

Epigenetic modulation of intestinal NHE3 expression by DNA methylation

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NHE3 plays an important role in Intestinal Na⁺ absorption and its down-regulation has been implicated in infectious and Inflammatory Bowel Diseases (IBD)-associated Diarrhea. Recent evidence also indicates a novel role of epigenetic mechanisms, such as DNA methylation in the pathophysiology of IBD. Whether changes in DNA methylation are involved in modulating Intestinal NHE3 gene expression is not known. Caco-2 and HUTU-80 cells were used as models of Human Intestinal Epithelial Cells (IECs). Normal C57/BL6, wild type or GADD45b KO mice were used as in vivo models. NHE3 gene DNA methylation levels were assessed by methyl-CpG binding domain-based capture assays. In vitro methylation of NHE3 promoter construct (p-1509/+127) cloned into a CpG free luciferase vector decreased the promoter activity in Caco2 cells. DNA methyltransferase (DNMT) inhibitor, 5-azacytidine (10 mM, 24h) caused a significant decrease in DNA methylation of the NHE3 gene and concomitantly increased NHE3 mRNA and protein expression in Caco2 cells. Similarly, 5-aza treatment increased NHE3 mRNA levels in HUTU-80 cells. 5-aza treatment for 3 weeks

(10 mg/kg body wt., i.p., 3x/wk) also resulted in an increase in NHE3 expression in the mouse ileum and colon. siRNA knock down of GADD45b (protein involved in DNA demethylation) in Caco2 cells decreased NHE3 mRNA expression. Furthermore, there was a significant decrease in NHE3 mRNA and protein expression in the ileum & colon of GADD45b KO mice. Our studies for the first time demonstrate that NHE3 gene expression is regulated by an epigenetic mechanism involving DNA methylation. These findings suggest that changes in DNA methylation may be involved in the inhibition of NHE3 Gene Expression in Intestinal Inflammation contributing to the pathophysiology of IBD-associated Diarrhea.

Speaker Biography

Seema Saksena, PhD is a Research Associate professor under the section of Digestive Diseases and Nutrition at University of Illinois at Chicago, USA. She did her PhD at Dr. R. M. L. University in India, her postdoc at Central Drug Res Institute, India. She has published more than 30 articles and abstracts.

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