Development of transrepression-selective liver X receptor (LXR) ligands

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[BACKGROUND] Liver X receptors (LXRs) are members of the nuclear receptor superfamily with two subtypes, LXR alpha and LXR beta. Oxysterols are physiological LXR agonists, and induce transcription of target genes through a mechanism called transactivation, resulting in prevention of cholesterol accumulation but in induction of hypertriglyceridemia. On the other hands, LXR activation also suppresses expression of genes, such as interleukin-6 (Il-6) and Il-1beta, a mechanism called transrepression. LXR ligands possessing transrepression activity might be anti-inflammatory drugs, but their transactivation activity would cause the potential adverse effect hypertriglyceridemia. We have developed transrepression-selective LXR ligands. Recently, LXR activation has been suggested as a potential therapeutic target in the treatment of cardiovascular disease via endothelial regeneration. We determined whether the transrepression-selective LXR ligands promote the regenerative activity.

[METHODS] LXR agonistic and antagonistic activities were measured with a mammalian two-hybrid luciferase reporter gene assay using GAL4-human LXR chimeric receptor. Transrepression activity was measured with ELISA assessing repressing effect on LPS-induced IL-6 expression. Gene expression and direct LXR interaction were analyzed with reverse transcription-PCR and TR-FRET, respectively. In addition, we investigated the effect of the transrepression-selective LXR ligands on differentiation of human induced pluripotent stem cells-derived endodermal progenitor cells (hEPC) into CDX2-positive intestinal epithelial cells.

[RESULTS] We found some styrylphenyl phthalimides having LXR transrepression activity, and the structural modification led to a series of compounds possessing potent transrepression without transactivation in reporter gene assays. In gene expression analysis, the compounds didn’t induce expression of the LXR target gene ABCA1 or SREBP-1c in cells. TR-FRET binding assay indicated that they bind directly to LXR. Interestingly, they could promote intestinal differentiation of hEPC, although the underlying mechanism remains unknown.

[CONCLUSIONS] We successfully developed transrepression-selective LXR ligands that have anti-inflammatory activity and can promote intestinal regeneration. These compounds may be promising drugs for the treatment of inflammatory bowel diseases.