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Role of Vascular Endothelial Growth Factors on Ethanol-Induced Lymphatic Endothelial Cell Hyperpermeability

- In recent studies we found that treatment with ethanol increases lymphatic endothelial cell (LEC) permeability. The increase in LEC permeability was not associated with disruption of LEC tight junctions, adherens junctions or changes in JNK or ERK ½ expression. Several other factors could be contributing to the ethanol-induced LEC hyperpermeability, including vascular endothelial growth factors (VEGFs). Binding of vascular endothelial growth factor C (VEGF-C) and vascular endothelial growth factor D (VEGF-D) to vascular endothelial growth factor receptor 3 (VEGFR-3) are regulators of LEC differentiation and proliferation. In addition, evidence has shown that lymphatic dysfunction was associated with VEGFR3 inactivation. Therefore, we hypothesize that ethanol induces LEC hyperpermeability via disruption of VEGFs. We will used an *in vitro* model of rat lymphatic endothelial cells. Alcohol-supplemented medium was added added at concentrations of 25 mM and 50 mM to confluent cells for 30 min and 7.5 h and RNA was isolated from the cells. Control cells were time matched but didn't receive ethanol treatment. We measured gene expression of PROX-1 and VEGFs C and D and VEGFR3. Ethanol significantly decrease gene expression of PROX-1, VEGF-D, and VEGFR-3 at 30 min of exposure. At 7.5h of ethanol exposure VEGFR-3 expression was still decreased. These data suggest that PROX-1, VEGF-D, and VEGFR-3 might be playing a role in alcohol-induced LEC permeability. Future studies using specific inhibitors of VEGF-D and VEGFR-3 on LEC permeability will elucidate the role of these molecules on ethanol-induced LEC hyperpermeability.