A Biomaterial Strategy for Treatment of Ulcerative Colitis

Timothy J. Keane[1-2], Shahab Shaffiey[1], David Hackam[1], Deborah Nagle[4], Stephen F. Badylak[1-3]
[1]McGowan Institute for Regenerative Medicine, [2]Department of Bioengineering, [3]Department of Surgery, University of Pittsburgh, Pittsburgh PA, [4]Beth Israel Deaconess Medical Center, Boston MA.

Statement of Purpose: Ulcerative colitis (UC) is a chronic disease with recurring symptoms and significant morbidity. The disease affects over 500,000 individuals in the United States, and the current therapy paradigm aims only to treat symptoms and induce remission rather than provide a cure [1]. The definitive treatment for UC is surgical removal of the affected tissue with associated colostomy. Surgical methods are invasive, associated with high morbidity, and negatively affect quality of life. A minimally invasive and curative regenerative medicine approach to UC would represent a disruptive technology that could change the standard of care.

The objective of the present pilot study was to determine the potential of a biomaterial-based strategy for restoration of normal colonic mucosa in patients with UC. The bioscaffold consists of xenogeneic extracellular matrix (ECM) and provides constructive cues for functional tissue remodeling. ECM scaffolds have been used to repair or remodel tissues throughout the body, including tissues in the gastrointestinal tract [2]. Results of the study indicate ECM treatment has the potential to restore normal colonic mucosa after aggressive and circumferential mucosal resection, a procedure, which without intervention would uniformly result in severe stricture.

Methods: Six healthy dogs were randomly assigned to two groups: ECM-treated (n=4) and mucosectomy only control (n=2). Following transanal full circumferential colonic mucosal resection (4 cm in length), the ECM-treated animals had a multilaminate tubular ECM placed at the site of resection. One control animal had 4 cm resection while the other had 2 cm resection to determine if the defect was critically sized (i.e., would result in stricture without treatment). To track temporal remodeling response, the surgical site was monitored using routine colonoscopy and biopsy specimen collection. Animals were sacrificed at 2 weeks (n=1), 8 weeks (n=1), and 12 weeks (n=2) for this proof-of-principle study. Control animals were sacrificed at 6 and 10 weeks. Tissue explants were stained with hematoxylin and eosin (H&E), Alcian blue, and immunolabeled for proliferating cell nuclear antigen (PCNA).

Results: Both control animals developed severe stricture and showed no signs of new mucosal coverage over the defect site. The 4 cm resection control animal developed substantial stricture that was refractory to manual dilation. The stricture resulted in fistula formation and the animal was sacrificed at 6 weeks post-surgery due to associated complications. While stricture formation occurred uniformly following circumferential mucosectomy, placement of an ECM scaffold mitigated stricture formation and led to site-appropriate tissue remodeling. The remodeling outcome in ECM treated animals at 2 weeks post-surgery was characterized by granulation tissue. However, by 8 weeks the site of mucosal resection showed columnar epithelium arranged in complex crypt structures that were nearly indistinguishable from native tissue. The entire length of the scaffold was replaced by normal mucosa with the exception of the distal anastomosis, where there was incomplete epithelialization followed by a transitional region of epithelialization to normal appearing mucosa proximally. PCNA staining showed the presence of proliferating cells in appropriate

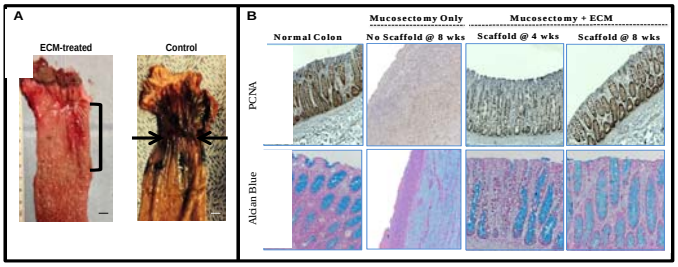

Figure 1. Gross (A) and histologic (B) images of ECM-treated vs. control colonic mucosectomy

anatomic location following mucosectomy and ECM treatment. Alcian blue staining indicated that site-appropriate goblet cells were present in the remodeled colonic mucosa (Fig 1). None of the ECM-treated animals developed clinically apparent stricture over the period of the study.

Conclusions: Surgical placement of a tubular SIS-ECM scaffold following mucosectomy has the potential to facilitate constructive remodeling of colonic mucosa in a canine model. Whether such a strategy (i.e., placement of an ECM scaffold over a long-segment mucosectomy) would similarly promote colonic mucosal healing in the presence of an inflammatory environment for treatment of ulcerative colitis remains unknown. However, long-segment mucosectomy is currently not likely to be readily translatable as a clinical strategy. A preferred approach to UC treatment would avoid mucosectomy but still mitigate colitis by diminishing inflammation and remodeling of colonic mucosa. Preliminary studies in a chemically induced rodent model of UC suggest topical (i.e., enema) delivery of an ECM hydrogel may be a potentially viable therapeutic strategy for treating patients with UC.

References:

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