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Liver X receptor α enhances the transcriptional activity of HIF-1α

Tae Young Na, Jun Seung Lee, Young-Gun Yoo, and Mi-Ock Lee

College of Pharmacy and Bio-MAX Institute, Seoul National University, Seoul, Korea

The Liver X receptor α (LXRα) is an orphan nuclear receptor that functions as a regulator of the cholesterol homeostasis in macrophages. The inflammatory responses are associated with the significant changes of cholesterol metabolism, which leads to the local hypoxia results in the induction of the proteins that promote blood flow and inflammation. Here we investigated the possible cross-talk between LXRα and hypoxia-inducible factor (HIF-1), a key regulator of hypoxic responses. We first observed that expression of LXRα was induced time-dependently under hypoxic conditions in a macrophage cell line. When the HIF-1α expression was repressed by transfection of siRNA duplexes targeting HIF-1α, the hypoxia-induced LXRα expression was eliminated. Similarly, transfection of As- LXRα inhibited the HIF-1α induction under hypoxia, suggesting an existence of a positive regulatory loop of induction of HIF-1α/LXRα. We also observed that activation of LXR α by either overexpression or TO901317, a specific ligand of LXRα, enhanced the expression and the transcriptional activity of HIF-1α under normoxia. Taken together, our results demonstrate a novel function of LXRα in the activation of HIF-1α and suggest a potential cross-talk between hypoxia and lipid metabolism that is mediated by LXRα.

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Lutein inhibits inflammatory gene expression in lipopolysaccharide-stimulated macrophages by suppressing IkB kinase-dependent NF-kB activation

Ji-Hee Kim, Gwangsoo Lee, Hee-Jun Na, Seon-Jin Lee, Kwon-Soo Ha, Young-Guen Kwon*, Young-Myeong Kim

Vascular System Research Center and Department of Molecular and Cellular Biochemistry, School of Medicine, Kangwon National University, Chunchon, Kangwon-Do 200-701, Korea; * Department of Biochemistry, College of Science, Yonsei University, Seoul 120

Lutein has no provitamin A activity but it displays biological activities that have attracted great attention in relation to human health. Lutein has shown anti-oxidant and anti-inflammatory activities; however, its molecular mechanism has not been clearly elucidated. We examined in vitro regulatory function of lutein on production of nitric oxide(NO) and prostaglandin E_2(PGE_2) as well as expression of inducible NO synthase(iNOS), cyclooxygenase-2(COX-2), tumor necrosis factor-α(TNF-α), and interleukin-1β(IL-1β). Lutein inhibited the expression and production of these pro-inflammatory mediators and cytokines in both lipopolysaccharide(LPS)-stimulated RAW264.7 cells and primary macrophages. Moreover lutein suppressed NF-β B activation and iNOS promoter activity in RAW264.7 cells stimulated with LPS. Furthermore, lutein blocked nuclear translocaion of NF-kB p65 subunit, which correlated with its inhibitory effect on IkBα phosphorylation and degradation. Lutein blocked the intracellular accumulation of reactive oxygen species(ROS) in RAW264.7 cells stimulated with LPS. These results suggest that lutein inhibits the production of inflammatory mediators by blocking NF-kB activation and suppression of IKK activity.

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Lysophosphatidylserine stimulates L2071 mouse fibroblast chemotactic migration via pertussis toxin-sensitive trimeric G proteins

Kyoung Sun Park, Ha-Young Lee, Mi-Kyoung Kim, Eun Ha Shin, Seong Ho Jo, Sang Doo Kim, and Yoe-Sik Bae

Department of Biochemistry, College of Medicine, Dong-A University, Busan, 602-714, Korea

Lysophosphatidylserine (LPS) may be generated after phosphatidylserine-specific phospholipase A2 activation. We observed that LPS stimulates an intracellular calcium increase in L2071 mouse fibroblast cells via G-protein coupled receptor-mediated phospholipase C activation. LPS-induced calcium mobilization was not inhibited by the lysophosphatidic acid receptor antagonist, VPC 32183, thus indicating that LPS binds to a receptor other than lysophosphatidic acid receptors. Stimulation of L2071 cells with LPS elicited the activation of two types of mitogen-activated protein kinase, namely, ERK and p38 kinase, which were inhibited by pertussis toxin, suggesting the role of pertussis toxin-sensitive G-proteins in the process. LPS stimulated L2071 cell chemotactic migration, which was completely inhibited by pertussis toxin, indicating the involvement of pertussis toxin-sensitive Gi protein(s). LPS-induced chemotaxis was also dramatically inhibited by LY294002 and by PD98059. This study demonstrates that LPS stimulates at least two different signaling cascades, one of which involves a pertussis toxin-insensitive but phospholipase C-dependent intracellular calcium increase, and the other, a pertussis toxin-sensitive chemotactic migration mediated by phosphoinositide 3-kinase and ERK.

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Lysyl tRNA synthetase inhibits shear stress–dependent activation of signaling molecules in endothelial cells

Hey-sun Meang, Sung-hoon Kim and Heon-yong Park

[1]Department of Molecular Biology, Dankook University, San 8, Hanmam-dong, Yongsan-ku, Seoul 140-714, Korea, [2]National Creative Research Initiatives, Center for ARS Network, College of Pharmacy, Seoul National University, Seoul, Korea

Fluid shear stress (SS), the mechanical force generated by blood flow, is a major determinant of vascular homeostasis and an anti-atherogenic factor. To investigate an SS-sensing receptors. We tested whether endothelial cells respond differentially to shear stress by pre-incubation with lysyl–tRNA synthetase (KRS), a binding molecule for endothelial cells. First, KRS was shown to inhibit the shear stress–induced ERK activity, like tryptophanyl tRNA synthetase, whereas p43, an associated factor of aminoacyl tRNA synthetases (ARSs), had no effect. Moreover, KRS inhibited protein kinase B (Akt) and endothelial NO synthase (eNOS) in a dose dependent manner. Interestingly, pre-treatment of sialic acid recovered the inhibitory effect of KRS. Previously, arterial sialic acid (Sia), a part of glycoproteins, was known to act as an anti-atherogenic factor. When endothelial cells were pre-treated with neuraminidase, a shear stress-mediated responses were disappered. Together, KRS inhibits shear–dependent activation of signaling molecules in endothelial cells via sialic acid–containing receptors.