CFTR and pH\textsubscript{i} regulation

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TO THE EDITOR: Using enteroids grown from crypts obtained from cystic fibrosis transmembrane receptor (CFTR) transgenic mice, Walker et al. (8) measured intracellular pH (pH\textsubscript{i}) regulation using a standard fluorescent dye-loading methodology. Based on results, the authors concluded that crypts originating in CFTR mice had elevated resting pH\textsubscript{i} and resistance to acidification. The authors stated that one possible consequence of this altered pH\textsubscript{i} regulation is increased cellular proliferation, which they stated could “provide a platform for neoplasia.”

Although CFTR mutation is unquestionably associated with neoplasia, in particular of the digestive organs, which would support the authors’ hypothesis, CFTR mutation is notably not associated with tumors in CFTR-expressing, bicarbonate-secreting epithelia that are present in the female reproductive tract and in the lung (6). Others have attributed tumor suppressor activity to CFTR independent of its transport function (4, 7).

We suggest that the authors overlooked evidence suggesting an alternative consequence of defective CFTR function, based on the paradoxical observation that the CF intestine is less prone to be the target of acid-related ulceration, despite an increased luminal acid load attributed to defective gastric, biliary, pancreatic, and intestinal bicarbonate secretion (1–3).

In 2004, we reported that duodenal enterocytes with defective CFTR had both altered pH\textsubscript{i} regulation and resistance to intracellular acidification, as measured in the intact mucosa of anesthetized transgenic mice (3). Our data directly supported the hypothesis that this alteration of pH\textsubscript{i} regulation protected the villous epithelium from injury in response to supernormal concentrations of luminal HCl that are present due to impairment of gastro-biliary-pancreatic HCO\textsubscript{3}\textsuperscript{-} secretion in CF (2).

Since CFTR and other membrane proteins implicated in HCO\textsubscript{3}\textsuperscript{-} secretion are expressed in the villus as well as in the crypt (5), this mechanism for defense against peptic ulcers is available to the multiple cell type in the intestinal epithelium.

We would propose that this other consequence of altered pH\textsubscript{i} regulation in the gastrointestinal tract of organisms bearing a mutant CFTR allele is also of physiological significance.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Y.A. and M.H.M. edited and revised manuscript; J.D.K. drafted manuscript.

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