From the gut to the eye: commensal microbes as potential triggers of autoimmune uveitis

Autoimmune uveitis is a group of inflammatory diseases that affect the retina of the eye and related tissues and constitute a major cause of human blindness. It is believed that the disease is triggered by the activation of circulating lymphocytes capable of recognizing the proteins (antigens) that are unique to the eye, whereupon they gain the ability to invade the healthy eye and induce uveitis. How and where these lymphocytes become activated has been a long-standing mystery, because the proteins that they are programmed to recognize which would activate them are inside the eye and are not accessible. Questions such as these cannot be studied in humans for reasons that are both ethical and practical (the patient comes to the clinic after disease has already developed). Therefore, researchers rely on animal models to study disease related processes in a setting that can be controlled and manipulated experimentally.

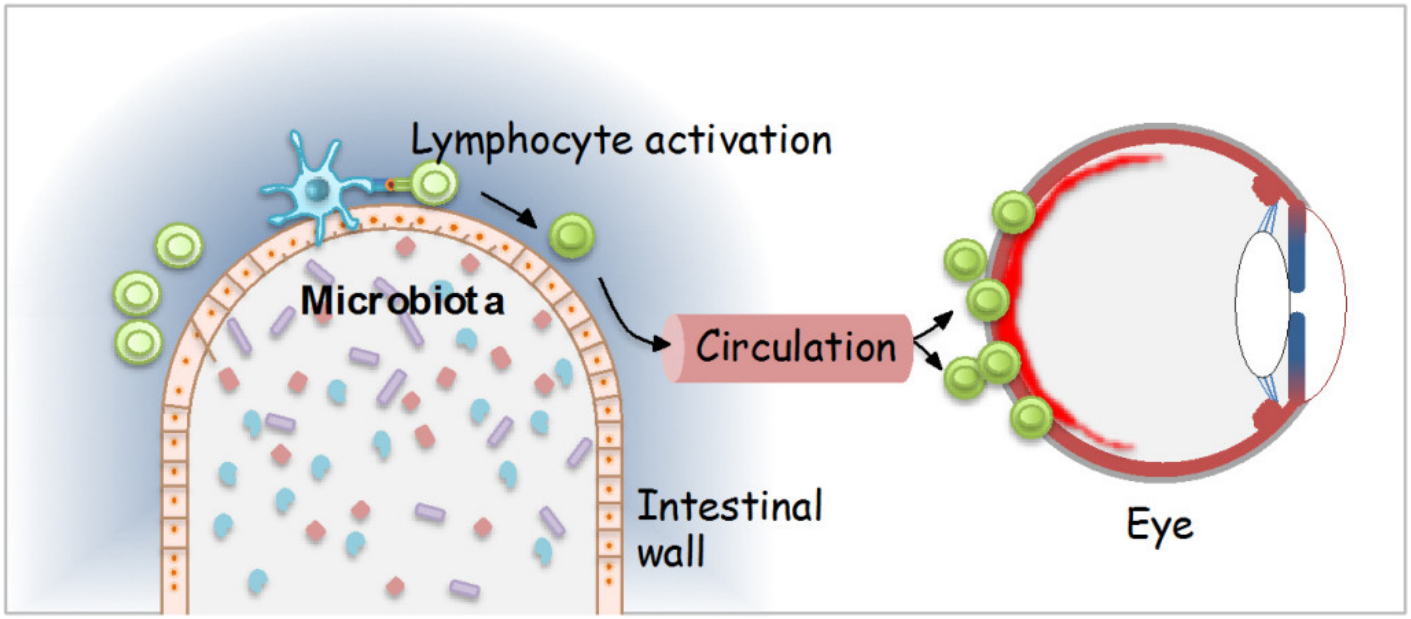

Fig. 1. Schematic representation of lymphocyte activation in the intestine on commensal microbiota, which endows them with the ability to induce uveitis. (Adapted from press release by the National Eye Institute).

In traditional animal models of uveitis, experimental mice or rats are immunized with proteins from the eye (incorporated into an emulsion of oil containing heat-killed tuberculosis bacteria, known as complete Freund's adjuvant, which amplifies immune responses). Their lymphocytes then become activated and the animals develop uveitis. However, these models are not appropriate to study natural causes of disease, as the trigger is provided by the researcher in the form of immunization.

We, therefore, developed a new model of autoimmune uveitis in genetically engineered mice that develop the disease spontaneously as a consequence of having an increased number of circulating retina-specific lymphocytes.

By studying these mice, which additionally contained a fluorescent reporter molecule to show lymphocyte activation, we observed that the retina-specific lymphocytes became activated in the intestine. This occurred even before the animals developed clinically apparent uveitis, and was still present in mice that had the retinal antigen genetically deleted. Treatment of the mice with antibiotics, or rearing them in germ-free conditions, resulted in strongly delayed and attenuated development of disease, pointing to bacteria in the intestine as a potential trigger. Indeed, further experiments demonstrated that circulating retina-specific lymphocytes isolated from the genetically engineered mice could be activated by culture with extracts of bacteria-rich intestinal contents. Moreover, these lymphocytes induced uveitis when subsequently injected into genetically normal recipients, whereas lymphocytes that were cultured by themselves, did not. Extracts from germ free animals did not have an activating effect. In the aggregate, these findings indicated that bacteria in the intestine make something (which we identified as a protein) that to the retina-specific lymphocytes “looks” similar to the retinal antigen that they are programmed to recognize. These lymphocytes then enter the circulation and make their way to the eye, which they are able to infilatrate due to their ativated state, and cause uveitis (Figure 1).

Due to the complexity of the intestinal microbiome, it has not yet been possible to identify the responsible organism(s) and to characterize their product. Bioinformatic and biological methods may help us achieve this, but there is still much work to be done. Irrespective of that, however, our findings have clear implications for the etiology of human uveitis. Furthermore, in view of the almost infinite variety of microbes living in and on our bodies, if they can mimic a retinal antigen, it is possible that they may produce substances that mimic tissue antigens involved in other autoimmune diseases. If that is true, commensal microbes might be a more common trigger of autoimmune diseases than is currently appreciated.

While the knowledge gleaned from these studies can help us understand the biology of the disease, the conclusions cannot yet be applied clinically. In view of what we know about the importance of microbiota for proper development and functioning of immunity, host defense and metabolism, prophylactic treatment with broad spectrum antibiotics is not feasible. Furthermore, we are not yet able to identify the individuals at risk for uveitis with sufficient certainty. However, as our knowledge advances and as our ability to control undesirable immunological responses in an increasingly selective fashion develops, specific immunological interventions or introduction of appropriate probiotics and prebiotics might become possible.

Publication

Microbiota-Dependent Activation of an Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site.

Horai R, Zárate-Bladés CR, Dillenburg-Pilla P, Chen J, Kielczewski JL, Silver PB, Jittayasothorn Y, Chan CC, Yamane H, Honda K, Caspi RR.

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