**Autoimmunity in Eye Triggered by Gut Microbiota**

**Abstract:**  Uveitis is an autoimmune eye disease that can lead to complete vision loss. Recently, studies have found that microbiota in the gut can trigger uveitis and its symptoms. Retina-specific T cells are activated by gut microbiota to attack specific eye proteins causing uveitis. These findings could mean that gut microbiota triggers to T cells are a bigger impact on autoimmune diseases than previously thought and could have strong implications for further research into this area.

**Introduction:** Commensal microorganisms exist within each mammal and largely impact many of our most basic functions and our overall health in many ways, including proper function of our immune systems. Scientists have known that the normal function of the immune system is impacted and dependant on gut commensal microorganisms. T cells, specifically, are activated by these organisms. T cells (T lymphocytes) are a type of white blood cell that play a crucial role in cell-mediated immunity. There are many types of T cells and, they are responsible for things such as immune system memory, destroying tumors and viruses, assisting other white blood cells, and shutting down immune response. Recently, scientists have discovered that autoimmune uveitis, a major cause of blindness and vision loss, is largely impacted by triggers from gut microbes. Uveitis is an eye disease that can either be autoimmune or the result of a tumor, infection, bruise, or other toxin in the body and eye. While labeled “rare” with fewer than 200,000 cases in the US per year, uveitis is still a relevant disease with drastic effects. Many animals and their microbiota have been studied to determine what the relationship between the T cells and gut microbes are. This study uses mice and focuses on uveitis and T cell responses. The study arose from the observation that although the eye is an immune-privileged tissue--meaning it is separated from its antigens, and those antigens need a trigger in order to cross the barrier--it is often host to autoimmune disorders. The question of where these T cells are activated and by what was the most baffling thing about the observation. The study uses mice to observe normal microbiota, retina-specific T cells, and their relationship to autoimmune disease.

**Recent Progress:** In order to figure out where the T cells are being activated, researchers studied the activated phenotypes of the pathogenic T cells in young mice at 4 weeks old, the age they normally acquire uveitis, and adult mice at 12 weeks old. The T cells found in the young mice were observed to be able to produce a cytokine that is pathogenic in autoimmune uveitis. They found that even in mice only days old, antigen receptor signaling was strong within the ileum. This lead to the conclusion that gut T cells are activated before uveitis onset and directly linked. In order to determine whether or not the mice’s gut commensal microbiota were related to the activation of T cells, a group of young mice were given antibiotics, and a study of their fecal matter showed that complexity and mass of microorganisms had been drastically reduced. In correlation with this, the antibiotic treated mice were seen to exhibit significantly slower onset of uveitis. The mice did still acquire uveitis, but their symptoms were not as drastic as those seen in untreated mice. The researchers studied whether it was just an effect of being consistently exposed to antibiotics instead of a result of the microorganisms themselves, but they found that it was indeed a result of the reduction of microorganisms themselves. Further correlation was found when researchers studied the T cell cytokine production. They found that in mice affected by uveitis, there was a significantly higher presence of T cells that produced the pathogenic cytokine not found in healthy mice. It was also found that uveitis affected mice were not lacking target antigen in their eyes. In order to show signaling in gut environment T cells, researchers examined dimers within ileal tissues. Immunofluorescent staining and flow cytometry showed activation of T cells and signaling from within the gut environment, and it showed the high levels of cytokine produced by those T cells. Next, researchers introduced healthy mice to uveitis afflicted mice and observed that the healthy mice developed uveitis with similar T cells and histology to that of the original uveitis afflicted mice. Next, bacteria-rich protein extracts were taken directly from the gut of uveitis mice and were cultured to see whether these extracts could directly trigger T cell activation and the production of cytokine. The extracts were introduced to a new host and were observed to trigger T cell activation. The proteins that were responsible for activation were dimer rich, not just innate stimuli alone. Extracts that had not yet been introduced, were exposed to proteinase K treatment and heat denaturation. Then, they were introduced to cells that were not seen to activate retina specific T cells in the uveitis afflicted mice. After introduction to the protein extracts, the naive cells reacted positively, but less vigorously due to the denaturation. Researchers also took protein extracts from mice not afflicted with uveitis and performed the same trials with those. The results indicated no up-regulation from naive cells, meaning that the dimer rich proteins were in fact responsible. All results indicated that retina specific T cells were activated by triggers from proteins of gut commensal microorganisms in turn causing antigens to permeate the retinal barrier and induce uveitis.

**Discussion:** This study further exposes the idea that the normal microbiota has an even larger effect on the entire body and immune system as a whole. The results indicated by this research suggest that normal gut commensals can trigger immune responses and activate T cells to cross the immune privileged barrier of the eye. This is the first study to link gut microbes with autoimmune eye disease, and it could open the door for further research into the immune system responses from microorganisms. The research could also open the door to further studies on autoimmune disease and its treatment. The results could also indicate and lead to a method of treatment for uveitis not previously thought of or attempted. While the specific bacterial species that causes T cell response was not identified, the list of likely candidates was very much narrowed due to antibiotic treatment. Further studies into specific responses from certain bacteria could lead to a breakthrough in this information as well as further treatment for the disease. This research exposes interesting breakthroughs in ways to study uveitis, the immune system, commensals, and other autoimmune diseases as a whole.

**Citations:** Horai, R., Zarate-Blades, C. R., Dillenburg-Pilla, P., Yamane, H., Honda, K., & Caspi, R. R. (2015). Microbiota-Dependent Activation of an Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site. *Immunology,* 343-353. Retrieved February 2, 2015, from https://microbiology.med.uky.edu/sites/default/files/Kaplan Article.pdf.