Small Chain Fatty Acid Phenylbutyric Acid Alleviated Inflammation-Induced Endoplasmic Reticulum Stress in Endothelial Cells

ABSTRACT

Endothelial cells (EC) have dynamic properties and high plasticity in response to microenvironmental change. A proinflammatory cytokine such as tumor necrotizing factor-α (TNF-α) can induce EC phenotype shift to osteoinduction properties by releasing a potent osteogenic cytokine, namely bone morphogenetic protein 2 (BMP2). Normally BMP2 acts as an osteoblast stimulating factor in bone and cartilage tissue. BMP2 activation in vascular tissue will invite osteoblast recruitment and mineralization and generated pathological vascular stiffening and calcification. Recently, endoplasmic reticulum stress (ERS) has been emerging as a new target therapy in many vascular diseases such as vascular stiffening and calcification. Some short-chain fatty acid like 4-phenyl butyric acid has been shown had anti-ERS properties. However, the role of 4-phenyl butyric acid in BMP2 inhibition in endothelial cells is still poorly understood. Hence, we investigated the role of 4-phenyl butyric acid in inflammation-induced BMP2 expression in human vein derived endothelial cells. Endothelial cells obtained from a baby born umbilical vein were cultured and pre-treated with TNF-α (5 ng/ml) as inflammation precondition. Multiple doses of 4-phenyl butyrate acid (4-PBA) 1 nM/mL, 2 nM /mL, and 3 nM /m were used as ERS inhibitors. The expression of two ERS biomarkers, glucose-related protein-8 (GRP78) and activating transcription factor-6 (ATF6), were measured. Statistical analysis was done using one-way ANOVA and Kruskal Wallis tests, and $P<0.01$ considered as significant. 4-PBA decrease luminal BMP2 at dose one nM/L, GRP78 at dose 1 nM/L, and translocated ATF6 expression at dose 1 nM/L in endothelial culture dose-dependently. Short-chain fatty acid 4-phenylbutyrate acid decreases luminal ERS marker GRP78 and translocated ATF6 expression in endothelial culture. ERS has a role in osteoinductive phenotype shifting in inflammation endothelial cells, which was the novelty of this research. Further research needs to elucidate ERS inhibition in in vivo experiment

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