A Novel Therapeutic Approach to Inflammatory Disease

A peptide sequence involved in T-cell signaling might be the key to controlling autoimmune disease.

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December 20, 2020 – Therapeutic options for the inflammatory diseases Rheumatoid arthritis and Kawasaki disease could move in a new direction after researchers discovered a peptide therapy that supports the principles of immune regulation rather than immune repression in humans.

In a recent interview with Alessandra Franco, MD, PhD, of the University of California, San Diego, in San Diego, California, Professor Franco detailed current advancements in characterizing mechanisms of inflammation regulation and the resulting impact it has on autoimmune disease.

“In the past, treatment of inflammation has focused on downregulating arms of the immune system that participate in the pro-inflammatory response. However, an alternative strategy is to stimulate the host’s endogenous systems to regulate inflammation,” explained Dr. Franco.

To this end, Professor Franco and her research group first defined a unique population of natural regulatory T cells (nTreg) that recognized and responded to the heavy constant region of IgG (Fc). In healthy individuals, Tregs control inflammation by secretion of interleukin (IL)-10, a lymphokine that suppresses pro-inflammatory signals. The group went on to identify the immunodominant Fc peptides of healthy donors and revealed that nTreg expansion was defective in two autoinflammatory disease models.

Specifically, the researchers reported that an aberrant nTreg response might contribute to the persistence of inflammation in adults with Rheumatoid arthritis (RA) and children with Kawasaki disease (KD).

Evidence for this claim was first noted in patients with RA, where isolated peripheral blood mononuclear cells (PBMC) failed to respond to intact Fc in culture, although the cells did maintain the ability to secrete IL-10 in response to Fc peptide in a canonical, Human Leukocyte Antigen (HLA)-restricted manner.

Further support was seen in patients with KD, an acute coronary artery vasculitis that is the most common cause of acquired pediatric heart disease. Prior to a standard therapy of high-dose (2 g/kg) intravenous immunoglobulin (IVIG), the presence of circulating Fc-specific nTreg in KD patients could not be found. Interestingly, two populations of patients became evident after IVIG treatment. In the first population of children with no cardiovascular complications, these individuals displayed circulating nTreg that expanded *ex vivo* and secreted IL-10 in response to intact Fc. In contrast, children that developed coronary artery aneurysms (CAA) were associated with a failure to expand Fc-specific nTreg *ex vivo*.

Commenting on the novel aspect of this work, Dr. Franco explained, “immunodominant Fc peptides have great [therapeutic] potential to boost and expand nTreg, and they may be used in a variety of clinical settings according to the novel concept of vaccination to [promote] adaptive immune regulation.”

Funding for a portion of this project was secured by a seed grant from the University of California Drug Discovery Consortium (UC DDC). In response to her novel Fc peptide discovery, Dr. Franco secured a licensing deal through the University of California and maintained further funding from the NIH of $870,000.

The scientific discoveries of Dr. Franco undoubtedly carry great promise for the development of new, affordable, therapeutic options that apply to an expandable number of inflammatory diseases. Despite the sensational aspect of this therapeutic, Professor Franco emphasized the importance of scientific persistence and consistency in ultimately leading to research translation.