How to Repeat a Success and Control a Bad Influence

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The manipulation of adaptive immunity is probably the most successful preventive and therapeutic strategy of modern medicine. Its roots go back to Edward Jenner, who in 1796 induced immunity to smallpox by inoculation with the related cowpox virus. Although the mechanism of action remained completely unknown for more than a century, the concept of vaccination spread rapidly around the world and had an immediate impact on population health. In Sweden, for instance, ≈20,000 people died of smallpox in 1800, just before the introduction of vaccination. Within 20 years, the death rate had fallen to 200! The insightful bishop, Esaias Tegnér, reported to the government that the population in his bishopric was increasing rapidly thanks to “peace, vaccine, and potatoes.” In 1980, the World Health Organization certified that smallpox had been eradicated in the entire world. From Pasteur and onward, the vaccination principle was used to control many other diseases in addition to smallpox. Together with the sanitation of water and foodstuff, it represents the most successful means of disease prevention ever accomplished.

Vaccination induces a T-cell response that helps B cells to react against antigen and start to produce high-affinity antibodies. The T-cell response also leads to the development of armed effector T cells with the capacity to kill target cells such as infected ones, and to the activation of macrophages to promote inflammation. In this way, the T-cell response initiates both humoral and cellular immunity to the immunogen. The relative importance of these 2 effector arms of adaptive immunity varies between vaccines, but the general principle operates in all vaccination protocols.

The immune response elicited by vaccination mimics the one triggered by an invading pathogen. It also resembles the pathological immune responses observed in autoimmune conditions and chronic inflammatory diseases. In these situations, autologous molecules are erroneously recognized as antigens. The ensuing immune response attacks tissues containing these molecules, leading to cell death, tissue destruction, and repair processes. Several immune effector systems contribute to these attacks, including cytotoxic T cells, complement-activating antibodies, phagocytizing macrophages, and other cells.

As a potentially dangerous defense system, the immune response is regulated by several sets of inhibitory cells and molecules. Foremost among them, regulatory T cells (Treg) dampen immune responses by inhibiting effector T-cell activity, B-cell and macrophage activation, and inflammatory responses. Several subtypes of Treg have been identified in the CD4 and CD8 T-cell families, with immunosuppressive activity mediated by the cytokines interleukin-10 and transforming growth factor-β.

Complex regulatory loops allow for fine-tuning of the immune response in such a way that an invading pathogen can be eliminated with minimal damage to the host organism. A slight imbalance in the response to a low-intensity pathogen or to endogenous molecules, can lead to a chronic inflammatory condition.

Successful treatment of pathological immune responses has been achieved by interfering with immune cell activation or with effector cytokines that drive pathological inflammation. The first immunosuppressive drug, azathioprine, was discovered by Gertrude Elion and George Hitchings, who were awarded the Nobel Prize in 1988. Azathioprine inhibits DNA synthesis that is required for the proliferation of activated B and T cells. It made organ transplantation between nonidentical humans possible and has been used to treat many autoimmune diseases.

Further progress was made when the T-cell–specific immunosuppressants, cyclosporine, sirolimus, and tacrolimus, were identified. Their side effects are less significant than those of azathioprine, and they are used not only to prevent graft rejection, but also to treat a broad range of chronic inflammatory diseases, from autoimmune hepatitis to arterial restenosis.

A second approach to immunotherapy is to eliminate T and B cells by using cytolytic antibodies. Monoclonal anti-CD20 antibodies that eliminate B cells have been particularly useful in the treatment of autoimmune diseases.

A third major breakthrough was achieved by blocking the action of proinflammatory cytokines that mediate immunopathology. Tumor necrosis factor was known to be a major proinflammatory cytokine and Marc Feldmann identified it as a driving force in joint inflammation. Together with Ravinder Maini, he developed tumor necrosis factor blockade as a therapy against rheumatoid arthritis, a strategy that has revolutionized the treatment of this disease. Additional strategies involve blockade of interleukin-1, interleukin-6, and several other cytokines.

All this progress in immunotherapy has had an enormous impact on transplantation, autoimmunity, and pathological inflammation. However, existing therapies all have potentially serious side effects and it would be desirable to have more subtle manipulations of the immune system at hand, particularly for chronic inflammatory conditions that require long-term treatment. Recent insights into immune regulation may offer possibilities for such treatment strategies.
Atherosclerosis is a chronic inflammatory disease elicited when cholesterol-containing lipoproteins accumulate in the arterial intima. Its pathology involves macrophages, different sets of T cells, and antibodies to low-density lipoproteins. Whereas early immune activity is observed in intimal lesions, advanced atherosclerosis is accompanied by periadventitial formation of tertiary lymphoid structures resembling germinal centers of lymph nodes.

