Desmosomal Cadherins Desmoglein-2 or Desmocollin-2 Regulate Intestinal Epithelial Barrier Function and Mucosal Repair

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The intestinal epithelial barrier plays a pivotal role in controlling mucosal homeostasis. In a number of pathological states such as inflammatory bowel disease, epithelial damage with disruption of the mucosal barrier results in a compromised intestinal mucosal homeostasis. To avoid chronic mucosal damage, efficient wound repair is critical in re-establishing epithelial barrier properties and homeostasis. Epithelial barrier properties are achieved by intercellular junction proteins in the apical junctional complex and desmosomes. Intestinal epithelial cells express desmosomal cadherins, desmoglein 2 (Dsg2) and desmocollin 2 (Dsc2). To analyze contribution of these cadherins in controlling epithelial adhesion and homeostasis we generated mice with inducible intestinal epithelial specific (VillinCre-ER\textsuperscript{T2}) deletion of Dsg2 or Dsc2. Inducible downregulation of Dsg2 or Dsc2 resulted in compromised epithelial barrier function as assessed by paracellular FITC dextran flux using an intestinal loop model. Additionally, perturbation of these cadherins increased susceptibility to dextran sodium sulfate induced acute colitis.

In addition to controlling epithelial barrier function, intercellular junction proteins have been reported to regulate signaling events involved in mediating repair. We therefore determined if desmosomal cadherins control intestinal mucosal repair. Knock-down of either Dsg2 or Dsc2 delayed colonic mucosal wound repair in a murine biopsy induced colonic injury model. Since epithelial wound closure is mediated by collective migration of cells which coordinates forward movement of the epithelial sheet to cover denuded surfaces, we analyzed adhesive and migratory properties of in vitro model intestinal epithelial cells lacking Dsg2 or Dsc2. These studies revealed that down regulation of Dsg2 or Dsc2 decreased cohesiveness of cells and affected adhesion to the matrix, thereby suggesting an important role of Dsg2 and Dsc2 in controlling adhesion and homeostatic properties of intestinal epithelial cells.