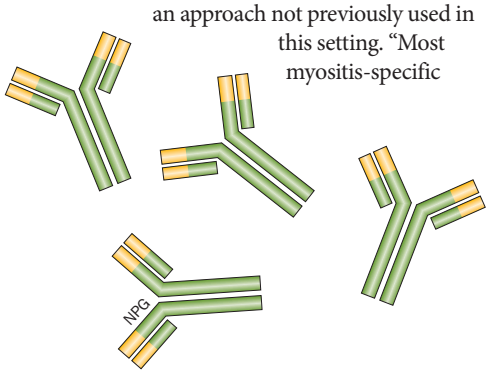
Nature Reviews Rheumatology | Published online 26 November 2015; doi:10.1038/nrrheum.2015.168

INFLAMMATORY MYOPATHIES

Anti-FHL1 antibodies linked to IIM

Mutations in the *FHL1* gene (which encodes FHL1, also known as skeletal muscle LIM-protein 1, a key modulator of muscle mass and strength) can cause severe X-linked hereditary myopathies. However, until now, FHL1 was not thought to be implicated in idiopathic inflammatory myopathies (IIMs). In newly published research, Inka Albrecht and colleagues show that anti-FHL1 autoantibodies are present in a subset of patients with IIM who have severe skeletal involvement and features indicating a poor prognosis. "Anti-FHL1 reactivity was predictive of pronounced muscle fibre damage, vasculitis, muscle atrophy and dysphagia," Albrecht clarifies.

The researchers used a muscle-specific cDNA library screen to identify novel autoantigen targets, an approach not previously used in this setting. "Most myositis-specific autoantibodies are directed against ubiquitously expressed intracellular antigens and are not muscle-specific," notes Albrecht. "We aimed to identify muscle-specific autoantigen targets involved in immune-mediated processes because we wanted to understand the initiation and perpetuation of chronic autoimmune mechanisms in muscle tissue affected by myositis." FHL1 was selected for further characterization owing to its known association with myopathy but, as Albrecht points out, this global methodology is also capable of identifying further autoantigens.



Sera from 141 patients with IIM were analysed alongside sera from patients with other rheumatic diseases (19 with mixed connective tissue disease, 67 with rheumatoid arthritis, 35 with primary Sjögren syndrome, 33 with systemic lupus erythematosus, 32 with systemic sclerosis), nine patients with non-inflammatory neuromuscular diseases and 126 healthy controls. 25% of the patients with IIM had anti-FHL1 autoantibodies, confirmed by ELISA, and their muscle tissue showed an altered expression pattern and cellular distribution of FHL1.

Albrecht *et al.* also showed that FHL1 can be cleaved *in vitro* by granzyme B, a protease linked to the formation of neoepitopes and breaking of self-tolerance in other autoimmune diseases. Moreover, in myositis-prone mice, immunization with FHL1 exacerbated muscle weakness and increased mortality. "Taken together," Albrecht concludes, "these data demonstrate a role for FLH1 in the pathogenesis of inflammatory myopathies." However, although FHL1 autoimmunity does occur early in the course of IIM, further investigation is needed to determine whether autoimmunity develops first and has adverse effects on muscle cells, or whether a pathogenetic process in muscle leading to the formation of neoepitopes drives the development of autoimmunity.

Albrecht and colleagues are now developing a standardized diagnostic assay for anti-FHL1 antibodies. This test could help to identify a subset of patients with severe myositis who are in need of specialized and aggressive treatment.

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ORIGINAL ARTICLE Albrecht, I. *et al.* Development of autoantibodies against muscle-specific FHL1 in severe inflammatory myopathies. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI81031