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EDITORIAL COMMENT

Taming Immune and Inflammatory Responses to Treat Atherosclerosis*

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Writ large, we can divide immune and inflammatory responses into the primitive innate immune response and the evolutionarily more recent adaptive immune response. Innate immunity mobilizes swiftly in response to signals derived from pathogens or damaged cells. Adaptive immunity arises more slowly but shows exquisite selectivity, with the ability to recognize a wide gamut of specific structures. The adaptive immune response encompasses both antibodies, generally derived from B lymphocytes, and cellular responses engendered by specific antigens mediated by T lymphocytes.

Although we have known that T cells reside in the human atherosclerotic plaque for more than 3 decades (1-6), the concept that adaptive immunity participates functionally in lesion formation and evolution took time to hold sway. The suggestion that immunity may play a role in atherosclerosis initially met considerable skepticism (7). Now, the bulk of the experimental evidence supports a causal role for the immune system as a modulator of atherosclerosis. Yet harnessing the adaptive immune response to modulate human atherosclerotic disease therapeutically has remained an elusive goal (8,9).

We continue to learn about the subtleties of the immune response during atherogenesis (10). The powerful arsenal of host defenses possessed by the immune system appears not only to potentiate disease development. Counter-regulatory mechanisms put a brake on immune responses to prevent runaway collateral damage to normal tissues while combating pathogens or repairing injury (**Figure 1**). Natural antibodies produced by B1 lymphocytes appear to protect against atherosclerosis, while antibodies made by B2 lymphocytes may boost lesion formation. Likewise, whereas proinflammatory T helper (Th) 1 lymphocytes aggravate atherogenesis, regulatory T cells may mitigate this process. Furthermore, signals derived from yet other T cell subtypes, such as Th2, T follicular helper cells, and Th17 cells, may also influence lesion composition by producing cytokines, promoting macrophage activation, or providing help to B cells in generating antibodies. Thus, adaptive immune mechanisms, Janus-like, can either promote or quell inflammatory responses. Trying to tame this multifaceted and complex armamentarium to alleviate atherogenesis without compromising host defenses represents a major translational goal of the field of immunology of atherosclerosis.

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In this issue of the *Journal*, Zeboudj et al. (11) present results obtained in hyperlipidemic, atherosclerosis-prone mice that furnish a new angle in the quest to modulate selectively adaptive immunity in a manner that could calm atherogenesis. These investigators take a page from the playbook of oncology, an example of the current convergence of cancer and cardiology. A number of targeted therapies have revolutionized cancer treatment. Checkpoint inhibitors unleash T lymphocytes to attack

