

Title: DNA dysmethylation is assoicated with visceral myopathies and other gastrointestinal diseases

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BACKGROUND & AIMS: DNA methylation is a key epigenetic modification that can regulate gene expression. Genomic CpG hypomethylation is commonly found in many gastrointestinal (GI) diseases. Dysregulated gene expression in GI smooth muscle cells in the GI tract (GI-SMC) can lead to motility disorders. However, the consequences of genomic DNA hypomethylation in GI-SMC are still elusive. **METHODS**: Utilizing Cre-lox models, we have generated SMC-restricted DNA methyltransferase1 (*Dnmt1*) knockout (KO) mice and analyzed the effects of *Dnmt1* deficiency. **RESULTS**: *Dnmt1*-KO pups are born smaller than their wild type littermates, have shortened GI tracts, lose complete peristaltic movement due to loss of the tunica muscularis in their small intestine which causes massive intestinal dilation, and death by post-natal day 21. Within smooth muscle tissue, significant DNA demethylation occurs across the genome at promoters, introns and exons. Additionally, there is a marked loss of differentiated SMC markers (Srf, Myh11, miR-133, miR-143/145), an increase in pro-apoptotic markers (Nr4a1, Gadd45g) and an accumulation of coated vesicles within SMC. Additionally, we observed consistent regulation patterns of enzymes involved in DNA methylation and demthlyation between both KO mice and diseased human GI tissue (Crohn's disease, diverticulitis, and colon/anal cancers). These data demonstrate that DNA hypomethylation in embryonic SMC via congenital *Dnmt1* deficiency causes massive dysregulation of gene expression and is lethal to GI-SMC. **CONCLUSIONS**: These results suggest a necessary role of *Dnmt1* in the embryonic primary gastrulation process of SMC development and human GI diseases.

Biography

Seungil Ro, obtained his Ph.D. in Cell and Molecular Biology from the University of Nevada, Reno, USA in 2002, where he has been Associate Professor (tenured) since 2015 in the Department of Physiology and Cell Biology in School of Medicine. His research interest includes gastrointestinal smooth muscle engineering, epigenetic remodeling, abdominal adhesions, and GI diseases (inflammatory bowel disease, gastroparesis, diverticulitis, and colon cancer). His research is currently supported by four NIH grants including two R01s. He has one US patent, has published 42 papers, and has been serving as a regular member of NIH grant review panel since 2015, and an editorial board member of *PLoS ONE* since 2013. He has trained/mentored 35 international/domestic undergraduate students, and 5 graduate students, and 5 postdoctoral fellows.

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