VIP Takes Center Stage in Autoimmune Disease

a review by C. M. Condo


My first exposure to autoimmune disease came in the fifth grade, when I made friends with a new girl in my class. The morning after our first sleepover, when my mom came to ask us about breakfast, my new friend said she had to check her blood sugar, take insulin, and then she could eat. As I watched in fascination and horror, she snapped a plastic puncture device on her ring finger, collected the blood on a plastic strip, and stuck it in a small electronic device, which after a few seconds, chirped in response. Then the eleven-year-old girl drew up medicine into a needle-tipped syringe and coolly injected herself in the thigh. I asked her when she could stop doing all this. She said, "Never."

Type 1 diabetes and other autoimmune disorders, including rheumatoid arthritis and multiple sclerosis, affect nearly 8% of the population of the U.S., and their numbers are increasing each year. The pathology of these disorders is defined by a loss of tissue from attack by the body's own immune system. Worse, once the damage has been done, it cannot be reversed; the cells do not regenerate. If there were a way to intervene early on in the process, before acute tissue destruction, an entire class of diseases could be powerfully reduced in severity, and their sufferers could look forward to much improved qualities of life.

The aforementioned articles, published in Science Direct by Mario Delgado, PhD and the Journal of Immunology and Cell Biology by Rebeca Jimeno and her doctoral mentor, Rosa P. Gomariz, PhD, discuss the mechanisms and treatment implications of a particular hormone that is key to autoimmune disease. These papers outline three important concepts: the influence of the Th1/Th2 cell ratio on autoimmune disease versus tolerance; how the endogenous form of the hormone vasoactive intestinal peptide (VIP) affects Th1/Th2 cell differentiation; and the potential...
clinical applications of these interactions to autoimmune diseases, specifically type 1 diabetes.

Mario Delgado, author of the Science Direct article, has made numerous contributions to the field of neuroimmunology; his current work focuses on the study of endogenous anti-inflammatory factors. Delgado appears in over 400 publications. He completed his PhD at the Complutense University of Madrid, Spain, and received his postdoctoral education at Rutgers University in New Jersey. Delgado is currently head of the Department of Immunology and Cell Biology at the Institute of Parasitology and Biomedicine in Granada, Spain, and serves on the Steering Committee of the International Regulatory Peptide Society. His lab researches the communication between immune and neuroendocrine systems, with the aim of finding clinical applications for the treatment of autoimmune disorders.

Rebeca Jimeno is a doctoral student of Rosa P. Gomariz, PhD at the Complutense University of Madrid, Spain (UMS). Gomariz received her PhD in Biological Sciences from the University of California, Los Angeles, and founded the Gomariz lab on the immunopeptides VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) at UMS. Her lab studies how these hormones affect immune cell activity and autoimmunity. Gomariz appears in over 60 publications.

The following definitions of a few key abbreviations and terms will be helpful in the discussion of the biomedical research detailed in these articles. A Th cell refers to a T-helper lymphocyte (white blood cell) produced in the thymus organ. Th cells are key to the chemical interactions discussed in both articles. A macrophage is a particular white blood cell that engulfs a tainted or damaged cell and breaks it down for either reuse or removal from the body. Certain macrophages trigger the formation of antibodies by B cells. B cells are immune cells synthesized in the bone marrow. VIP is the hormone vasointestinal peptide, so named because it was first discovered in the gastrointestinal tract. For the purposes of this review, hormone will be taken to mean any chemical messenger, not just the steroid hormones associated with reproductive processes.

While there are a number of types of T-helper (Th) cells at play in immune system function, this review will focus just on the activities of Th1 and Th2 cells. Th1 cells are responsible for the immune function with which most of us are familiar; macrophage activity and B cell production of antibodies; they cause inflammation around injured or infected tissues. Th2 cells handle viruses and...
parasite invasions, increase allergic-type reactions including anaphylaxis, and inhibit the activity of Th1 cells, suppressing macrophage activity and antibody production. (While it is outside the scope of this paper, the improvements in hygiene and reduction in parasite exposure in Western societies may be implicated in the higher prevalence of reduced immune tolerance, as a result of lowered Th2 cell activity.)

The short explanation for why a system will move into autoimmune disease as opposed to tolerance (lack of an autoimmune response) is that it is due to an imbalance of Th1 versus Th2 cells in the body. A ratio that favors Th1 cells produces an autoimmune response, whereas the converse (one that favors Th2) promotes tolerance. Management of Th1/Th2 cell differentiation patterns is a promising frontier in autoimmune therapy.

