Bartter 증후군의 새로운 치료 전략: 무의미 돌연변이에 대한 translational read-through 유도

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Translational Read-through Induction of a Nonsense Mutation in the CLCNKB Gene: A New Therapeutic Strategy of Bartter Syndrome

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Bartter syndrome (BS) is clinically classified into antenatal/neonatal (aBS) and classic BS (cBS), as well as five subtypes based on the underlying mutant genes; SLC12A1 (BS I), KCNJ1 (BS II), CLCNKB (BS III), BSND (BS IV), and CASR (BS V). As a nationwide multicenter study, we analyzed the clinico-genetic features of 26 Korean children with BS and tried translational read-through induction of p.W610X, a common nonsense mutation in the CLCNKB gene, using G418, an aminoglycoside.

The clinical diagnosis was aBS in 8 cases (31%), cBS in 15 cases (58%), and mixed Bartter-Gitelman phenotype in three cases (12%). Genetic study revealed that 3 patients with aBS had BS 1, BS II, and BS IV, respectively, and all of the remaining 23 patients had BS III. Among the CLCNKB gene mutations, p.W610X (25 of 46 alleles, 54%) and total/partial deletion of the gene (10 of 46 alleles, 22%) were two most common mutations. There was no genotype-phenotype correlation in patients with BS III. For translational read-through induction of the p.W610X mutation, MDCK cells were transiently transfected with the mutant or wild-type CLCNKB cDNA. After treating G418, expression of the full-length ClC-Kb protein, a product of the CLCNKB gene, in the basolateral membranes was detected in the cells transfected with the mutant gene.

In conclusion, the genotypes of the Korean patients with BS are unique; (1) more than a half of the patients with aBS and all of the patients with cBS or mixed Bartter-Gitelman phenotype had CLCNKB mutations, and (2) p.W610X is a common mutation in CLCNKB. A therapeutic strategy based on translational read-through induction by aminoglycosides in patients with the pW610X mutation in CLCNKB is worth trying.

Key Words: Bartter 증후군, CLCNKB 유전자, 돌연변이
Bartter syndrome, CLCNKB gene, Nonsense mutation