LOX-1, an OLR1 gene product, has been found to be the receptor for oxidized low density lipoprotein (LDL) to induce endothelial dysfunction. Animal studies suggested that LOX-1 promotes atherosclerosis, aggravates myocardial infarction, and enhances restenosis. Although researchers have mainly focused on coronary artery disease, reports on ischemic stroke are gradually accumulating. In parallel, more human epidemiological and clinical studies are being reported. Here we describe ligands and the receptor LOX-1 separately to clarify the current status.

**Lipoprotein Ligands**

As LOX-1 recognizes various modified LDLs, we developed a novel assay system for modified LDL based on LOX-1-binding activity. In the assay, modified LDL concentration is expressed as a biological activity to bind to LOX-1, named LOX-1 ligand containing apoB (LAB) activity. With this assay, a cohort study was performed on ~2300 healthy people with 11-year follow-up period. As a result, the top quartile of serum LAB activity, compared with the bottom quartile, had two times the risk in cardiovascular disease and three times in ischemic stroke after adjustment of confounding factors.

Shen et al. undertook another approach to measure highly electronegative fraction of LDL, named L5, which exerts its action via LOX-1 on endothelial cells and platelets. They found that circulating L5 concentration was elevated in ischemic stroke patients. Furthermore, they also found that L5 administration aggravated ischemic stroke, and anti-LOX-1 antibody suppressed the effects of L5 in a mouse model of middle cerebral artery occlusion.

**LOX-1 and Soluble LOX-1**

From the point of the expression manner, similar to C-reactive protein and interleukin 6, LOX-1 belongs to acute phase reactant and immediate early gene. The expression level quickly increases ~100 times upon stimuli. Soluble LOX-1 (sLOX-1), a proteolytically cleaved form of LOX-1, goes into circulation after being liberated from the plasma membrane. Reflecting the expression manner of LOX-1, sLOX-1 clearly increases on acute coronary syndrome and is useful for the diagnosis of acute coronary syndrome as well as troponin T and C-reactive protein. Recently, Yokota et al. reported that circulating sLOX-1 concentration increases in stroke patients, although the increase was not sufficient for use in diagnosis. It is yet to be determined if the increased expression of LOX-1/sLOX-1 would affect the pathogenesis and/or prognosis of stroke.

**Genetics**

Different from these sLOX-1 analyses at the onset of cardiovascular events, the genetic analyses of OLR1 performed so far were related to basal expression and function. Recently, the genetic analysis of OLR1 for ischemic stroke began to be reported from East Asian groups.

In this issue of J Atheroscler Thromb, Guo et al. reported the association between LOX-1 polymorphism and atherosclerotic cerebral infarction. The authors performed a case-control study with 526 patients with atherosclerotic cerebral infarction and
increases in response to stimuli. The effects of OLR1 polymorphisms, mostly to basal expression level and function, might not reach significant level compared with the magnitude of OLR1 expression induction level. Considering Guo et al.’s report, we would say, however, that it would be a hope for East Asian researchers to find some genetic effects of OLR1 in humans because of the relatively smaller variation in genetic background and higher incidence rate of cerebral infarction in the East Asian people.

Conflict of Interest
None.

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| Table. LOX-1 in ischemic stroke |
|--------------------------------|
| Animal study                  |
| • Upregulation of LOX-1 expression more than 10 times in a lesion in a rat model of transient ischemic stroke. |
| • Aggravation of cerebral infarction by L5 and suppression of the effects by OLR1 gene-knockout or anti-LOX-1 antibody administration in a mouse model. |
| Biomarker study in human      |
| • High LOX-1 ligand activity as a risk factor for ischemic stroke. |
| • Elevation of L5 concentration in ischemic stroke patients. |
| • Elevation of sLOX-1 in stroke patients |
| Human Genetics                |
| • Association of minor allele of rs1050283 or rs11053646 with ischemic stroke |
| • Association of minor allele of rs1050283 with concurrent stenosis in extracranial and intracranial vessels |

640 healthy controls, analyzing rs1050283 SNP in the 3’-untranslated region of LOX-1, OLR1. They found that rs1050283 T allele was associated with higher expression level of LOX-1, higher serum concentration of sLOX-1, and they also found increased risk of atherosclerotic cerebral infarction in a Chinese population. Preceding this study, Man et al. also reported case-control study with 191 Han Chinese stroke patients and 167 healthy control patients in Hong Kong. They found that TT allele in OLR1 rs1050283 was associated with concurrent stenosis in extra and intracranial blood vessels, which indicates a higher risk of stroke. On the other hand, Liu et al. reported the association of G501C polymorphism (rs11053646) of OLR1, which causes amino acid change K167N, with cerebral infarction in northern Chinese Han population, on analyzing 386 patients with cerebral infarction and 386 healthy controls. They, however, could not find significant association between rs1050283 polymorphism and cerebral infarction. In addition, Au et al. performed meta-analysis of the influence of OLR1 rs11053646 on ischemic stroke including 1898 cases and 2119 controls and showed that C allele of OLR1 rs11053646 (G501C) increased the susceptibility risk of ischemic stroke.

In case of coronary artery disease (CAD), the 3’UTR SNP (rs1050283) of OLR1 was reported to be strongly associated with CAD. Knowles et al. reported that rs3736232 and rs1050286 are in near perfect linkage disequilibrium and that in a study on 1809 cases of CAD and 1734 controls, minor allele of rs3736232 was weakly associated with increased risk of CAD, whereas they could not replicate the effect of SNP in a large population cohort (~13000 individuals) in the ARI study. Considering this example, we should be cautious about jumping to conclusions from Guo et al.’s study.

In summary, LOX-1 is a kind of acute phase reactant so that the expression level of OLR1 sharply
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