Experimental Immunohistochemical Study on Persistent Vascular Remodeling related to Development of Arteriosclerosis or Atherosclerosis in Kawasaki Disease

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Introduction
Atherosclerotic coronary heart disease has recently emerged as a clinical issue among young individuals with a history of Kawasaki disease (KD), which is a systemic vasculitis unique to children. However, whether or not and how KD promotes atherosclerosis remains unclear. We hypothesized that, analogous to the pathogenesis of arteriosclerosis or atherosclerosis, endothelial injury and the resultant intimal thickening are induced in coronary arteries after attenuation of vasculitis.

Methods
We used a rabbit model of KD developed by Onouchi et al. and performed histopathological analysis of the coronary arteries at acute (1, 3, 5, and 7 days) and chronic (3 months) phases of the disease.

Results
In these rabbit models, a pan-arteritis with significant intimal cellular hypertrophy was histologically detected in the acute phase, and arterial intimal thickening was observed during the chronic phase. Immunohistochemical analysis of the coronary arteries revealed that the thickened intimal lesions observed during the chronic phase comprised abundant α-smooth muscle actin (α-SMA)-positive cells, most of which concomitantly expressed vascular cell adhesion molecule-1 and nuclear factor-κB. Although macrophages positive for RAM11 were barely detected, macrophage colony stimulating factor was strongly expressed in migrating smooth muscle cells in the intimal layer. In addition, the accumulation of proteoglycan as extracellular matrix was distinctly visible in the thickened intima, indicating progressive accumulation of lipids and proliferation of smooth muscle cells within the lesion.

Conclusions
These findings suggest that, in KD-associated vasculitis, the migration of α-SMA-positive cells into the thickened intima might induce continuous vascular inflammation and remodeling, which might progress to coronary arteriosclerosis or atherosclerosis.