Systematic Protein-Protein Interaction and Pathway Analyses in the Idiopathic Inflammatory Myopathies

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Lay Summary

What was already known?

The Idiopathic Inflammatory Myopathies, also known as myositis, are a group of diseases where patients generally experience weakness and inflammation of skeletal muscles alongside a variety of other possible problems including difficulties swallowing, lung disease and skin rashes. Myositis is a complex disease, meaning that certain people are more likely to develop the disease due to their genetics but there is also some sort of trigger which may include lifestyle, pollution or other illnesses. Recently DNA samples were collected from myositis patients and healthy people across Europe and the US. These were used to find out which small changes in DNA are associated with the increased risk of developing myositis. Our current lack of understanding of how myositis is caused and exactly how it results in muscle damage means that there is also a lack of specific and effective treatments for myositis.

Myositis is an autoimmune disease, meaning that the body's immune system which normally protects against infections is actually damaging the body. Antibodies are normally produced as part of the body's immune response to infection and help to identify and stop the bacteria or virus by binding to particular proteins. In autoimmune diseases like myositis the immune system can incorrectly target proteins produced by the body as if they are parts of bacteria or viruses; these antibodies are known as autoantibodies. Many myositis patients have one or more autoantibodies. Autoantibodies have different effects depending on what proteins they target; in myositis it is currently unclear what role autoantibodies play in the disease. However, different autoantibodies are associated with different types of disease. For example, myositis patients with the autoantibody anti-TIF1γ are more likely to develop cancer.

What was discovered?

This study used online databases and programs to further investigate the genetic changes associated with myositis and how these might link to the proteins targeted by autoantibodies in myositis patients. Three types of associations were investigated; physical interactions between proteins, the pathways which these proteins are part of and the keywords that link these genes and proteins in previously published work.

Physical interactions between proteins

A program called 'Disease Association Protein-Protein Link Evaluator' (DAPPLE) was used to build networks of proteins that have been found to physically interact in previous experiments. These networks showed significant interactions between the proteins which may be affected by the DNA changes in myositis and the proteins targeted by autoantibodies in myositis. This means that these groups of proteins may be involved in the same pathways or processes in the body which, when they go wrong, contribute to myositis. In particular one protein, called TRAF6, acts as a 'hub' linking many of the proteins from each group. TRAF6 and other proteins found to have a significant number of links in the network are good candidates to be investigated in the laboratory in myositis patient samples or cell-lines.

Pathways

The genes/ DNA changes associated with myositis were also put into a search tool called the 'Database for Annotation, Visualisation and Integrated Discovery' (DAVID). DAVID shows how many of the genes in a list are in known biological pathways. This confirmed the known roles of some of the autoantibody targets and that the DNA changes associated with myositis probably affect genes involved in the immune response.

Keywords

To look at these DNA changes and autoantibody targets in a slightly different way, another tool called 'Gene Relationships Across Implicated Loci' (GRAIL) was used. This identifies where these gene names have been mentioned in published research and what keywords link them across these papers.

For the genes that may be affected by the DNA changes in myositis, the proteins targeted by autoantibodies and the two groups combined, the only keyword present in all three lists was 'ubiquitin'. Four out of five of the proteins with significant number of links in DAPPLE are known to be involved in a process called ubiquitination. These results suggest that this pathway may be involved in the disease process in myositis.

Why is this important/what is the benefit to patients?

This study suggests which proteins and genes to focus on in future laboratory work. This may help to direct research on myositis with the ultimate goal of finding targets for new treatments for myositis.