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Function and mechanism of estrogen in regulating vascular endothelial barrier

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Context: The risk of cardiovascular disease (CVD) is lower in premenopausal women than postmenopausal women or men of the same age, suggesting vascular benefits of estrogen. Studies have shown estrogen may play a role in vascular endothelial barrier. However, its cellular functions and molecular mechanisms remain largely unknown.
Objective: To investigate the role of estrogen in regulating vascular endothelial barrier and its underlying mechanisms in vitro.
Methods: Human umbilical vein endothelial cells (HUVECs) were isolated from vein of umbilical cord. Permeability across the endothelial cell monolayer was measured by transwell permeability assay. Endothelial cell-cell junctions and endothelial integrity were assessed by immunofluorescence staining. The images were collected on an inverted confocal microscope. Protein expression and phosphorylation were evaluated by Western Blot.
Patients: None.
Interventions: None.
Main Outcome Measure: Permeability across the endothelial cell monolayer, Endothelial intercellular junctions, protein expression and phosphorylation.
Results: HUVECs were isolated and identified. Treatment of thrombin, a known factor in destroying endothelial barrier, dramatically increased the permeability of HUVECs monolayer, while estrogen pretreatment significantly inhibited the increasement of endothelial permeability ($P < 0.05$). In the presence of estrogen, HUVECs partly resisted the impairment of cell-cell junctions and the disruption of endothelial integrity induced by thrombin treatment. Mechanistically, estrogen enhanced the phosphorylation of SHP2 and ERK in HUVECs, indicating activation of SHP2-ERK signaling. SHP2, a protein tyrosine phosphatase, is highly expressed in vascular endothelia and has been shown to be a critical mediator in regulating barrier function. Knockdown of Shp2 in HUVECs significantly increased barrier permeability ($P < 0.05$).
Conclusions: Estrogen regulated the permeability of HUVECs monolayer and maintained endothelial integrity, suggesting a possible protective role in vascular endothelial barrier. The mechanism may involve SHP2 protein tyrosine phosphatase and ERK signaling. This study added knowledge to the functions and mechanisms of estrogen in CVD.

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