

## **Upregulation of Lectin-like Oxidized LDL Receptor by Advanced Glycation End Products in Endothelial Cells**

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**Objective:** Lectin-like oxidized LDL receptor-1 (LOX-1) is a class E oxidized LDL specific scavenger receptor and LOX-1 expression is inducible. LOX-1 has been implicated in atherogenesis and LOX-1 expression is increased in diabetes. It has been suggested that advanced glycation end products (AGE) may contribute to the induction of LOX-1 in diabetes and we have investigated the signaling pathway(s) involved.

**Methods:** Human aortic endothelial cells were treated with AGE-BSA or BSA in the presence or absence of either antibody of receptor for advanced glycation end products (anti-RAGE), mammalian target of rapamycin (mTOR) inhibitor rapamycin, NF- $\kappa$ B inhibitor (BAY11-7085) or phosphoinositide 3-kinases (PI3K) inhibitor (LY294002). Western blot analyses on LOX-1, phosphorylation status of phosphoinositide-dependent kinase 1 (p-PDK1) and p-mTOR protein were performed.

**Results:** AGE-BSA induced LOX-1 expression in a dose-dependent manner and pretreatment with anti-RAGE antibody resulted in a significant reduction in LOX-1 expression. The effect of AGE-BSA on LOX-1 expression was not blocked by BAY11-7085 but by rapamycin. Adding rapamycin reduced protein expressions of p-mTOR by 41% ( $p < 0.05$ ), and LOX-1 by 61.5% ( $p < 0.01$ ), suggesting involvement of mTOR signaling. To investigate whether AGE/RAGE interaction triggered mTOR signaling via activation of PI3K, cells were pretreated with LY294002. This resulted in a reduction of p-PDK1 (downstream effector molecule of PI3K) by 26.7% ( $p < 0.01$ ), p-mTOR by 62.5% ( $p < 0.01$ ) and LOX-1 by 72.7% ( $p < 0.01$ ).

**Conclusion:** AGE binds to its cellular receptor RAGE, activates PI3K/PDK1/mTOR signaling pathway and thereby induces LOX-1 expression. The induction of LOX-1 by AGE may contribute to the increased atherosclerotic risk in diabetes.