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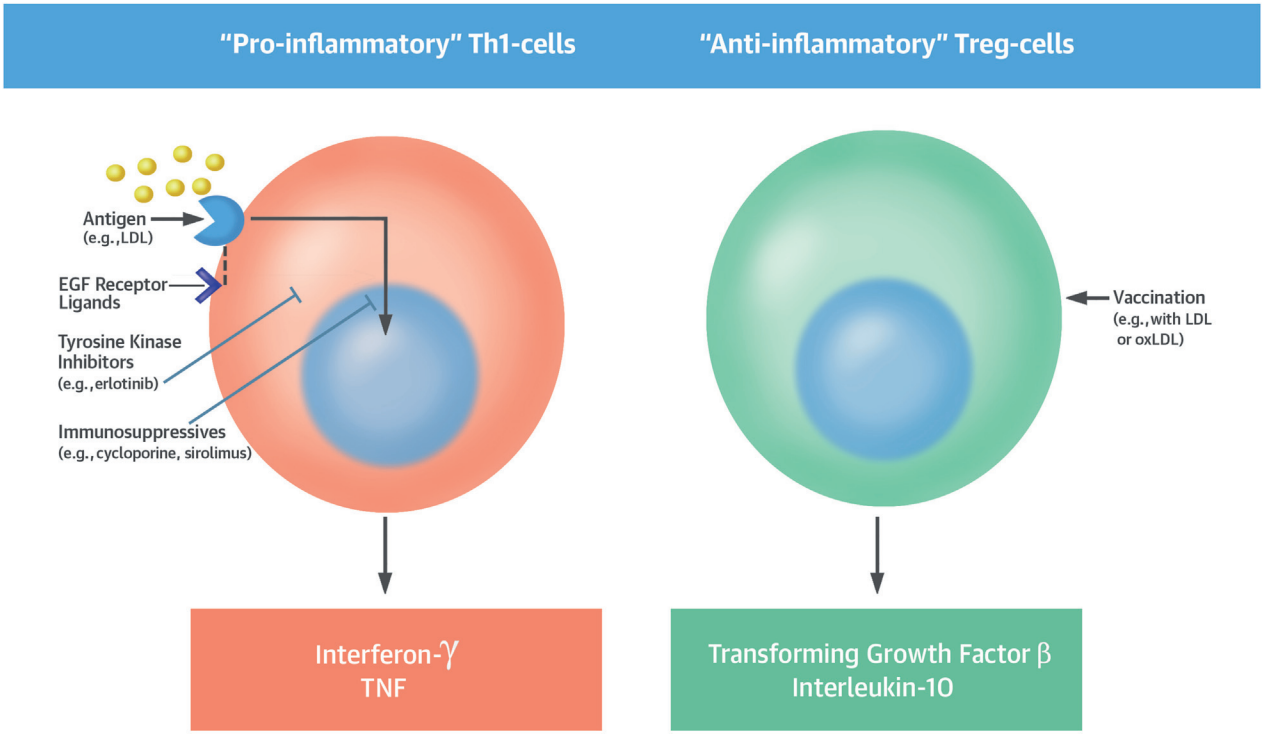
FIGURE 1 T Cell Subsets Can Either Promote or Mute Immune Responses



T cells with a proinflammatory functional slant (e.g., T helper [Th] 1 lymphocytes) secrete cytokines, such as interferon-gamma and tumor necrosis factor (TNF), that generally promote atherogenesis. Specific antigens activate T cells in a process that is enhanced by epidermal growth factor (EGF) receptor signaling. Immunosuppressive agents and tyrosine kinase inhibitors that inhibit signaling from the EGF receptor (and some other receptors) can impede T cells and render them unresponsive to antigenic stimulation. Other classes of T cells (e.g., regulatory T cells) exhibit an "anti-inflammatory" slant upon antigen-dependent activation. Regulatory T cells secrete proteins that on the balance limit inflammation, such as transforming growth factor–beta and interleukin-10. Yet other classes of T cells (Th2 and Th17) modulate lesion development in other ways (22). Vaccination strategies may promote the predominance of atheroprotective, anti-inflammatory T lymphocyte populations. LDL = low-density lipoprotein; oxLDL = oxidized low-density lipoprotein.

tumors and have in some cases rendered previously ineluctably progressive cancers a chronic disease. Selective inhibitors of various tyrosine kinases can inhibit the intracellular signaling that follows binding to their receptors of protein growth factors that drive certain tumors and block the growth factors' pro-proliferative actions. For example, epidermal growth factor (EGF) and other protein ligands of the EGF receptor can promote proliferation of cells in lung cancers. A selective inhibitor of the tyrosine kinase, erlotinib, which mediates the action of the EGF receptor, has clinical utility in the treatment of such tumors.

Zeboudj et al. (11) found that mouse T cells can express the EGF receptor and that this inhibitor of the tyrosine kinase that mediates EGF receptor action blocked the proliferation of T cells stimulated with a polyclonal activator in vitro. Treatment of atherosclerosis-susceptible mice with erlotinib interfered with T cell responsiveness, lowered the burden of T cell accumulation in the experimental atheromata, and limited lesion formation. Further experiments using various genetic approaches pinpointed the EGF receptor on CD4-positive T cells as responsible for these protective actions on experimental atherogenesis. As erlotinib has received approval for clinical use by regulatory authorities, these exciting observations in mice suggest a novel therapy for atherosclerosis.

These elegant experiments raise a number of questions that provide a fertile field for future research. Curiously, the investigators found no increase in the supposedly anti-inflammatory cytokines interleukin-10 and transforming growth factor-beta in regulatory T cells, which could limit immune stimulation in response to certain interventions. The detailed cellular and molecular pathways of the inhibition of lesions will require further elucidation.

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