Lysophosphatidic Acid Stimulates Lymphangiogenesis in Human Lymphatic Endothelial Cells

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Abstract
Lymphangiogenesis is the process by which new lymphatic vessels sprout and grow from existing vessels whether under developmental, immunological, or cancerous conditions. Proper lymphatic vessel formation is important in working alongside normal angiogenesis in order to help regulate the body's tissue fluid as well as in immunosurveillance. Various factors regulate lymphangiogenesis such as members of the vascular endothelial growth factor family (VEGF). Another factor that has recently been identified to play a role in lymphangiogenesis is the bio-active phospholipid lysophosphatidic acid (LPA) however the molecular mechanism by which LPA regulates lymphangiogenesis has not been well characterized. In this study, human lymphatic endothelial cells (HLECs) were treated with LPA in the presence or absence of VEGF and the late stage effects of lymphangiogenesis were examined. Preliminary evidence suggests that VEGF and LPA induces proliferation in HLECs; however there is no increase in this stimulation when both factors are added together. A Matrigel tube formation assay revealed that LPA induces an increase in cellular extensions as well as in tubule length as compared to the control.

Introduction
Lymphatic vessel formation, lymphangiogenesis, is known to occur during normal development and during tissue stress such as inflammation and wound healing. In an inflammatory response, there is an excess collection of fluid near the wound. Lymphatic vessels grow into the damaged area to relieve the fluid and to allow more leukocytes or white blood cells to enter the affected area [1]. Thus, lymph vessel formation is vital for regulating the body's tissue fluid and recruiting leukocytes as part of the body's immune response. One important mediator of the inflammatory response is the bio-active phospholipid phosphatidic acid (LPA). LPA belongs to a family of lipid growth factors that is present in low concentrations in serum and biological fluids but is found in higher concentrations at sites of inflammation and tumor growth [2]. LPA has been shown to modulate inflammatory responses through the stimulation of chemokines, cytokines, and cytoskeletal rearrangement and migration of target cells. LPA evokes its biological effects through binding to G-protein coupled receptors. There are five known receptors for LPA, LPA1-5 [3]. It has previously been found that binding to LPA1 induces the production of pro-angiogenic factors such as VEGF, Interleukin-8 (IL-8) and Interleukin-6 (IL-6) [4].

In this study, I will look at the effect of LPA on lymphangiogenesis using human lymphatic endothelial cells (HLECs). Using an in vitro assay, I measured the ability of HLECs to proliferate in the presence of LPA in the presence or absence of vascular endothelial growth factor (VEGF).

LPA Structure

Figure 1. Diagram of the structure of lysophosphatidic acid

Literature Cited

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Conclusions
• Preliminary evidence suggests LPA stimulates proliferation in HLECs.
• No significant co-stimulatory response detected with both LPA and VEGF-A.
• Results from Matrigel lymphangiogenic tube formation assay suggest that at two hours, compared to control, 1 µM LPA exposure resulted in an increase in both cell extension number and length while 10 µM LPA induced more extensions but no difference between extension length was found.
• At 6 hours, there was a significant difference in tube length between 1 µM LPA and the control with a p value of 0.0003.