Medicine, Drug discovery

Pathogenesis of dermatomyositis

Department of Dermatology, Graduate School of Medicine
Professor Manabu Fujimoto

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Abstract

Dermatomyositis is a prototypic connective tissue disease, of which the pathogenesis is autoimmunity. Autoantibodies against transcriptional intermediary factor 1-γ (TIF1-γ) are positive in approximately 20% of patients. increase. In this study, we established a novel mouse myositis model that was induced by the immunization with human TIF1-γ protein. This new animal model is considered to mimic the pathophysiology of human dermatomyositis, and is expected to serve as a useful tool for development and screening of new therapeutic agents.

Background & Results

Connective tissue diseases are classified as systemic autoimmune diseases. They are life-threatening intractable diseases, and therapy based on specific pathogenesis has yet been developed, except for rheumatoid arthritis. Dermatomyositis presents with muscle weakness due to muscle inflammation and characteristic skin lesions. The elucidation of the pathogenesis has been delayed, mainly because there have been no animal disease model relevant with human disease.

In recent years, a number of myositis-specific autoantibodies have been discovered in dermatomyositis. Since they correlate closely with clinical manifestations, they are not only useful biomarkers for predicting complications and treatment responsiveness, but also for studying molecular mechanisms of how the disease develops. One of the major dermatomyositis-specific antibodies is the anti-TIF1-γ antibody. In this study, we established a mouse model that develops myositis by immunization with TIF1-γ protein.

A human TIF1γ full-length protein with post-translational modification similar to that of mammals was prepared and purified using a synthetic system using baculovirus, and repeatedly subcutaneously administered to mice together with adjuvant. As a result, we found that myositis developed in the thigh muscles. Histopathological findings included the infiltration of inflammatory cells, mainly CD8+ T cells surrounding the muscle fibers as well as perifascicular atrophy, a typical finding of human dermatomyositis. Furthermore, the transfer of CD8+ T cells from mice in which myositis has been induced to naive mice was able to induce myositis. Thus, CD8+ T cells have an essential role in this myositis model.

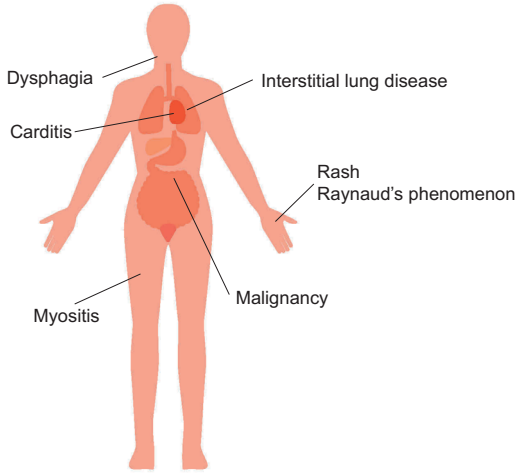
Type I interferon is considered to be strongly involved in the development of human dermatomyositis. In this study, mice deficient for type I interferon receptor were shown to exhibit milder muscle disease. In addition, administration of a Janus kinase (JAK) inhibitor, which blocks cytokine signals such as type I interferon, suppressed the development of myositis.

Significance of the research and Future perspective

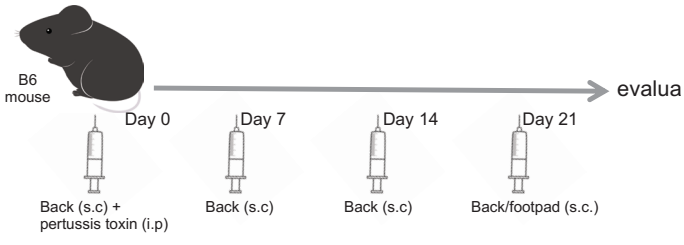
This myositis mouse model can be induced by immunization of self-antigens that have been present in human diseases. Therefore, this model will be useful for the development as well as evaluation of therapeutic agents.

Anti-TIF1-γ antibody-positive dermatitis is known to be associated with malignancy. It is postulated that mutation in the TIF1-γ gene, which acts as a tumor suppressor gene, in malignant tumors induces an autoimmune response. Then, as was demonstrated in this study, the immune response to TIF1-γ actually causes myositis. In this way, we can comprehensively explain the whole processes of a prototypic connective tissue disease. Therefore, this novel mouse model of myositis is considered to have great significance for elucidating the molecular mechanism of how this disease develops.

Various manifestations in dermatomyositis and polymyositis



Mouse myositis model induced by TIF1γ immunization



Human TIF1g recombinant protein and adjuvant

Patent
Treatise Okiyama, N; Ichimura, Y; Shobo, M; Tanaka, R et al. Immune response to dermatomyositis-specific autoantigen, transcriptional intermediary factor 1 γ can result in experimental myositis. Ann Rheum Dis. 2021 Sep; 80(9): 1201-1208. doi: 10.1136/annrheumdis-2020-218661.
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