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Ion transport defects in Microvillus Inclusion Disease (MVID)

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Abstract: MVID is a rare congenital disease that results in severe secretory diarrhea (SD) and death in newborns. B rush border (BB) defects, villus atrophy and microvillus inclusions (MVIs) in enterocytes are associated with the diarrrhea. Loss of function mutations in the actin motor Myosin Vb (Myo5b) is responsible for most cases of MVID. How loss of Myo5b results in secretory diarrhea is unknown. The study used Myo5b loss of function human MVID intestine, polarized intestinal cell models of secretory crypt (T84) and villus resembling (C2BBe) enterocytes lacking Myo5b in conjunction with immunofluorescence confocal gSTED imaging, immunohistochemical staining, TEM, shRNA silencing, immunoblots, and electrophysiologic approaches to examine the distribution, expression and function of the major BB ion transporters (Na+ (NHE3), Cl- (CFTR) and Cl-/HCO3- (SLC26A3, DRA), that control intestinal fluid transport. NHE3 and DRA localization and function were markedly reduced on the BBM of human MVID enterocytes and Myo5bKD C2BBe cells, while CFTR localization was preserved. Forskolin-stimulated CFTR ion transport in Myo5bKD T84 cells resembled that of control.

Conclusions: Preservation of functional CFTR in immature enterocytes, reduced functional expression of NHE3 and DRA contribute to Cl- and Na+ stool loss in MVID diarrhea.

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