Defensins and Efflux Transporters Meet Their Fate in 2008: No Major Role in the Pathogenesis of Inflammatory Bowel Disease

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In their paper, Heike Gutmann [1] and her colleagues from Basel, Switzerland, nicely tell the story of the rise and fall of a suspected candidate in inflammatory bowel disease (IBD) pathogenesis by demonstrating that the efflux transporters BCRP (breast cancer resistance protein) and P-gp (P-glycoprotein) play no major role in the pathogenesis of ulcerative colitis (UC).

Among other organs important for uptake and elimination of toxic substances, the intestine expresses BCRP and P-gp in the apical membrane of the enterocytes [2–6]. Previous genetic studies have reported that the P-gp and BCRP production is down-regulated in patients with active UC [7–10] and data indicated that their genetic locus is associated with a susceptibility for UC [11, 12]. However, previous studies did not differentiate between the transporter expression in inflamed or unaffected mucosa and did not take into account whether the UC patients took anti-inflammatory medication. Therefore, Gutmann et al. [1] evaluated transporter expression in both unaffected and inflamed mucosa of patients with active UC, in drug-naïve and treated patients with UC and compared the results to transporter expression in healthy subjects. They confirmed that P-gp and BCRP production is significantly reduced in the inflamed mucosa of treated and untreated patients with active UC, but they found that unaffected mucosa of UC patients showed no difference to healed mucosa of UC patients in remission and to mucosa of healthy controls. They concluded that the reason for a reduced protein production is very likely the inflammatory process per se.

Although not having received the same level of attention, efflux transporters now share their fate with the α-defensins: a major role in the pathogenesis of IBD has been ruled out. In a recent publication in Gut, Lisa Simms [13] and her Australian colleagues had taken the α-defensin story apart in a similar examination of a large series of more than 100 patients and controls with Crohn’s disease. They showed that surface epithelial cells loss as a consequence of tissue damage by inflammation seems to be the main reason for the reduced protein expression of α-defensins in patients with Crohn’s disease. Gutmann and Simms have taught us that IBDs are more than an efflux transporter or defensin deficiency syndrome.
References


13 Simms LA, Doecke JD, Walsh MD, Huang N, Fowler EV, Radford-Smith GL: Reduced α-defensin expression is associated with inflammation and not NOD2 mutation status in ileal Crohn’s disease: Gut 2008;57:903–910.