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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

The Ugly Duckling of Thiopurines Becomes the Beautiful Swan of Colitis-associated Cancer Management

Colorectal cancer (CRC) is a leading cause of cancer-related deaths worldwide,[1] and patients with inflammatory bowel disease (IBD) are at increased risk for developing CRC.[2,3] Thiopurines are purine antagonists that inhibit DNA and RNA synthesis and have been widely used in the treatment of IBD based on their efficacy in other autoimmune disorders, such as systemic lupus erythematous and rheumatoid arthritis.[4] The beneficial therapeutic effects that thiopurines have in treating IBD have been well documented in prospective, double-blind, placebo-controlled trials, with data supporting such effects in inducing and maintaining disease remission, as well as in chemoprevention of CRC.[5–7] While azathioprine (AZA) and mercaptopurine (MP) thiopurines have been better characterized in their proven efficacy in reducing the incidence of dysplasia in IBD patients,[6,8] less is known about thioguanine (TG). The mechanism through which thiopurines exert their immunosuppressive activity is by binding 6-TGTP to the GTPase Rac1,[9–11] which represents an important intracellular mediator involved in T cell activity.[12] Blockade of Rac1 signaling by thiopurines results in suppression of proinflammatory T cell responses, mainly by induction of T cell apoptosis and impairment of synapse formation between T cells and antigen-presenting cells.[9,10]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Sheng et al[13] investigate the role of TG in CRC, exploring how TG might alleviate colitis-associated cancer (CAC). Chronic inflammation that occurs in poorly controlled ulcerative colitis can promote CAC. The authors examine whether the effects of TG are mediated via autophagy. The role of autophagy in regulating CAC is quite controversial. Despite its well-established role in preventing inflammation and cancer,[14] dysregulated autophagy may also promote the progression of more established CRC.[15] The reason for such dichotomous regulation of CAC tumorigenesis and progression by autophagy is possibly due to the different types and stages of cancers, as well as to the complicated tumor microenvironment.[15]

Using in vitro and in vivo approaches, Sheng et al[13] define a pathway, independent from autophagy and inflammation, in which physiological concentrations of TG inhibit Wnt/β-catenin signaling dependent on Rac1, reducing proliferation of epithelial cells and protumorigenic genes transcription, therefore reducing the risk of CAC. The present work sheds light on mechanism of action of this less characterized thiopurine, building on observations of its role in the context of altered microbiome-dependent colitis.[16]

Using human colon cancer cell lines harboring a β-catenin transcriptional reporter, and TG intrarectal administration in a well-established murine model of CAC, they demonstrate that TG specifically inhibits β-catenin transcriptional activity and downstream colitis-associated tumorigenesis. The same TG administration protocol is repeated on mice deficient for the Atg7 core autophagy protein, resulting in a significant reduction of tumor load independent of inflammation, which is in line with the anti-inflammatory effect of intrarectal TG being autophagy dependent. The present work's data suggest that, unlike AZA and MP, the mechanism of rectal TG administration involves a direct effect of TG on epithelial cells in abrogating colitis and preventing CAC, with negligible systemic toxicity. These in vivo results were corroborated using short interfering RNA Atg7 knockdown in vitro experiments on the same human colon cancer cell lines, in which β-catenin activity was reduced by TG treatment in a dose-dependent fashion. In addition, in vitro silencing experiments showed that TG suppression of β-catenin was dependent on Rac-1 at lower physiological concentrations, whereas it was Rac-1 independent at supraphysiological higher concentrations.[13]

As a member of the Ras superfamily of Rho GTPases, GTP-bound Rac1 mediates a plethora of cellular processes including actin reorganization and gene transcription. It is possible that the TG Rac1 interaction may result in other cellular effects independent of β-catenin transcriptional activity, to inhibit CAC development, which warrants further investigation in future work.

The major concern that has inhibited the clinical use of thioguanine, as opposed to AZA or MP, has been the because of its link nodular regenerative hyperplasia (NRH) and veno-occlusive disease (VOD). However, recent evidence using an animal model for TG-induced NRH/VOD has shown that NRH/VOD is dose dependent.[17] Furthermore, in human trials, TG has proven to be safe and efficacious for celiac disease when used at doses below those commonly prescribed.[18] This has reignited interest in TG because of its higher efficacy and faster action compared with other thiopurines and immunosuppressants. This study provides further evidence in support of the potential therapeutic utility of TG.

Altogether, this study demonstrates an effect of topical TG on colonic epithelial cells and a mechanism of TG action in attenuating CAC. Biochemical dissociation of TG-mediated Rac blockade from autophagy may be useful to consider in refining therapeutic discovery efforts in these pathways and in consideration of management strategies for utilization of TG in the clinic.

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Conflicts of interest
The author discloses no conflicts.

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