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EDITORIAL

New Mouse Models for Microvillus Inclusion Disease (MVID): Where Do the Inclusions Come From and Are They Cause or Consequence?

In 1978, Davidson et al[1] first described a chronic, watery, life-threatening diarrhea typically beginning in the first hours to days of life. The disease was classified as a congenital enteropathy marked by villus atrophy and severe diarrhea with malabsorption. Patients' intestinal epithelia showed a dramatic loss of brush-border microvilli. Electron microscopic examination of jejunal biopsy specimens showed that some cells had microvilli trapped within electron-dense vacuoles. Over time, this disease has been referred to as Davidson disease,[1] congenital microvillus atrophy,[2] and microvillus inclusion disease (MVID). Cutz et al[3] introduced the latter name in 1989, thereby setting the diagnostic standard and already providing an early hypothesis on the origin of microvillus inclusions. At this stage, however, it was not clear if the microvillus inclusions were a cause or consequence of this severe loss of epithelial polarity; a classic chicken or egg problem.

In 2008, mutations in *MYO5B* were identified as causal for MVID.[4] With the identification of mutations in a second causative gene, *STX3*,[5] molecular and genetic analyses gained pace to unravel the pathophysiology of MVID and the specific functions of the motor protein Myo5B and the SNARE syntaxin 3 in polarized epithelial cells.[6] Previously, 2 mouse models for *MYO5B* deletion had been generated to study the disease at an organism level.[7,8]

In the present issue of *Cellular and Molecular Gastroenterology and Hepatology*, Weis et al[9] provide an additional 3 elegant *MYO5B* models that are used to both complement previous data and advance our understanding of MVID pathophysiology. The authors generated a germline mutation, a targeted and inducible intestinal MYO5B knockout and crossed the C57BL/6 knockouts onto the outbreed CD1 strain, thereby providing a very relevant disease model for future therapeutic studies that is, in genetic terms, close to the human setting.

The data help to unravel the complexity of MVID, especially in the context of the earlier-mentioned chicken or egg paradigm. The first conclusion emphasizes that microvillus inclusions are not a cause but rather a consequence of MYO5B loss. The data clearly show that the prevalence of microvillus inclusions depends on when one deletes the *MYO5B* gene in mice. Although germline deletion and constitutive targeted deletion did induce microvillus inclusions in duodenum, induction of *MYO5B* loss in adult mice did not result in significant numbers of inclusions but caused many other hallmarks of the disease. This indicates that lack of *MYO5*B in the neonatal period has a critical impact for disease development and Weis et al[9] postulated an apical macropinocytotic route being responsible for this. This contrasts with other groups who have hypothesized that the microvillous inclusions may represent autophagocytosed/endocytosed apical plasma membrane or de novo–formed, ectopic apical domains.[8]

Liver disease in MVID patients previously has been noted as being quite variable. Interestingly, Weis et al[9] did not observe any significant impact on the liver in the germline knockouts, implying that liver involvement in MVID may be a secondary effect of the extended parenteral nutrition that is required to sustain life in patients. This also suggests that the villus atrophy phenotype observed in MVID patients in their second or third month of life (when diagnosis usually is confirmed by biopsy) could reflect a combination of changes resulting from the genetic mutation as well as extended bowel rest. Notably, the diarrheal phenotype in the mice was most prominent in the duodenum and less pronounced in the ileum already, possibly making MVID diarrhea amenable to treatment using strategies that exclude the duodenum and promote ileal adaptation. Therefore, the results of these studies also suggest that it may be worthwhile to reconsider therapeutic use of total parenteral nutrition in MVID patients in favor of some enteral feeding along with parenteral nutrition.

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Conflicts of interest
The author discloses no conflicts.

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