CALL FOR PAPERS | Integrative and Translational Physiology: Inflammation, Immunity, and Organ System Physiology

Just not himself these days: an invitation to submit papers on the topic of inflammation and immunity in organ systems physiology and pathophysiology

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When someone is acting oddly, it is often said that she or he is “not herself” or “not himself.” This generally refers to a change in personality, either due to distraction, stress, or some other emotional alteration. During the past decade, a new interpretation of this phrase has arisen. This relates to the contribution of immunity to a variety of common, chronic diseases.

The concept of self, when used in the context of immunity has a very different connotation compared to its use above. A fundamental property of immunity is to recognize non-self and to protect self. This is an extremely primitive response, present in single-cell organisms, prokaryocytes, and nonvertebrates. For example, bacteria contain restrictionendonuclease enzymes, now commonly used as tools for molecular biology research, which chop up DNA of viruses but not their own DNA. Sponges, which evolved during the metazoan period, possess the capacity to engulf bacteria into specific cells, display signaling responses to bacterial products, and produce reactive oxygen species and nitric oxide to kill foreign organisms (6). Sponges will not graft with those of other species, but will readily form allografts with sponges of the same species (24).

On the basis of these considerations, diseases have been dichotomously classified as autoimmune and everything else. The classic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, systemic sclerosis, Sjogren’s syndrome, vasculitides, and inflammatory bowel diseases are unique, unfortunate conditions in which the immune system fails to recognize self, attacks various tissues leading to severe, life-threatening pathology. These disorders often respond to immune suppression, and new therapies have been developed that modulate, but do not entirely suppress the immune response, which have been used successfully to treat these conditions.

The problem with this simple division of diseases is that it is overly simplistic. Cells of the innate and adaptive immune system show up in various tissues affected by diseases not traditionally viewed as autoimmune. As an example, we have known that cells of both the innate and adaptive immune system are present in atherosclerotic lesions of humans for more than a century and a half (8). This isn’t terribly surprising, because monocytes and lymphocytes travel in and out of tissues as part of immune surveillance, and these cells might be simply “cleaning up” diseased cells or walling off an inflammatory process. In the last three decades, however, it has become clear that these cells are activated and are releasing mediators, or cytokines, that contribute to the disease process (11). Studies of mice with experimental atherosclerosis have revealed that these T cells and their mediators contribute to lesion formation. More recently, the adaptive immune system has been implicated in experimental hypertension. T cells and macrophages infiltrate the vasculature and kidneys of hypertensive mice and rats and contribute to blood pressure elevation in these models (12). These cells also accumulate in adipose tissues of overweight humans and animals (27) and seem to contribute to insulin intolerance, atherosclerosis, endothelial dysfunction, and dyslipidemia, which accompany obesity (19). T cell activation and cytokines contribute to bone loss caused by estrogen deficiency (10). Microglial cells, which are resident macrophages of the brain, are activated in hypertension and over nutrition (21, 26).

There are also numerous instances where immune-mediated diseases overlap with nonimmune diseases. As an example, it has recently been shown that asthmatics have more than a twofold increase in type 2 diabetes and about a 1.5-fold increase in coronary artery disease (28). Cardiovascular diseases such as hypertension and coronary artery disease are increased among subjects with systemic lupus erythematosus, psoriasis, and rheumatoid arthritis (3, 7, 16).

Why do cells designed to protect us against disease begin to attack our vessels, kidneys, bones, liver, and brain to promote chronic diseases such as hypertension, atherosclerosis, diabetes, and osteoporosis? An attractive paradigm is that in these conditions, initial triggers alter endogenous molecules such that they are no longer recognized as “self.” This could involve extracellular release of proteins or other molecules that are generally intracellular, posttranslational modification of endogenous molecules, cleavage of proteins to expose intramolecular sites normally not available for immune recognition or by attachment of an unusual epitope to a molecule in a hapten-like fashion. Immunoreactive molecules such as these have been found in the serum of humans with cancer (5), in inflammatory diseases such as halothane-induced hepatitis (15), in patients with glomerulonephritis (25), and in the setting of osteoarthritis (14). Molecules proposed to cause immune responses in atherosclerosis include oxidized LDL, heat shock proteins, platelet glycoproteins, and others, although no specific antigen has been identified with certainty (9).

There are two predominant theories to explain how these altered molecules, no longer recognized as self, produce dis-
ease. One concept is that these serve as new ligands for various pattern recognition receptors that promote innate immune responses. An example is activation of toll-like receptors (TLRs) by modified lipoproteins, heat shock proteins, fibronectin, and breakdown products of the extracellular matrix. Oxidized lipoproteins activate TLR4 in a manner similar to bacterial coat proteins (22, 18). TLR ligation activates NF-κB, leading to production of myriad cytokines, chemokines, and molecules involved in T cell costimulation. TLR ligation on T cells and dendritic cells directs T cell polarization that in turn has long-lasting effects on the inflammatory milieu (23). A second theory as to why modified “self” molecules cause disease is that they serve as neoantigens. This is less well understood, but posttranslationally modified proteins can be processed by antigen-presenting cells and activate CD4+ T cells (13). Oxidatively modified proteins, taken up by scavenger receptors of macrophages can activate CD4+ cells (20), and adoptive transfer of CD4+ cells activated in this fashion aggravates atherosclerosis in ApoE−/− mice (29). Oxidized lipoproteins also stimulate formation of auto-antibodies and are targets of naturally occurring IgM antibodies (1, 2).

Numerous diseases seem to involve these kinds of responses. These include experimental autoimmune encephalitis induced by myelin basic protein injection, experimental colitis induced by chemicals that form haptons to colonic proteins, uveitis induced by injection of melanin-associated antigen, and experimental arthritis induced by collagen injection. It is very possible that the human equivalent of these disorders are caused by similar stimuli. The postpericardiotomy syndrome has been suggested to be triggered by release of cardiac proteins not normally encountered by the immune system, resulting in formation of autoantibodies (4).

Another mechanism underlying failure to identify self is modification of the immune system with aging. An example of this is the loss of CD28 in senescent T cells. The lack of CD28 limits the ability of these cells to be normally stimulated by classical T cell receptor ligation; however, they demonstrate abnormal gene expression and low levels of activation that contribute to aging-related rheumatoid arthritis and unstable coronary syndromes (17).

Why should there be a call for papers by the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology on the topic of Integrative and Translational Physiology: Inflammation and Immunity in Organ System Physiology and Pathophysiology? First, immune and inflammatory responses epitomize integrative biology and physiology. These require orchestrated signals from peripheral tissues, secondary lymphoid organs, the bone marrow, the vasculature, and the central nervous system. Second, this topic is clearly important. The concept that many chronic diseases such as atherosclerosis, osteoporosis, hypertension, and obesity are in part caused by smoldering autoimmunity represents a paradigm shift in understanding human disease and systems biology. Third, there has been enormous growth in our understanding of immunity, and new animal models, assays, and tools have made it possible to study other fields in substantial depth not previously possible. Finally, we clearly need additional information about this topic. We don’t understand the biochemical, physical, and molecular changes that activate the immune system in these conditions and how to stop this shift from “self” to “non-self.” Better comprehension of this topic could lead to specific therapies that would either halt this shift or modify the immune responses that promote disease. We hope that this call for papers begins to fill some of these needs and will spur the further work in this direction by talented integrative physiologists.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

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