Higher body temperature alters key protein in autoinflammatory disorder

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Professor Mike Rogers. Credit: Garvan Institute of Medical Research

A new study from the Garvan Institute of Medical Research shows how rises in core body temperature may trigger the inflammatory flares in people with a rare genetic autoinflammatory disease.

The recessive disorder, called mevalonate kinase deficiency (MKD), is caused by mutations in the gene for mevalonate kinase, an essential enzyme present in all cells in the body. Lack of this enzyme leads to a build-up of abnormal proteins, which causes cells of the immune system to malfunction and trigger inflammation.

The condition usually appears in early childhood, and patients experience regular episodes of high fever and skin rashes, ulcers, swollen lymph nodes and abdominal pain. Very severe disease also causes neurological and developmental problems and can be fatal.

"Our research provides exciting new insights into the underlying physiology of MKD and what may be triggering the inflammatory flares, opening up potential new ways of treating this devastating disorder," says Professor Mike Rogers, Head of the Bone Therapeutics lab at Garvan.

The new study is published in the *Journal of Clinical Investigation.*

"There has been very little progress in understanding MKD, and in particular, what causes disease flares in MKD patients. One of the main reasons for this lack of knowledge is the absence of appropriate animal models to study the mechanisms of disease," says Garvan's Dr. Marcia Munoz, lead author of the study.

The team used gene editing approaches to develop new mouse models that mimic the metabolic mutation present in MKD patients. "An increase in core body temperature, for example, which could occur with stress or a mild infection, worsened the impact of the mutant enzyme and led to a dramatic build-up of abnormal proteins. This is a likely cause of the inflammatory flares in patients," says Dr. Munoz.

Why MKD has a broad range of disease severity is poorly understood. "The disease is caused by having two copies of the mutant gene and

there are more than 250 known mutations, so it's difficult to predict what combination causes a mild or severe version of MKD," says Professor Rogers.

The researchers developed different mutation combinations in models of the disease, with enzyme activity at 10% or 20% of normal levels.

"We discovered that there's a threshold of enzyme activity. At about 20% activity, there is no disease. Disease starts to appear if enzyme activity falls below this threshold, when the effect on proteins really kicks in," says Professor Rogers.

Mice with 20% enzyme activity had very mild disease, while animals with 10% activity had clear signs of disease and higher levels of abnormal proteins.

Importantly, raising the body temperature decreased enzyme activity to almost undetectable levels, leading to very high amounts of the abnormal proteins.

"We can start to use this information predictively; for example, by measuring the level of abnormal proteins in samples of blood we may be able to foresee the severity of the symptoms" says Professor Rogers. "Clinicians could use this knowledge to help diagnose and manage the disease."

Importantly, the researchers also discovered that a protein called NLRP3 plays a role in the inflammatory process of MKD. Because of its involvement in a wide variety of inflammatory disorders, there is currently major interest in developing NLRP3 blockers for use in the clinic. The finding suggests that targeting NLRP3 could be a new approach for the treatment for MKD.

The new findings are welcomed by Natalie Billiard, parent of a 13-year-old girl living with a rare autoinflammatory disorder she was diagnosed with as a baby. "Fifty years ago my daughter's illness was termed 'not compatible with life.' We have come a long way thanks to people like Professor Rogers and the research his team is doing. It's giving our kids a chance at life," she says.

More information: Increased core body temperature exacerbates defective protein prenylation in mouse models of mevalonate kinase deficiency, *Journal of Clinical Investigation* (2022). dx.doi.org/10.1172/JCI160929

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