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파브리병에서 혈관내피세포 중간엽 세포변이

이화여자대학교 의학전문대학원 신장내과

유민아 · 장양희 · 류은선 · 최진옥 · 정성철 · 류동열 · 최규복 · 강덕희

Globotriaosylceramide (Gb3)-induced Endothelial-to-Mesenchymal Transition as a Novel Mechanism of vascular damage in Fabry Disease

Mina Yu, Yang-Hee Jang, Eun-Sun Ryu, Jin-Ok Choi
Sung-Chul Jung, Dong-Ryeol Ryu, Ku-Bok Choi, Duk-Hee Kang

Nephrology, Ewha Womans University School of Medicine, Seoul

Fabry disease is a lysosomal storage disease which is characterized by excessive accumulation of globotriaosylceramide (Gb3) in major organs such as the heart and kidney. Defective lysosomal alpha-galactosidase A (Gla) is responsible for excessive Gb3 accumulation, and vascular endothelium is one of the sensitive cells to the effects of Gb3 accumulation. Although endothelial dysfunction is known to be associated with Fabry disease, it is not certain whether it plays any roles in the development of organ damage in Fabry disease or whether Gb3 per se is related to endothelial dysfunction. Recent data suggest that endothelial-to-mesenchymal transition (endo-MT), which is characterized by a loss of endothelial cell markers and an acquisition of mesenchymal cell markers, is a potential mechanism of endothelial dysfunction. We investigated whether Fabry kidney showed an evidence of endo-MT and whether Gb3 induced endo-MT in cultured human endothelial cells. Immunostaining with RECA or CD-31 in the kidney of animal model of Fabry disease, Gla deficient mice, showed a decreased microvascular endothelial staining both in glomerular and peritubular capillaries compared to wild type mice with an appearance of α-SMA (+) endothelial cells. However, a loss of glomerular and peritubular endothelial cells was not demonstrated by electron microscopy, suggesting that not a loss of endothelial cells but a phenotypic transition is present in Fabry mice. Treatment of Fabry mice with of recombinant adeno-associated virus (rAAV) vector encoding alpha-Gal A cDNA (rAAV2/8-hAGA) resulted in the clearance of accumulated Gb3 in kidney with concomitant elevation of alpha-Gal A enzyme activity. rAAV2/8-hAGA therapy also ameliorated endo-MT of glomerular and peritubular capillary endothelial cells. Stimulation of HUVEC with Gb3 (0.1-10 μM) down-regulated the expression of CD31 and VE-cadherin with an up-regulation of α-SMA from 48 hours in a dose- and time-dependent manner. Gb3 also induced a decrease in nitric oxide production from HUVEC. These finding suggest that Gb3-induced endo-MT is one of the mechanisms of endothelial dysfunction and nephropathy in Fabry disease.

Key Words: 파브리병, 혈관내피세포 중간엽 세포변이
Fabry Disease, Endothelial-to-Mesenchymal Transition