Association of Complement Inhibitors With Connective Tissue Matrix in Atherosclerotic Lesions

To the Editor:

We read with great interest the article by Oksjoki et al.1 regarding association between complement Factor H and proteoglycans in early human coronary atherosclerotic lesions. We would like to add several comments to this recently published article.

Several studies have demonstrated the presence of terminal complement complex C5b-9 in human atherosclerotic arteries.2–4 Quantitative determination in the human aorta by ELISA showed that C5b-9 levels were highest in intimal thickening and with detectable levels in both normal and fatty streaks intima.5 Our data indicate that activation of complement starts early during the prelesional stages of the atherosclerotic process. The activation is more intense in initial stages than in advanced fibrous plaques. Similar prelesional C5b-9 deposition was found in experimental atherosclerosis.6 In contrast to these findings, Oksjoki et al.1 show that C5b-9 was immunohistochimically absent in grossly normal human coronary artery. This difference in the results might be explained by the higher sensitivity of the ELISA for C5b-9.

We have previously examined the relationship between C5b-9 and the complement inhibitor S-protein/vitronectin.7 S-protein/vitronectin prevents C5b-9 insertion in the cell membrane by binding to C5b-7. The formed SC5b-9 complex is cytolytically inactive. Using immuno-electron microscopy, S-protein/vitronectin was localized in association with elastin fibers, collagen bundles, and cell debris in the vicinity of elastin.7 Cell debris embedded in collagen matrix were S-protein/vitronectin negative. In contrast, all cell debris were positive for C5b-9 deposits. These data suggested that connective tissue matrix by associating S-protein/vitronectin play an important role in regulation of terminal complement pathway in atherosclerotic wall. Because C5b-9 deposits are not always associated with S-protein/vitronectin, the inhibition of terminal pathway activation seems to be only partially effective.

Oksjoki et al.1 extend our previous observation demonstrating an association between another complement inhibitor, factor H and a connective tissue matrix component, versican proteoglycan. In the deeper parts of the intima, they found C5b-9 deposits in the absence of factor H. Because the immunostaining does not distinguish between membrane inserted C5b-9 and SC5b-9, it is possible that some of the staining seen in the deep layers of human coronary artery may represent cytolytically inactive SC5b-9. The C5b-9 complex was also colocalized with macrophages and smooth muscle cells in the atherosclerotic arterial wall.8,9

Association of C5b-9 with cellular plasma membrane can induce mitogenesis of aortic smooth muscle cells.10 These data suggest that complement inhibitors associated with connective tissue matrix play a regulatory role for complement activation in the arterial wall. Despite the presence of inhibitors, full complement activation is achieved, indicating that complement system and C5b-9 assembly play an important role in the inflammatory pathogenesis of atherosclerosis.

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