Crystal Structure of Human C-type Lectin-like Oxidized LDL Receptor 1(LOX-1)

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C-type lectin-like oxidized low-density lipoprotein (LDL) receptor 1, LOX-1, is the major receptor for oxidized LDL (OxLDL) in endothelial cells. LOX-1 plays a critical role in endothelial dysfunction that leads to atherosclerosis. Lox-1 is also expressed in macrophages and smooth muscle cells; these cells progress atherogenesis in sub-endothelial space through interaction with OxLDL in the intima. Thus, LOX-1 is recognized as a therapeutically important target receptor for the pathogenesis of vascular disorder, especially atherosclerosis. To gain the insight into the binding surface structure of LOX-1 to OxLDL, we have determined the crystal structure of the ligand-binding CTLD domain of LOX-1, with a short stalk region connecting the domain to the membrane-spanning region, as a homodimer linked by an inter-chain disulfide bond. . In vivo assays using LOX-1 mutants revealed that the “basic spine”, consisting of linearly aligned arginine residues spanning over the dimer surface, is responsible for ligand binding. Single amino acid substitution in the dimer interface caused the severe reduction of LOX-1 binding activity, suggesting that the correct dimmer arrangement is crucial for the binding to OxLDL. Based on the LDL model structure, the possible binding modes of LOX-1 to OxLDL are proposed.

Keywords: atherosclerosis, membrane receptors, three-dimensional protein structure