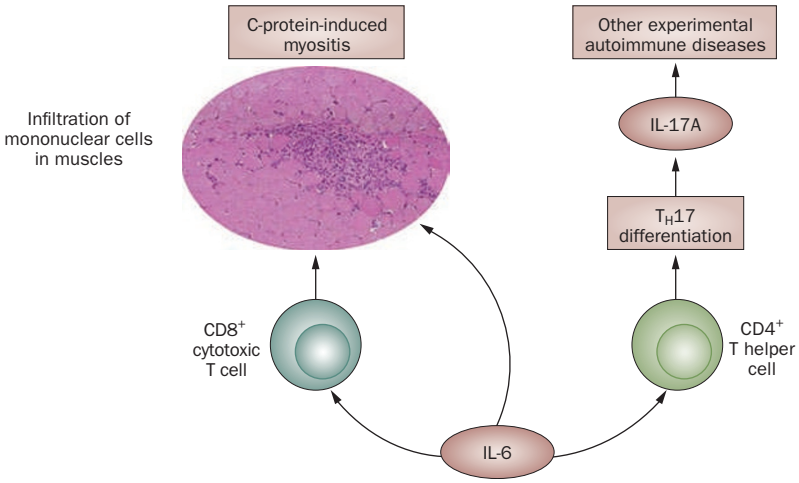
INFLAMMATORY MYOPATHIES

Polymyositis therapy: is there a place for IL-6 blockade?

New research from Tokyo, Japan could help clarify the role of proinflammatory mediators in the pathogenesis of chronic inflammatory myopathies, such as polymyositis and dermatomyositis. Elevated interleukin (IL)-17 levels are increasingly implicated in experimental models of autoimmune diseases, but Hitoshi Kohsaka and colleagues have now shown that mice lacking IL-17A can still develop polymyositis. The investigators suggest that IL-6 might be the culprit and could, therefore, be a candidate for future studies of myositis therapy.



Therapeutic options for patients with idiopathic inflammatory myopathies are limited, partly owing to a lack of suitable animal models in which to explore disease pathways and possible therapeutic targets. In 2007, Kohsaka and colleagues developed a novel model of myositis that involved injecting B6 mice with fragments of recombinant skeletal C-protein, a myosin-binding protein that regulates the structure and function of muscle filaments. "C-protein-induced myositis [CIM] is much more like human polymyositis in pathology than previous models, including the commonly used experimental autoimmune myositis, which is induced with crude myosin extract," explains Kohsaka.

IL-17A is thought to be vital for the induction of experimental autoimmunity, and the role of IL-6 in the development of IL-17-producing T cells is well known. In addition, IL-6 blockade has been shown to attenuate disease activity in several models of autoimmune disease, presumably via the suppression of T-helper-17 cell differentiation and IL-17 secretion. To further explore the contribution of the IL-6–IL-17 pathway in polymyositis, Kohsaka *et al.* injected B6 mice lacking either IL-6 or IL-17A with recombinant C-protein. As their previous study had shown a strong correlation between muscle function and histological scores, they obtained sections of the femoral and extensor muscles for histological analysis. As expected, 21 days after immunization with C-protein, most of the IL-6 knockout mice (five of six) showed no histological signs of CIM. By contrast, six out of the seven IL-17A-null mice developed CIM, which was characterized by increased mononuclear cell infiltration and IL-6 expression in the muscle tissue. "Therefore, CIM is the first inducible model that does not depend on IL-17A," says Kohsaka.

Next, the researchers looked at the effects of IL-6 blockade in this model. Mice injected with anti-IL-6 receptor monoclonal antibodies at the time of immunization had reduced disease incidence and less-severe histology scores than their wild-type littermates. Furthermore, 7 days after immunization, the point at which mononuclear cell infiltration first became evident, anti-IL-6 treatment alleviated disease. "Although IL-6 blockade abrogated IL-17A-producing cells, the latter were dispensable for a therapeutic effect. Researchers tend to think that IL-6 works in autoimmune models by interfering with T helper cell differentiation, but they might need to be careful about making this assumption," warns Kohsaka.

Professor Ingrid Lundberg, head of the myositis research team at Karolinska University Hospital, Sweden, believes that these results are of great interest and "give support for a role of IL-6 in this animal model of myositis". Lundberg points out, however, that the study has some limitations. "Weaknesses of the study include the lack of muscle strength and fatigue testing ... Likewise, data on IL-6 expression in the muscles after antibody treatment would be of interest, as would assessments of MHC class I expression in the muscle fibers before and after treatment with IL-6 antibodies." MHC class I expression is a characteristic histopathological feature of myositis, and seems to correlate with the presence of muscle weakness both in patients and in an animal model of myositis.

Biologic agents targeting IL-6 (such as tocilizumab) are already used in the clinic to treat other autoimmune inflammatory disorders including rheumatoid arthritis, prompting Kohsaka *et al.* to suggest that more research into IL-6 blockade for the treatment of inflammatory myopathies is warranted. Lundberg agrees: "It would be very interesting to test treatment with IL-6 antibodies in patients with polymyositis, and probably also dermatomyositis."

Negin Nassabeh

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