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
2. General disorganization of Brush Borders, MI
3. Microvillus Inclusions MI in mature enterocytes **
4. Reduced apical actin, Positive Actin

W. J. Al-Daraji et al, 2010
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**

- Apical exocytosis
- Loss of function
- Mutations in MYO5B and STX3 lead to MVID

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

- CFTR
- NHE3
- NBC
- SLC4A7 (NHE3)
- SLC26A6 (CFTR)

SECRETORY DIARRHEA:

- Intestinal ion transporters
- Cl-/HCO3- and Na+ transport
- 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 MVID vesicles
- 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

- CFTR localization, expression and ion transport are like WT in 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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