Absence of ABCG2-mediated mucosal detoxification in patients with active inflammatory bowel disease is due to impeded protein folding

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In patients with active IBD the reduced expression of xenobiotic transporter hampers normal protection of the intestinal epithelium from toxic luminal compounds. Proper protein folding of ATP-binding cassette transporter proteins such as ABCG2 is crucial for their membrane localisation and function. Inflammation is associated with increased protein misfolding leading to activation of endoplasmic reticulum (ER) stress pathways.

The expression of ABCG2 and the unfolded protein response (ER-stress) marker GRP78, were studied by immunohistochemistry in colon biopsies from healthy individuals (n=9), and patients with inactive (n=67), or active (n=55) IBD, ischemic colitis (n=10), or infectious colitis (n=14). In addition, tissue-specimens throughout the small bowel from healthy individuals (n=27), and from patients with inactive (n=9) or active (n=25) Crohn’s disease were stained for ABCG2 and GRP78. The effects of ER-stress on ABCG2 expression and function were studied using live-imaging of ABCG2 expressing cells.

In all biopsies from patients with active inflammation, irrespective of the underlying disease the reduced epithelial ABCG2 expression was associated with increased GRP78 expression. Inflammatory mediators, like nitric oxide, activate the unfolded protein response (ER-stress) resulting in a reduction in membrane localisation and transport activity of ABCG2.

A novel mechanism by which patients with active intestinal inflammation are less protected against xenobiotics is described. Likely due to impeded protein folding mechanisms ABCG2 is reduced in expression and function.