

Ion Transport Defects in Microvillus Inclusion Disease(MVID)

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Microvillus Inclusion Disease (MVID)

- First described 1978, Davidson.
- Rare Congenital Diarrhea (autosomal recessive) intractable life-threatening **Secretory Diarrhea** in infancy- high stool Cl⁻, Na⁺
- Diarrhea worse than cholera
- Early form-severe, late form-milder
- Patients die unless supported by TPN/bowel transplant
- Clusters in certain populations: Navajo Indians, Middle East
- Consanguinity

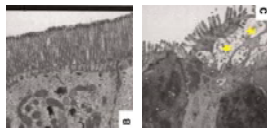
MVID features

1. Villous atrophy



H&E

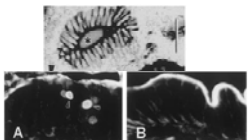
2. General disorganization of Brush Borders, MI



EM

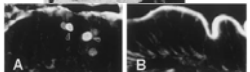
W.I. Al-Daraji et al, 2010

3. Microvillus Inclusions MI in mature enterocytes **



MI

4. Reduced apical actin, Positive Actin

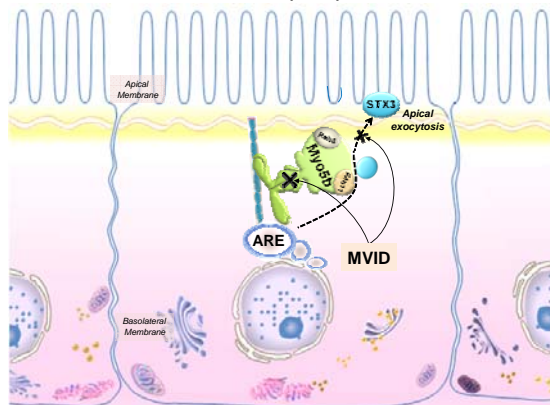


IFL

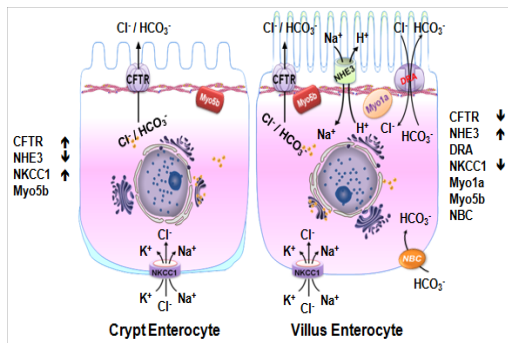
Ameen, Traffic 2000, 1: 76-83

Why does MVID lead to secretory diarrhea?

LOSS OF FUNCTION MUTATIONS IN MYOSIN VB(MYO5B) AND SYNTAXIN 3 (STX3) LEAD TO MVID



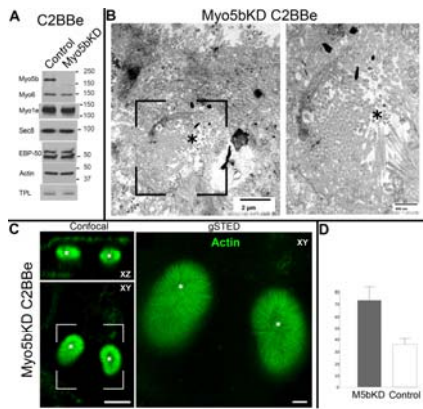
Intestinal ion transporters critical for Cl⁻/HCO₃⁻, Na⁺ transport and secretory diarrhea



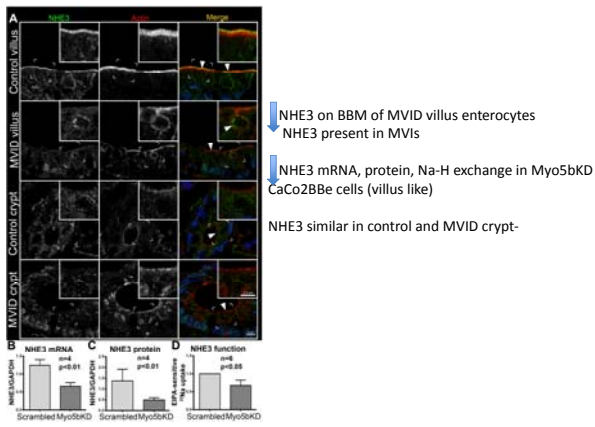
MODELS TO STUDY ION TRANSPORT DEFECTS IN MVID

- INTESTINAL CELLS- CACO2BBE- resemble villus
- T84 cells- resemble crypt
- shRNA silencing Myo5b expression
- Human MVID intestine- Myo5b loss of function
- CFTR- major BB transporter responsible for SD
- NHE3- Na absorption in villus, SD
- DRA – Cl absorption in villus

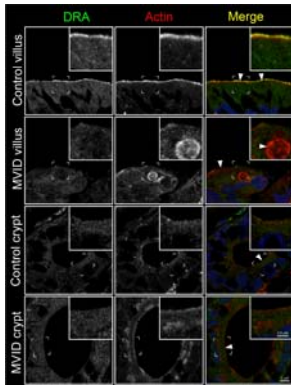
Myo5bKD CACO2BBE – recapitulates MVID villus enterocytes



NHE3 expression and function in MVID

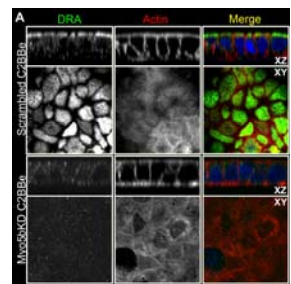


DRA (SLC28A3) localization in human MVID

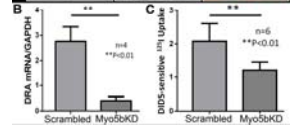


↓ DRA on the BBM of MVID villus enterocytes
 No DRA in MVIs
 DRA similar in control and MVID crypt

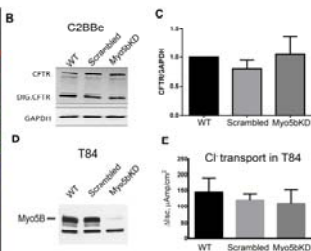
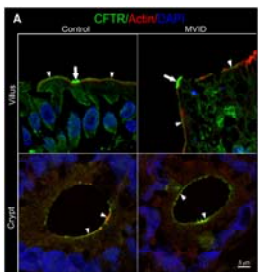
DRA (SLC26A3) localization, expression and function in Myo5bKD CaCo2BBE cells



↓ BBM DRA in Myo5bKD CaCo2BBE cells
 Resembles redistribution in villus MVID
 ↓ DRA mRNA, and Cl/HCO₃⁻ exchange activity
 In Myo5bKD CaCo2BBE cells



CFTR localization, expression and ion transport are like WT in Myo5b loss of function MVID



Conclusions

Combined BB ion transport defects: lead to secretory diarrhea in MVID:

- unopposed CFTR-mediated Cl⁻/HCO₃⁻ secretion
- Reduced NHE3 mediated Na⁺ absorption
- Reduced DRA mediated Cl⁻ absorption
- Explains secretory diarrhea and stool profile of human MVID

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