Vasoactive intestinal peptide (VIP) is a hormone produced by cells in a number of different organs, including the pancreas and the thymus, originally thought to do most of its work in the gastrointestinal tract. VIP manages the flow of material through the stomach into the small intestines and acts as an anti-inflammatory in the intestinal lining. The work of Delgado, Jimeno, and Gomariz has uncovered a crucial mechanism for T cell differentiation directly related to a certain type of VIP produced by lymphocyte cells.

According to Delgado, VIP that is produced by the immune system has an inflationary effect on the production of Th2 cells, and also promotes their survival by selectively inhibiting Th2 cell apoptosis (programmed cell death). While this is not a new development in and of itself, it was Delgado who made the discovery that it is the endogenous form of VIP (VIP produced by lymphocytes acting on cells in the thymus itself) that does this specific work. The endogenous VIP up-regulates a receptor called VPAC2 that causes cells to deviate towards increased Th2 cell production, and rather than being mitigated by the increase, which is the usual case in biological processes, this loop increasingly self-perpetuates. Cells both continue to produce more VPAC2 receptors and preferentially differentiate to Th2 cells. Delgado’s article cites studies showing that in mice that express the VPAC2 receptor, stimulation with endogenous VIP caused increased VIP production and Th2 activity, and suppressed Th1 responses. The studies go on to demonstrate that in transgenic mice bred not to have the VPAC2 receptor, the opposite was the case.

Jimeno and Gomariz took Delgado’s work a step further, in applying it to treat mice bred to have type 1 diabetes. (This is the autoimmune form of the disease, not the one that occurs later in life in high-risk populations.) Type 1 diabetes occurs when Th1 cells migrate to the pancreas and destroy the β cells in the Islets of Langerhans. β cells are responsible for production of insulin, a hormone that is released when high glucose levels are detected in the blood, as in after a meal. Insulin instructs the body to take up this glucose for storage in various tissues. Without insulin supplementation, the body's fuel use and storage mechanisms fail. This form of diabetes is fatal if untreated; once these β cells are destroyed, the body does not produce any more.

Jimeno and Gomariz constructed a protocol to test the hypothesis that early intervention with endogenous VIP could tip the balance of Th1/Th2 cells back
towards tolerance and suppress β cell destruction in the pancreas, and a study conducted over the course of thirty weeks bore this out. Female type 1 diabetic mice were injected intraperitoneally (in the abdomen) every other day from 4 to 30 weeks of age with a solution of 2.5 µmol of VIP in 200 ml phosphate-buffered saline. (Control animals received saline alone.) Levels of β cell destruction were markedly reduced in mice that received VIP injections over mice that did not. A number of Th2 cell chemical markers, in addition to blood glucose levels, were measured weekly. Mice that received VIP injections showed significantly increased Th2 cell activity and developed diabetes much more slowly, and to a much lesser degree, than their saline-injected counterparts.

Autoimmune diseases like Type-1 diabetes, while serious, are manageable with existing therapies such as blood glucose monitoring and insulin supplementation. Other autoimmune disorders, however, are more serious. In multiple sclerosis (MS), the Th1 cells slip past the blood/brain barrier that normally segregates blood from nervous tissue and attack the myelin sheaths on nerves. These sheaths are responsible for the transmission of electrical impulses to and from the brain. Their destruction results in an inability of the brain to control both voluntary and autonomic movements and impulses, and is eventually fatal. In rheumatoid arthritis (RA), Th1 cells send inflammatory macrophages to the joints, and the resulting proliferation of rapidly dividing inflammatory cells destroys the joint capsule and then invades the surrounding bone and muscles.

RA is both debilitating and painful. And like type 1 diabetes, neither MS nor RA can be cured or reversed.

Unlike diabetes, however, the only available treatments for MS and RA are palliative. If there were a way to interrupt the autoimmune response at an early stage, the progression of these syndromes could be paused or delayed, and patient outcomes could be much improved. Crippling disorders could be transformed into chronic ones, and untold pain and suffering could be prevented. While researchers are years away from clinical applications, initial studies are both exciting and promising. And as the number of Americans with autoimmune disease continues to rise, the new developments can't come fast enough.