

## Activation of an innate immune receptor, Nod1, accelerates atherogenesis in Apoe<sup>-/-</sup> mice

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Atherosclerosis is essentially a vascular inflammatory process in the presence of excess amount of lipid. We have recently reported that nucleotide-binding oligomerization domain (Nod)-1 ligands activated endothelial cells in vitro, and oral administration of a Nod1 ligand FK565 induced vascular inflammation in vivo. No studies, however, have proven the association between Nod1 and atherosclerosis in vivo.

We orally administered FK565 to Apoe knockout (Apoe<sup>-/-</sup>) mice for 4 weeks intermittently, and performed quantification of atherosclerotic lesions in aortic roots and aortas, immunohistochemical analyses and microarray-based gene expression profiling of aortic roots. FK565 administration accelerated the development of atherosclerosis in Apoe<sup>-/-</sup> mice, and the effect was exclusively dependent on Nod1 in vascular cells of non-bone marrow origin by bone marrow transplantation experiments. Immunohistochemical studies revealed the increases in the accumulation of macrophages and CD3 T cells within the plaques in aortic roots. Gene expression analyses of aortic roots demonstrated a marked up-regulation of chemokine (C-C motif) ligand 5 (Ccl5) gene during early stage of atherogenesis, and the treatment with Ccl5 antagonist significantly inhibited the acceleration of atherosclerosis in FK565-administrated Apoe<sup>-/-</sup> mice. In addition, as compared with Apoe<sup>-/-</sup> mice, Apoe and Nod1 double knockout mice showed reduced development of atherosclerotic lesions from early stage as well as their delayed progression towards more advanced stages, and a significant reduction in Ccl5 mRNA levels at 9 weeks of age.

We show that Nod1 signaling pathway in vascular cells of non-bone marrow origin contributes to the development and progression of atherosclerosis.

### Biography

Toshiro Hara MD Kyushu University 1977, Ph.D. Kyushu University 1983, 1996-present Professor and Chairman, Department of Pediatrics, Kyushu University, 2009-2012 Principal Investigator, Japanese Society for the Promotion of Science (JSPS), 2011-present Honorary Member of American Pediatric Society.

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