Scientists figure out how the immune system and brain communicate to control disease

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In a major step in understanding how the nervous system and the immune system interact, scientists at The Feinstein Institute for Medical Research have identified a new anatomical path through which the brain and the spleen communicate. The spleen, once thought to be an unnecessary bit of tissue, is now regarded as an organ where important information from the nervous reaches the immune system. Understanding this process could ultimately lead to treatments that target the spleen to send the right message when fighting human disease.

Mauricio Rosas-Ballina, MD, working with colleagues in the laboratory of Kevin J. Tracey, MD, figured out that macrophages in the spleen were making tumor necrosis factor, a powerful inflammation-producing molecule. When they stimulated the vagus nerve, a long nerve that goes from the base of the brain into thoracic and abdominal organs, tumor necrosis factor (TNF) production in the spleen decreased. This study complements previous research performed in Dr. Tracey's laboratory, which showed that stimulation of the vagus nerve increases survival in laboratory models of sepsis.

The findings were published today in the *Proceedings of the National Academy of Sciences*. Many laboratories at The Feinstein Institute study the immune system in health and in disease. Every year, about 500,000 people develop severe sepsis, a syndrome triggered when the body's immune system wages an attack on the body that is well beyond its normal response to an invader. Sepsis kills about 225,000 deaths in the United States each year.

A hundred years ago, the spleen (located in the upper quadrant of the abdomen) was thought to be only reservoir for blood. It has only been in recent years that scientists discovered that the spleen is a manufacturing plant for immune cells, and a site where immune cells and nerves interact. The spleen defends the body against infection, particularly encapsulated bacteria that circulate through the blood.

The hope is to modulate other immune functions like antibody production through the spleen (via vagus nerve stimulation) as a way to modify the course of infections and possibly some autoimmune disorders.

Dr. Rosas-Ballina began following the winding path of the vagus nerve to establish the route it follows to reach the spleen. He was trying, without much luck, to find fibers of the vagus nerve in this organ. And then he went a little further south to the splenic nerve, the nerve that innervates the spleen. Their results indicate that the vagus nerve inherently communicates with the splenic nerve to suppress TNF production by macrophages in the spleen.

According to the prevailing paradigm, the autonomic nervous system is anatomically and functionally divided in sympathetic and parasympathetic branches, which act in opposition to regulate organ function. "The division between the parasympathetic and sympathetic nervous systems is not clear cut," said Dr. Rosas-Ballina, explaining that the vagus nerve (the major parasympathetic nerve) acts through the splenic nerve to modulate immune function.

He said that results of this study suggest that there may be two separate ways the brain communicates with the spleen to regulate immune function. This points the way to a possible solution for treating sepsis. It may be more effective to take advantage of the central nervous system to control cells of the spleen. This way, "you know where the treatment is

going," said Dr. Rosas-Ballina.

Source: North Shore-Long Island Jewish (LIJ) Health System