S-E2

파브리병의 혈관손상기전의 새로운 기전으로서의 Globotriaosylceramide로 유도되는 내피-중간엽 세포변이

이화여자대학교 의과대학 신장내과[1], 생화학교실[2]

유민아[1], 장양희[1], 김미진[1], 류은선[1], 최학선[1], 최진옥[2], 정성철[2], 강덕희[1]

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

Mina Yu[1], Yang-Hee Jang[1], Mi-Jin Kim[1], Eun-Sun Ryu[1], Hak-Sun Choi[1]
Jin-Ok Choi[2], Sung-Cheol Jung[2], Duk-Hee Kang[1]

Ewha Womans University School of Medicine, Nephrology[1], Biochemistry[2]

The lysosomal storage disorder Fabry disease is characterized by excessive globotriaosylceramide (Gb3) accumulation in major organs such as 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 known 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 the 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. Gb3 inhibited cell proliferation and induced LDH release at a dose-dependent manner from a concentration of 50 μM, but no effect with Gb4. Gb3 (10 μM) induced a morphological transformation of HUVEC from elongated oval appearance to spindle shaped scattered fibroblast-like cells at 48hrs. Stimulation of HUVEC with Gb3 (0.1-10 μM) down-regulated the expression of CD31 with an up-regulation of α-SMA from 48 hours in a dose- and time-dependent manner. These finding suggest that Gb3-induced endo-MT may be one of the mechanisms of endothelial dysfunction and nephropathy in Fabry disease.

Key Words: 파브리병, 내피-중간엽 세포변이
Fabry disease, Endothelila-to-mesenchymal transition