Despite 50 years of research, the cause of Kawasaki disease (KD), the most common cause of acquired heart disease in children, remains a mystery. Fueled by epidemiological and clinical clues that the disease is triggered by an infectious agent that elicited a dramatic immune response in genetically susceptible children, investigators vigorously searched for the responsible agent. Thus far, a long list of discarded pathogens is all that remains of these attempts to find the inflammation-causing agent. Application of reverse genetics to engineer synthetic antibodies to track down a putative new virus has shown some promise, but the agent remains elusive.

In the absence of knowledge of the etiologic agent, animal models were created that recapitulate the pathological changes observed in human tissues. KD was a prime candidate for modeling: The disease was rarely fatal, so well-preserved autopsy tissues were difficult to find; the primary target of the vasculitis, the coronary arteries, could not be biopsied in living children; and a better understanding of disease pathogenesis was needed to devise new therapeutic approaches. It was in the spirit of meeting these challenges that 2 major mouse models of KD were created. The first, created by Dr Murata in Tokyo, used intraperitoneal injection of a cell-wall extract of Candida albicans to induce a coronary arteritis in susceptible inbred strains of mice. The model recreated the histopathology and features of the immune activation seen in children with KD, and the extract created inflammation only in certain genetic backgrounds. Furthermore, the induced inflammation could be quelled with the same immunomodulatory treatments shown to be effective in children.

The second major model was an outgrowth of a rat arthritis model in which a single intraperitoneal injection of Lactobacillus casei cell-wall extract (LCWE) induced polyarthritis in rats and coronary arteritis in mice. The coronary arteritis is responsive to treatment with intravenous immunoglobulin, the mainstay of therapy for children with KD. This model has also been exploited to demonstrate the beneficial effects of monoclonal antibody blockade of tumor necrosis factor-α, an approach that is currently under study in 2 clinical trials of pediatric patients with acute KD. Other therapies demonstrated to be beneficial in this mouse arteritis model include matrix metalloproteinase inhibition with doxycycline and atorvastatin. Conversely, blockade of the transforming growth factor-β signaling pathway with the angiotensin receptor blocker losartan proved deleterious and exacerbated the coronary arteritis.

In the article by Lee et al in this issue of Circulation, a new therapeutic target for KD is identified. With the LCWE mouse model, a logical progression of experiments demonstrated that (1) bone marrow–derived macrophages secrete high levels of interleukin-1β (IL-1β) and tumor necrosis factor-α, (2) IL-1β is processed from pro–IL-1β by caspase-1 through the NRP3 inflammasome, (3) exogenous treatment with IL-1β recreates the inflammatory phenotype in caspase-1–deficient mice, and (4) IL-1 receptor–deficient mice or mice treated with the recombinant IL-1 receptor antagonist anakinra fail to develop the arteritis lesions. Of particular note, only blockade of IL-1β, but not blockade of tumor necrosis factor-α, reduced the myocarditis in the LCWE-injected mice. The dramatic nature of the coronary artery aneurysms in KD tends to overshadow the potential importance of the concomitant myocarditis that is present in 100% of patients. The significance of the myocarditis with the potential for postinflammatory fibrosis as a sequela has not been adequately studied. Therefore, it is of interest that anakinra was able to reduce both coronary arterial and myocardial inflammation in the LCWE model.

Studies documenting elevated levels of both IL-1β transcript and protein in KD patient peripheral blood are well summarized by Lee et al. Given our knowledge of the proinflammatory state in our patients and the implied involvement of IL-1β in this inflammatory cascade, should this new study lead to clinical trials of IL-1β blockade in children with KD? Although both the LCWE and Candida albicans models have correctly mirrored the responses to immunomodulatory agents seen in our patients, a cautionary word is in order. In the LCWE model of IL-1β blockade, anakinra was injected either before or up to 3 days after induction of the arteritis. Data from a variety of sources suggest that the vasculitis of KD in humans has been active for weeks before the onset of fever and the clinical presentation with mucocutaneous inflammation. The lines of evidence to support this concept are varied and include the presence of circulating effector memory T cells that take weeks to mature and be detectable in the peripheral blood. In addition, patients can present with aneurysms within the first few days after the onset of fever, and two-thirds of patients have a normocytic,
normochromic anemia at presentation that is consistent with suppression of erythropoiesis and the anemia of chronic disease.19 Thus, we must question whether antiinflammatory therapy in KD is always too little, too late. That said, a number of safe, approved therapeutic options for IL-1 blockade are currently available. The newest therapy, canakinumab (anti–IL-1 monoclonal antibody), is currently in clinical trials for various pediatric inflammatory diseases. In cardiovascular disease, the effect of IL-1 blockade is under study in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial, which will examine the combined cardiovascular end points of recurrent myocardial infarction, stroke, and cardiovascular death after treatment with canakinumab (anti–IL-1 monoclonal antibody) in a cohort of patients with atherosclerosis and a history of myocardial infarction.20

Given the current state of therapy in KD with 15% to 20% of patients failing to respond with cessation of inflammation after a single dose of intravenous immunoglobulin, pediatricians are eager for alternatives that will be safe and effective. On the basis of the current data from both mice and children, a clinical trial of intensification of initial therapy with a combination of intravenous immunoglobulin and IL-1 blockade may be warranted.

Disclosures

None.

References

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