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Infections May Set the Stage for Chronic Inflammatory Diseases

Immune Architecture Altered After Gut Infection in Mouse Study

A new study led by NIAID researchers has shown in mice that a single gut infection can trigger long-term consequences that compromise the immune system's balance, impair immune function, and cause persistent inflammation in the gut-associated adipose (fat) tissue. While scientists have long suggested that infections may initiate the development of chronic inflammatory diseases, direct evidence supporting this idea has been lacking.

In the new study, researchers show that after an infection, the immune architecture in the gut is disrupted, preventing the immune system from communicating with nearby tissues. Furthermore, microbes found in the intestinal tract, part of the body's naturally occurring microbiome, maintain the immune imbalance despite clearance of the initial infection. The study appears in the October 8, 2015, edition of *Cell*.

Form Fits Function for the Mucosal Immune System

While the immune system is known for clearing infectious microbes, it also has a lesser-known but equally important role in restoring a damaged area back to its normal, balanced state, also known as tissue homeostasis. The most visible example of this function is wound healing on skin, which is orchestrated in part by immune cells. Internally, tissue homeostasis is particularly important at other barrier sites—the respiratory and digestive tracts—where tissues interface with the environment and host the body's microbiome. Here, tissue architecture is key for preventing the microbiome from crossing the barrier, with strategic hubs of immune cells located at lymph nodes connected by lymphatic vessels that weave throughout the body.

During a respiratory or gut infection, the local tissue architecture changes drastically and becomes inflamed as immune cells move in to limit and clear the infection. While these changes are mostly transient, it is unknown whether such infections produce long-term, negative effects. Importantly, diseases that involve barrier sites, including inflammatory bowel disease and asthma, may be linked to infection and downstream tissue re-modeling.

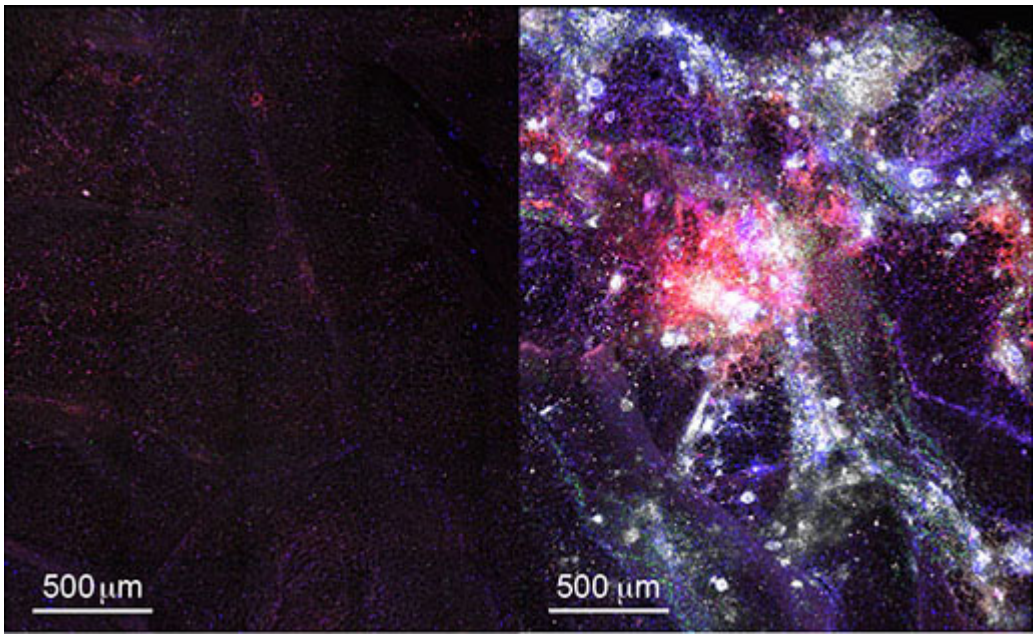
A New Role for the Microbiome

The NIAID-led team designed a mouse study to examine long-term effects of a single infection by *Yersinia pseudotuberculosis*, a foodborne pathogen that also infects people. Similar to what has been observed in humans, some mice recover normally while others exhibit long-term abnormalities in the gut, including enlarged lymph nodes

and chronic inflammation, despite clearing the infection.

The researchers compared mice that recovered normally to those that did not, and the team discovered a number of important differences. The abnormal mice were unable to mount a proper immune response after receiving an oral vaccine, suggesting that immunity in the gut was compromised. Furthermore, the mice did not generate normal levels of regulatory T cells, which are important for turning off an immune response, suppressing inflammation, and preventing allergic responses.

When the researchers imaged the tissues around the gut, they observed abnormalities in the mice that did not recover normally from infection. Most notably, immune cells that should be located in lymph nodes were found in surrounding fatty tissues. Upon examination, the team found that lymphatic vessels in the gut were leaky, shunting dendritic cells to the wrong location. Due to this leakage, immune cells could not interact in lymph nodes nor communicate properly, leading to gut inflammation and defective immunity.



Immune cells (color) are measured in the adipose (fat) tissue found around the gut. Compared to mice that recovered normally after infection with Y. pseudotuberculosis (left), mice that did not recover normally (right) had "leaky" lymphatics—a conduit for the immune system—that shunted immune cells into surrounding tissues, causing inflammation and other disruptions.

Curiously, the abnormalities persisted despite clearance of the infectious microbe, suggesting that other signals were responsible for maintaining the deleterious effects started by the infection. Because gut tissues host much of the body's microbiome, the researchers gave the mice antibiotics to clear the microbes normally found in the gut. Antibiotic-treated mice had reduced inflammation, indicating that the microbiome maintained the harmful immune changes in the gut caused by *Y. pseudotuberculosis*. These results suggest that targeting the microbiome may be a strategy to restore immune balance.

Next Steps

The new findings provide a framework for understanding a number of barrier diseases. For instance, many of the changes seen in the mice are reminiscent of what is observed in Crohn's disease patients. Therefore, lymphatic vessels and damage to the immune architecture should be explored more closely in inflammatory bowel diseases.

In addition, these results may explain why orally administered vaccines tend to be less effective in lower income countries compared to higher income countries. Persistent gut infections and lack of health care may contribute to the remodeling of gut immunity that leads to dysfunctional immune responses. However, more work is needed to explore and develop this new discovery.

Reference

Fonseca DM, Hand TW, Han SJ, Gerner MY, Glatman Zaretsky A, Byrd AL, Harrison OJ, Ortiz AM, Quinones M, Trinchieri G, Brenchley JM, Brodsky IE, Germain RN, Randolph GJ, Belkaid Y. Microbiota-dependent sequelae of acute infection compromise tissue-specific immunity (http://dx.doi.org/10.1016/j.cell.2015.08.030). *Cell* (2015).

Dr. Belkaid's Lab

Immunology Advance: How Gut Infections Cause Long-Term Damage

Content last reviewed on October 8, 2015

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