Human atherosclerotic lesions contain both CD4+ and CD8+ T cells. In contrast, murine lesions are dominated by CD4+ T cells and nearly all mechanistic studies of the cellular immunology of atherosclerosis have focused on the CD4+ subtype. Similarly, most experimental research on humoral immunity in atherosclerosis has dealt with natural immunoglobulin M antibodies produced by B1 type B cells, although significant numbers of high-affinity immunoglobulin G (IgG) antibodies can also recognize low-density lipoprotein.

The role of B cells in atherosclerosis is controversial. Transfer of spleen cell preparations containing both B1, marginal zone, and B2 cells protects against atherosclerosis, whereas antibody depletion data point to a proatherosclerotic role of B2 cells. Therefore, B1 cells were proposed to be atheroprotective, but B2 cells were assumed to exert a bad influence on atherosclerosis. The control of these disease-regulating immune activities has remained unclear.

In this issue of Circulation, Marc Clement, Antonino Nicoletti, and their coworkers have elucidated an important regulatory loop that controls atherogenesis via B-cell modulation. They unravel a sophisticated network for disease control in which mature B cells (B2) producing high-affinity IgG antibodies are stimulated by help from antigen-specific T-helper follicular (Tfh) type CD4+ T cells. The latter are, in turn, controlled by a negative signal from CD8+ Treg.

Although B1 cells make low-affinity natural antibodies continuously and as a direct response to antigen, the production of high-affinity IgG antibodies by B2 cells and plasma cells requires T-cell help. In this way, the T cell can control the ensuing immune response by directing only certain antigen-specific B cells to divide, reorganize their immunoglobulin genes, and start producing high-affinity IgG antibodies to the antigen in question. The Tfh cell type is specialized in providing help for B cells. To perform this function, it is present in lymphoid follicles of secondary lymphoid organs, where B-cell differentiation takes place. When follicular B cells react to antigen presented by follicular dendritic cells in the presence of Tfh cells, large amounts of high-affinity antibodies can be produced within a short period of time. This response plays a crucial role in host defense against many bacteria, virus, and toxins. If the stimulus persists, tertiary lymphoid structures are formed when Tfh and B cells migrate into inflamed organs and tissues such as the adventitia surrounding atherosclerotic lesions.

If B cells start to produce high-affinity IgG antibodies that react to self-molecules, a potentially detrimental autoimmune situation arises. Therefore, Tfh cells are controlled by inhibitory signals from CD8+ Treg. The latter cells depend for their activity on an major histocompatibility complex molecule called Qa-1 in the mouse and HLA-E in humans.

Clement et al first observed that Tfh and mature, germinal center (GC)-type B cells expanded during atherosclerosis in Apoe−/− mice. They probed the Treg-Tfh axis by using a point mutation that abrogates the interaction between Qa-1 molecules on Tfh cells and the T-cell receptor on CD8+ Treg. In the absence of Treg-mediated inhibition, the Tfh population expanded further, as did GC B cells. In the Apoe-deficient mouse, atherosclerotic lesions were significantly increased in this situation, as were the size and number of adventitial tertiary lymphoid structures harboring IgG producing B cells and plasma cells.

To confirm the critical role of the Treg-Tfh axis, the authors bypassed the defective Qa-1 molecules by ligating the inducible costimulatory molecule that directly inhibits Tfh cells. This treatment reversed the phenotype of the Qa-1 mutation and normalized lesion size.

Finally, the authors established that the Tfh-GC B-cell axis operates in human vascular disease. This was possible in patients who underwent surgery for abdominal aortic aneurysms. During this procedure, the entire aortic wall is removed including the adventitia. In contrast, atherosclerotic lesions are usually treated by procedures that do not permit examination of the adventitial layer. Abdominal aortic aneurysm adventitia contained B-cell follicles with Tfh cells, similar to tertiary lymphoid organs of mice with advanced atherosclerotic disease. Importantly, abdominal aortic aneurysm tissue released IgG molecules, indicating the production of these immunoglobulins by GC B cells and plasma cells, and also interleukin-21, a signature cytokine of Tfh cells.

The take-home message of the Clement article is that the Tfh-GC B-cell axis is proatherogenic, that it operates in adventitial tertiary lymphoid organs, that it is controlled by CD8+ Treg, and that it can be manipulated. Thus, interference with Treg-Tfh signaling increased atherosclerosis, whereas the direct delivery of an inhibitory signal to Tfh cells reduced it.

The findings by the Nicoletti-Caligiuri laboratory may offer an opportunity to inhibit atherosclerosis by dampening the GC B-cell response. Will it result in benefit of the same magnitude as that achieved, for instance, by Feldmann and Maini? If not, we will need to know if the Treg-Tfh-GC B-cell axis contains therapies suitable for attack in human atherosclerotic disease. The magnitude of the medical problem argues that this line of research should be pursued vigorously.

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Disclosures

None.

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