Differential Mechanisms of LPA1 and LPA4 Receptors in Regulating Cell Migration

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Lysophosphatidic acid (LPA) is a bioactive lipid which can bind to six LPA receptors (LPA1-6) on the cell membrane and regulate various cell activities. Previous studies have shown that LPA1 and LPA4 have antagonistic effects in regulating cell migration. However, the mechanism of this functional difference has not been fully investigated. In this study, the effects of LPA1 and LPA4 on cell migration were detected by cell scratch assay. Moreover, RosettaFold, AutoDock Vina and PUP-IT proximity labeling technology were used to explore the mechanisms in the differential roles of LPA1 and LPA4 in regulating cell migration from three aspects: receptor structure, LPA binding sites, and downstream signaling. It was found that cell migration was promoted by LPA1 and suppressed by LPA4. While LPA 1 and LPA 4 have similar structure, their LPA binding sites are different. Four amino acids in LPA 1 (Lys39, Tyr34, Arg124, Lys294) and three amino acids in LPA4 (Lys112, Thr296, Arg124) were shown to be essential in extracellular LPA binding, which may lead to different conformational changes of the receptors. Three possible downstream proteins (LMO7, MUSK, IMPDH2) were identified in the LPA1 signaling pathway promoting cell migration, and two possible downstream proteins (SFRP4 and NAA16) were identified in the LPA4 signaling pathway inhibiting cell migration. This study provided insights into the differences between LPA1 and LPA4 in the critical amino acids of the LPA binding sites and their downstream signaling pathways, which underlie their antagonistic functions.

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