S08-3 Identification of the intrinsic ligand for BLT2 receptor

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Leukotriene B4 (LTB4) is an arachidonate-derived lipid mediator and known as a potent attractant for phagocytes. We cloned two GPCRs for LTB4, BLT1 (high-affinity) and BLT2 (low-affinity), and are studying the *in vivo* roles of LTB4 receptors by generating and analyzing KO mice of BLT1 and 2. As very high concentration of LTB4 is required for the activation of BLT2, we speculated the presence of other ligand(s) for BLT2 than LTB4. We identified BLT2-specific agonistic activity in the acetone-soluble lipid fraction of rat small intestine, partially purified the agonistic lipid, and finally determined the structure using HPLC/MS/MS analysis. This BLT2 ligand was 12-HHT (12(S)-hydroxyheptadeca-5Z, 8E, 10E-trienoic acid), which had been known as a by-product of thromboxane biosynthesis without reported biological activities. Synthetic 12-HHT binds and activates BLT2, but not BLT1, leading to the calcium mobilization, adenylyl cyclase inhibition and chemotaxis at the lower concentration than LTB4. Bone marrow-derived mast cells (BMMCs) migrated to 12-HHT in a Boyden chamber assay, but BMMCs of BLT2-KO mice did not migrate to 12-HHT, showing that 12-HHT acts on intrinsically expressed BLT2. Any biological activity of 12-HHT as a BLT2 ligand will be revealed in the future.

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