Microscopic Colitis Foundation

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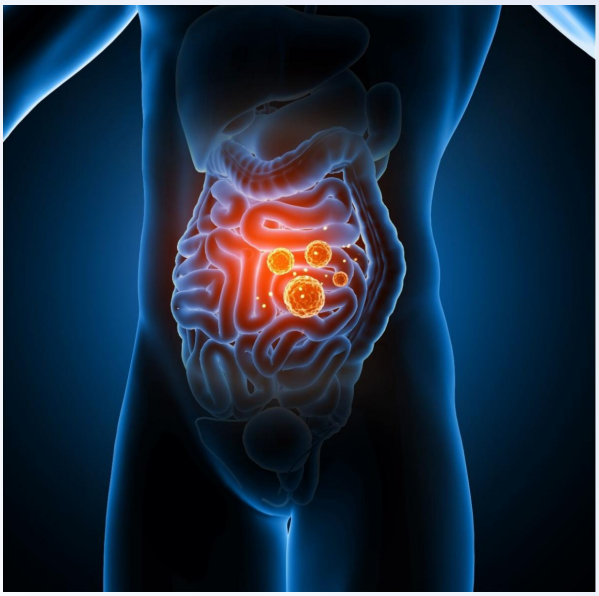

Why Is Intestinal Healing with MC So Slow? New Research Sheds Light

by Wayne Persky and Rosalyn Upson

For a couple of decades (since soon after I developed microscopic colitis [MC]), I've wondered why intestinal healing of the damage caused by this disease is so incredibly slow, compared with the normal healing times for other organs. This is true for individuals who have celiac disease, also. Although kids can heal in one to three years, adults require much more healing time. Increasing age, and higher levels of damage before beginning a gluten-free diet, are associated with longer intestinal healing times.

MC and celiac disease are both symptoms of gluten sensitivity.

A Mayo Clinic study of adult celiac patients looked at how well the intestinal mucosa heals after following a gluten-free diet (Rubio-Tapia, et al., 2010)[1]. The study found that 34% achieved mucosal recovery after two years, and 66% after five years. The intestines of some celiacs never entirely heal.

A search of the Internet for specific research regarding intestinal healing times for MC doesn't locate any results, so apparently the topic hasn't been investigated. But since gluten sensitivity is associated (and is a dominant issue) with both syndromes, it's very likely that healing times will probably be very similar.

Normally, the lining of the colon is replaced every 3 to 5 days.

The cells in the epithelia of the colon are replaced on such a frequent schedule because of the difficult conditions under which they normally perform their duties. The gut's continuous renewal process, allows for the maintenance of the intestinal barrier and helps to repair damage caused by food, bacteria, and other environmental factors. The process is driven by intestinal stem cells located at the base of the crypts in the colon, which constantly divide and differentiate into various cell types that make up the epithelial

layer.

Factors such as inflammation, infection, or disease can influence the rate of this turnover, often accelerating or impairing the process, depending on the condition. For instance, in inflammatory conditions like MC, the normal regenerative process can be disrupted, leading to prolonged symptoms and impaired healing.

> **Healing is slow with microscopic colitis.**

> **It can take years for the gut to recover and appear normal.**

Researchers discover why intestinal healing due to inflammation is so slow.

Recent research conducted by teams at Baylor College of Medicine and the University of Michigan has revealed significant findings regarding the effects of inflammation on intestinal stem cells (ISCs). The study, published in Cell Stem Cell, focuses on how inflammatory conditions, particularly those arising from graft-versus-host disease (GVHD), can impose lasting changes on ISCs that hinder their regenerative capabilities (Zhao, et al., 2024)[2]. This discovery has critical implications for understanding intestinal health and resilience, especially in the context of inflammation-based autoimmune diseases (which surely includes all IBDs), and therapies such as bone marrow transplantation.

> **Stem cells continually repair the intestine.**

> **Inflammation causes long-standing changes to stem cells.**

GVHD is a serious complication that can occur after bone marrow transplantation, where immune T cells from the donor attack the recipient's cells, particularly in the gut. This inflammatory response can lead to significant damage to ISCs, which are crucial for maintaining the integrity and function of the intestinal lining.

But we're not interested in GVHD. We're here hoping to learn more about how to control MC, and these

findings on the effects of inflammation on ISCs have important implications for patients with MC, and presumably other IBDs (including celiac disease). Discussions of the details of this research found in other articles, can be helpful for understanding some of the implications of these research findings (Baylor College of Medicine, 2024, September 3; Chiu, 2024, September 3)[3,4].

Inflammation causes long-term effects.

The researchers found that inflammation leaves long-lasting damage to ISCs, reducing their regenerative capacity, even after the inflammation has subsided. This implies that the chronic inflammation associated with MC could inhibit the intestinal lining's ability to heal and regenerate, thereby leading to prolonged symptoms and delayed recovery.

Many of our experiences lead to epigenetic changes in our DNA.

Epigenetics refers to changes in gene expression that don't involve alterations to the underlying DNA sequence. These changes are caused by chemical modifications that affect how genes are turned on or off without changing the genetic code itself. There are several key mechanisms by which epigenetic regulation occurs, including acetylation and methylation, for example.

Think of epigenetics as a set of instructions that tell our genes when to switch on or off, kind of like a light dimmer. Imagine our DNA as a big cookbook, and our genes are the individual recipes in that book. Epigenetics doesn't change the recipes (our genes) themselves, but it does influence which recipes are used and how often they are used.

Things such as diet, stress, and exposure to chemicals can all affect our epigenetics. So, while we inherit our genes from our parents, how our body reads and uses those genes can be influenced by our life experiences — and sometimes these changes can even be passed on to our children! It's a way the environment and our lifestyle can interact with our genetic code to influence our health.

Inflammation promotes epigenetic changes in ISCs.

Inflammation can cause ISCs to accumulate metabolic byproducts like succinate. This accumulation reprograms the ISC's DNA, a process called "epigenetic change". This reduces their ability to regenerate. In microscopic colitis, similar mechanisms could explain why some patients experience occasional unexplained flare-ups. The inability of the ISCs to return to full function after inflammation might contribute to the cyclical nature of some IBDs. Because of these epigenetic changes, the ability of ISC's to regain

their functionality after an inflammatory episode (especially an extended inflammatory episode) has subsided, appears to be very limited.

These changes cause reduced ISC resilience to future stress.

The research showed that ISCs exposed to inflammation had a diminished capacity to recover from

subsequent challenges, such as further inflammation or injury. For microscopic colitis patients, this could mean that ongoing (extended) inflammation weakens the gut's defenses, making it more difficult for the disease to be brought to remission, because of the compromised healing ability of the intestine.

And this could also make it more likely that recovery from future flareups will become more difficult. This emphasizes the importance of controlling inflammation early and effectively, in order to prevent or minimize long-term damage to intestinal stem cells.

This discovery may answer a lot of important questions about MC.

These findings may explain why difficult MC cases (that have been active for long periods of time), and MC cases that seem to be refractive to treatment, are so difficult to resolve. They actually are much more difficult to resolve because of the (probably cumulative) epigenetic changes that impair the ability of intestinal ISC's to repair intestinal damage, and guard against future damage. Future research will probably focus on attempting to discover treatments that can boost the regeneration of impaired ISC functionality, although that will almost surely be a difficult goal to accomplish.

> **Inflammation impairs intestinal stem cells' future ability to respond to stress.**

> **Control inflammation early to minimize damaging changes to intestinal stem cells.**

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The Association Between Perfectionism and MC

The ETS2 Gene and IBD

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