Lysophosphatidic acid stimulates the proliferation and motility of malignant pleural mesothelioma cells through lysophosphatidic acid receptors, LPA_1 and LPA_2.

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Lysophosphatidic acid (LPA) is one of the simplest natural phospholipids. This phospholipid is recognized as an extracellular potent lipid mediator with diverse effects on various cells. Although LPA is shown to stimulate proliferation and motility via LPA receptors, LPA_1 and LPA_2, in several cancer cell lines, the role of LPA and LPA receptors for malignant pleural mesothelioma (MPM) has been unknown. MPM is an aggressive malignancy with a poor prognosis. Therefore, the development of novel effective therapies is needed urgently. In this study, we investigated the effect of LPA on the proliferation and motility of MPM cells. We found that all 12 cell lines and four clinical samples of MPM expressed LPA_1, and some of them expressed LPA_2, LPA_3, LPA_4 and LPA_5. LPA stimulated the proliferation and motility of MPM cells in a dose-dependent manner. Moreover, LPA-induced proliferation was inhibited by Ki16425, an inhibitor of LPA_1, and small interfering RNA against LPA_1, but not LPA_2. Interestingly, LPA-induced motility was inhibited by small interfering RNA against LPA_2, but not LPA_1, unlike a number of previous reports. These results indicate that LPA is a critical factor on proliferation though LPA_1, and on motility though LPA_2 in MPM cells. Therefore, LPA and LPA receptors, LPA_2 as well as LPA_1, represent potential therapeutic targets for patients with MPM.

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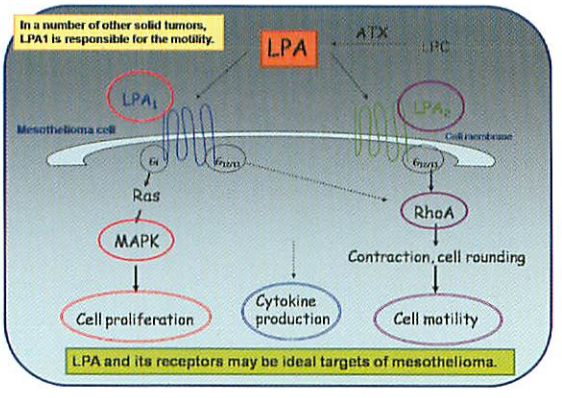

Figure A Signal transduction pathway of LPA-induced metastasis of MPM cells. LPA stimulated the proliferation via LPA_1 and facilitated the motility via LPA_2 in MPM cells.