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Autotaxin-Lpar3 Signaling Regulates Kupffer's Vesicle Formation and Left-Right Asymmetry in Zebrafish

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Abstract

Left-right (L-R) pattering is essential for proper organ morphogenesis and function. Calcium fluxes in dorsal forerunner cells (DFCs) are known to regulate the formation of Kupffer's vesicle, a central organ for establishing L-R asymmetry in zebrafish. Here we identify the lipid mediator lysophosphatidic acid (LPA) as a regulator of L-R asymmetry in zebrafish embryos. LPA is produced by autotaxin (ATX), a secreted lysophospholipase D, and triggers various cellular responses through activation of specific G protein-coupled receptors (LPAR1-6). Knockdown of Atx (*atx*) or LPA receptor 3 (*lpar3*) by morpholino oligonucleotides perturbed asymmetric gene expression in lateral plate mesoderm and disrupted organ L-R asymmetries, while overexpression of *lpar3* partially rescued those defects in both *atx* and *lpar3* morphants. Similar defects were observed in embryos treated with ATX inhibitor HA130 and LPAR1-3 inhibitor Ki16425. Knockdown of either *atx* or *lpar3* impaired calcium fluxes in DFCs during mid-epiboly stage and compromised DFC cohesive migration, KV formation and ciliogenesis. Application of LPA to DFCs rescued the calcium signal and laterality defects in *atx* morphants. This LPA-dependent L-R asymmetry is mediated via Wnt signaling, as shown by the accumulation of β-catenin in nuclei at the dorsal side of both *atx* and *lpar3* morphants. Our results suggest a major role for the Atx-Lpar3 signaling axis in regulating KV formation, ciliogenesis and L-R asymmetry via a Wnt-dependent pathway.

Keywords: autotaxin, lysophosphatidic acid, calcium, Left-right asymmetry.

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