September 26, 2018

Microbiology

Absent microbial teachers and immunological hooliganism

by Jun Miyoshi [1] | Postdoctoral Research Fellow; Eugene B. Chang [2] | Professor

[1]: Knapp Center for Biomedical Discovery (KCBD), The University of Chicago, Chicago, USA

This Break was edited by Anatoly Kozlov, *Scientific Editor* - TheScienceBreaker

ABSTRACT

Various factors including "just in case" use of antibiotics can affect the microbiome of babies, and that can sabotage their immune system

Image credits: Pixabay – CC0

The trillions of microbes that live in our gastrointestinal tract are known as the gut microbiome. It is an "acquired organ" of the body that is essential for the development of immune and metabolic systems and for nutrient digestion and absorption, among other things. As newborns, the microbial organ forms through the continuous acquisition of microbes from mothers, other family members, and from environmental sources such as household pets, foods that we eat, and anything that babies want to put into their mouths. As this occurs, the immune system, which itself is in a naïve state, takes lessons from microbial educators so that it can prepare for challenges later in life.

The immune system is a defense system of our body that protects us from harmful factors such as infectious pathogens. The naïve system needs to learn which targets they should eliminate and one important lesson is to be exposed to microbes and their products. This educational process appears to take place in a relatively short time during early childhood during which a properly schooled immune system will learn what types of microbes should be "tolerated". Once school is over, the educated immune system can make appropriate decisions about which microbes are good or bad. In this way, the well-educated immune system serves to protect and, at the same time, maintain the stability of indigenous microbial communities.

A breakdown in this educational process may underlie the observed increase in complex immune disorders over the past century, particularly in

industrialized societies where rapid changes in environment factors, lifestyle, diet, and exposure to xenobiotics (e.g. antibiotics) are occurring. All these events have the potential to disturb the flow of information provided by microbial educators to host immune cells in ways that promote immunological imbalance and risk for disease.

Such a scenario has been suggested for inflammatory bowel diseases (IBD). IBD includes two clinical disease types, Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the gastrointestinal tract, while UC is characterized by inflammation in the colon. Both types of IBD often involve chronic relapsing. The causes of IBD remain unclear. These patients often carry genetic risk variants, but this alone is usually insufficient to explain why only a few will develop disease. Over 200 gene mutations have been reported to be associated with increased risk for IBD. These unfortunate few likely encounter certain triggering and risk factors that set into motion a cascade of events that ultimately leads to the development of chronic intestinal inflammation. We are only now becoming aware of the fact that many of these events may be happening early in life to skew the development of the gut microbiome and set the stage for immunological mischief or "hooliganism". Several epidemiological studies (Gevers et al., 2014; Ungaro et al., 2014; Örtqvist et al., 2018), for instance, have shown that increased risk for developing IBD is associated with the use of broad-spectrum antibiotics during the peripartum period (during pregnancy and early childhood) that cause disturbances in the gut microbiome. On the other hand, these studies have not been able to establish a causal link because they analyzed subjects retrospectively and it was impossible to control background variables strictly. Research on human subjects has inherent limitations and it is challenging to design and conduct a study to approach the causality.

Recently, given these limitations of human studies, we performed a study with a mouse model prone to develop colitis and obtained some insights into this issue (Miyoshi et al., 2017). This mouse model is widely used as an experimental IBD model. A broad spectrum antibiotic was administered to the mothers late in pregnancy and during the nursing period. As would be expected, many of the major groups of maternal intestinal microbes were eradicated, which markedly affected what was acquired by the offspring. In fact, many of the important microbial "teachers" critical for proper immune education and development were never acquired by the pups. As these mice reached adulthood, most developed colitis presumably because the immune system viewed these otherwise "good" microbes as unfriendly, having never seen them during their schooling process.

This study provides several important conceptual and mechanistic insights. It demonstrates the essential role of the gut microbiome for early stage immune education and development. It also showed that factors and events that perturb the proper development of the gut microbial organ can have long-term consequences, especially in individuals who have a genetic predisposition to certain types of diseases. Second, this study offers a cautionary note that may and hopefully will change practices in the management of mother and child during the peripartum period. Too often, antibiotics are prescribed by health care providers or obtained over the counter for "just in case" indications. These practices have to be revisited. A casual misstep in someone's life at this stage can have long-lasting unintended consequences that negatively impact their well being into the future.