modified mice that lack endogenous rodent Abeta appear to have increased susceptibility to pathogens (16). Conversely, high levels of LL-37 in patients are associated with the pathology of several presumed noninfectious diseases, which remarkably includes plaques in atherosclerosis (17). A recent study showed that Abeta possesses potent antimicrobial activity against at least 8 clinically important bacteria and may thus function in vivo as an AMP and play a role as an effector molecule of innate immunity (4). It is possible that this process becomes maladaptive in response to chronic subclinical infection, raising the specter once again of an infectious etiology for vascular dysfunction, atheroma, and plaque rupture.

In conclusion, the study of Stamatakopoulos et al. (2) highlights a potential link between Abeta and CVD mortality (2). It is an observation that requires replication but stimulates debate about the normal function of Abeta and its role, if any, in vascular disease. Is it a biomarker or mediator of chronic subclinical vascular inflammation and/or a poorly studied natural AMP defense against a hitherto unidentified chronic infectious agent implicated in the development of atheromatous disease? Intriguing questions indeed.

**REFERENCES**


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