commentary

Scap and the intestinal epithelial stem cell niche: new insights from lipid biology[1]

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SCAP is required for proteolytic cleavage and activation of sterol regulatory element-binding proteins (SREBPs). Once activated, SREBPs translocate to the nucleus to initiate transcription of genes required for fatty acid and sterol synthesis. Liver specific *Scap* deletion protects mice from fatty liver and carbohydrate-induced hypertriglyceridemia (1). As such, SCAP inhibition is a potential therapeutic target for disorders linked to hyperlipidemia and hepatic steatosis. Both statins and ezetimibe increase the abundance of nuclear SREBP and provoke a compensatory increase in intestinal cholesterol synthesis. The requirement of SCAP for SREBP activation suggests that targeted inhibition could potentially also augment the efficacy of statins and ezetimibe. In this issue of the *Journal of Lipid Research*, McFarlane et al. (2) examine the role of Scap in the mouse intestinal epithelium and provide new insights into the biology of the epithelial stem cell niche.

The single layer of epithelial cells lining the mammalian gut mediate nutrient absorption and form a critical physical and immunological barrier between the host and its external environment. Perturbation of normal epithelial function occurs in a variety of disease states including enteric infection and the chronic inflammatory bowel diseases. Clinical signs of these enteropathies include diarrhea, weight loss, and systemic illness. Until recently, a lack of adequate scientific tools hindered study of normal intestinal epithelial cell physiology. In recent years, more powerful tools have enabled directed investigation of gut epithelial cell function in vivo and in vitro.

In vivo studies of the epithelium are facilitated by mouse models with tissue-specific gene knockdown using the Cre-Lox system (3). Adding an on-switch for the Cre recombinase (e.g., tamoxifen) enhances this technique by enabling the study of embryonically lethal genes and expanding the capacity for examining the temporal nature of genotype-phenotype interactions.

More recently, identification of the requisite factors for sustained ex vivo culture of primary intestinal epithelial cells (organoids) has transformed in vitro study of the intestinal epithelium (4). This technique overcomes biases inherent to colon cancer cell lines and enables reductionist studies on epithelial cells from genetically unique mice or humans (5). McFarlane et al. use both organoids and the Cre-Lox system to elegantly define a critical role for Scap in mouse small intestinal epithelial cell viability. In doing so, their findings illuminate the potential for gastrointestinal toxicities that might occur with SCAP inhibition in the intestine.

The investigators first demonstrate that Scap activity is critical to maintaining intestinal epithelial integrity in vivo. Tamoxifen-induced, intestine-specific deletion of *Scap* (*Scap-IKO*) induced a rapid decrease in small intestinal and colonic Scap mRNA (90% at 2.5 days) with a corresponding reduction in nuclear SREBP levels. At this point, mice exhibited clinical signs of enteropathy, which was confirmed on histology. By day 4, *Scap-IKO* mice were moribund with histology revealing epithelial collapse and widespread epithelial necrosis.

Although epithelial Scap mRNA was drastically reduced in this in vivo model, changes in the downstream targets of SREBPs were less profound. Small intestinal sterol synthesis was decreased by 37% and 54%, respectively, in the proximal and distal small bowel and not significantly reduced in the colon. Fatty acid synthesis was reduced only in the distal small bowel whereas total cholesterol content stayed the same in both the colon and throughout the small bowel. Still, mice demonstrated signs of enteropathy. Based on this and prior findings, the authors hypothesized that Scap activity was essential to provide the high levels of epithelial lipid synthesis necessary for epithelial cell proliferation. As exogenous sterols and fat could not adequately rescue the in vivo phenotype, the investigators next turned to organoid culture for mechanistic investigation and to confirm their hypothesis.

In mouse derived organoids, Cre activation rapidly reduced Scap levels and led to collapse of organoid viability

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by day 3. This effect was prevented by adding cholesterol plus the unsaturated fatty acid oleate (but neither alone), indicating that Scap was necessary for epithelial crypt cell proliferation. Whether other fatty acids, varying by saturation or chain length, might similarly synergize with cholesterol to maintain organoid viability remains to be determined.

Overall the findings of this study are convincing and have significant implications. Though a pharmacologic approach was not used in this study, these results should certainly temper enthusiasm for the clinical development of SCAP inhibitors that that do not exclusively target hepatic SCAP. Evaluation of small molecule inhibitors along this pathway should prove interesting in studies focused on the epithelium. Betulin, for example, is a small molecule inhibitor of SERBP processing and a naturally occurring pentacyclic terpene found in birch bark. Male C57Bl/6 mice treated with betulin by oral gavage exhibited improved insulin resistance and ameliorated diet-induced obesity (6). Importantly, there was no evidence of intestinal toxicity in botulin-treated mice. In view of the striking organoid phenotype observed in the current study, this approach will be a valuable tool for further high-throughput investigations interrogating the interaction between lipids and intestinal epithelial cell viability.

This study also raises important fundamental questions surrounding the role of lipid biology in the intestinal epithelial stem cell niche. What epithelial cell types drive the architectural collapse observed in small intestine of *Scap-IKO* mice (e.g., Paneth cells, resident or actively cycling stem cells)? This knowledge may have relevance to human inflammatory bowel diseases as variants of the autophagy protein ATG16L1 are linked in Crohn's disease to abnormal Paneth cell function as well as enhanced expression of genes related to lipid metabolism (7). Furthermore, because colitis was less apparent than enteritis in the Vil-Scap knockout mice, what is the effect of this pathway on the colon epithelial stem cell niche? Are human intestinal epithelial cells similarly dependent on SCAP and SREBP? Fortunately, new advances in the field of intestinal organoid and epithelial stem cell culture provide the technical capacity (5) that should hasten finding answers to the important questions this study raises.

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