Regenerating Reputations: Are Wnt and Myc the Good Guys After All?

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Inflammatory bowel disease (IBD) is one of the biggest challenges facing gastroenterologists today, due to the lack of efficacy of many of its treatments, its widespread morbidities, and its increasing incidence [1]. One of the etiological factors thought to contribute to IBD pathogenesis is diminished intestinal barrier function, which at least in theory permits luminal antigens such as bacterial products to enter the submucosa [2]. Hence, a major unmet need in IBD treatment is a strategy to reverse barrier breaches by directly promoting mucosal restitution and repair. While the importance of this endpoint has been widely acknowledged [3], no IBD therapies currently in use directly target regeneration of the intestinal or colonic epithelium. Rather, it is currently a case of “Mucosa, heal thyself!” in which repair is expected to occur secondarily to the blockade of inflammation. Nevertheless, a wounded mucosa and its attendant disrupted barrier are thought to contribute to ongoing inflammation. Thus, directly bolstering mucosal regeneration may provide an improved alternative or adjunct approach to IBD treatment. In this issue of *Digestive Diseases and Sciences*, Raup-Konsavage and colleagues report proof-of-concept data supporting pharmacologically targeting glycogen synthase kinase

(GSK)-3 β to promote intestinal repair and regeneration through a c-Myc-dependent pathway [4].

The Wnt signaling pathway and the Myc transcription factor are central regulators of cell division that for years have been theoretical clinical targets. They have typically been investigated as targets for inhibition, due to the strongly oncogenic effects of constitutively activating mutants. However, an emerging literature suggests that harnessing these pathways’ ability to promote cell division could be an effective therapeutic approach for the treatment of injury and inflammation, including in the gut. The Yochum laboratory has previously characterized a mouse with a deletion in the 3’ Wnt responsive DNA element of the Myc gene [5]. This mouse displayed a moderate increase in Myc protein expression, heightened intestinal crypt proliferation, and accelerated recovery from dextran sulfate sodium (DSS)-induced experimental colitis. Thus, in the current study, they tested whether indirectly inducing Myc by pharmacologically activating Wnt signaling with LiCl promotes healing. The data show that LiCl does indeed stimulate recovery when given to mice with established acute DSS colitis, and that this protection is sensitive to pharmacological Myc inhibition. The authors also demonstrated direct effects of LiCl and Myc on epithelial cells in vitro by observing lithium-induced accelerated scratch assay restitution, which was reversed by the Myc inhibitor. They consequently outline a surprisingly specific pathway driving recovery from an inflammatory insult in the gut, using a drug related to compounds already widely used in human patients with psychiatric disorders, such as Li₂CO₃.

This study is distinct from previous experiments with lithium or Myc activation in mouse colitis models in that the investigators gave lithium therapeutically rather than prophylactically. The therapeutic approach is an important

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step that is all too rarely taken in preclinical models, in part because it is often simpler to design experiments where the drug is given throughout. Yet, since patients are initially evaluated in the clinic only after the development of symptoms, experimental designs that mirror clinical treatment, as was done by the authors, are potentially more relevant.

A key question that needs to be explored for any therapeutic approach that promotes cell proliferation is whether the treatment carries with it an increased risk of cancer development. This is especially important in the context of IBD patients who are already at elevated risk for colorectal cancer. As Wnt signaling—effectively the target of GSK-3 β inhibition—is intimately tied to the development of colorectal cancer, there is certainly reason for caution. Still, several factors suggest that this approach is likely to be safe and may in fact reduce rather than increase cancer risk. While mutations that constitutively activate the Wnt/ β -catenin signaling pathway have been amply described in the literature, and thus Wnt signaling is an actively pursued target for cancer [6], transiently activating an endogenous pathway with a soluble agonist is potentially quite different than the constitutive activation of a mutated pathway stuck in the “always-on” mode. In part due to the lack of availability of ligands for many targets, this difference is not well explored for most proto-oncogenes. Yet, loss-of-function studies of some proto-oncogenes such as epidermal growth factor receptor [7] have demonstrated paradoxical tumor suppressor (or at least tumor suppressor-like) functions for the wild-type form of these pathways. This appears to be especially true in the context of colitis-associated cancer, where restraining the tumor-promoting effects of chronic inflammation may have a stronger influence on outcome than transient mitogenesis. Given the findings reported by Raup-Konsavage et al., further studies of lithium’s effects on models of colitis-associated cancer are certainly in order.

There is evidence from mouse models of sporadic tumorigenesis such as the Apc^{min} mouse that lithium administration does not appreciably accelerate or worsen tumorigenesis induced by mutations in the Wnt signaling pathway [8]. Furthermore, over decades of clinical experience, no data support an enhanced cancer risk in patients taking lithium for bipolar disorder [9]. In light of the new findings discussed herein, it would also be quite informative to know whether patients taking lithium who also have IBD are protected from flares, or whether colorectal cancer incidence in lithium-taking IBD patients is lower.

The form of lithium used in this study, LiCl, is no longer typically administered to human patients. Nevertheless, different lithium salt formulations are pharmacokinetically very similar [10]. Given the apparent specificity of the signaling pathways described by Yochum and colleagues,

it seems likely that Li₂CO₃ will have similar effects on colitis, although this is yet to be tested prospectively. Some support for the translatability of these findings comes from a case report from 1972 describing a patient receiving Li₂CO₃ for a psychiatric disorder who was also diagnosed with ulcerative colitis. For this patient, lithium therapy was associated with improvement in both diseases [11]. On the other hand, in the same year another case report suggested lithium treatment as the cause of an acute ileitis in a patient [12], though the response was acute and likely not due to IBD per se. Surprisingly, there are no published meta-analyses examining the incidence of Crohn’s disease or ulcerative colitis in patients taking lithium versus the general population. Still, the data from preclinical rodent models combined with the already demonstrated clinical safety of the drug strongly support the notion that lithium could be an effective treatment option worthy of thorough investigation.

The results presented in this paper are consistent with increases in intestinal epithelial regeneration and stem cell activity, as would be predicted by the key contribution of Wnt signaling to both of these processes. What is not yet well understood is the cell-type specificity of these effects. Are epithelial cells the key target, or is the therapeutic response to lithium due to signaling in multiple tissues? Given the likely effects of β -catenin and Myc signaling on immune cells and the potential contributions of the enteric and central nervous systems to colitis pathogenesis, it might be anticipated that effects on these cell types would also contribute to the lithium response in IBD. Yet, at this time little is known about the tissue specificity in this setting.

In conclusion, Raup-Konsavage and colleagues have shown that the Wnt and Myc signaling pathways hold considerable promise as potential targets of pharmacological activation to maintain the intestinal barrier. During inflammation, direct support of epithelial survival and regeneration could tip the balance in favor of resolution/remission. While questions about safety and mechanism of action will certainly have to be addressed in future studies, the long history of safe use of lithium compounds in the clinic gives reason for optimism and supports further investigation of this potential therapeutic avenue.

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