AUTOINFLAMMATORY DISEASES

New autoinflammatory disease caused by non-cleavable RIPK1 variants

> “mutations in *RIPK1* prevent caspase 8 from cleaving the mutated protein, thereby promoting RIPK1 activation and leading to an autoinflammatory response”

Two groups have independently identified patients with an early-onset autoinflammatory disorder caused by heterozygous mutations in the gene encoding RIPK1, an important regulator of apoptosis, necroptosis and innate immune signalling pathways. As reported in separate studies published in *Nature*, the dominantly inherited mutations in *RIPK1* prevent caspase 8 from cleaving the mutated protein, thereby promoting RIPK1 activation and leading to an autoinflammatory response.

The affected individuals experienced periodic fevers, lymphadenopathy, splenomegaly, arthralgia and anaemia, and most were responsive to IL-6 inhibition with tocilizumab. The combination of clinical observations, genetic data and mouse studies provided an understanding of the underlying mechanisms.

Xiaochuan Wang, co-author of the first study, explains that the research reflects their ongoing work to explore what is happening in patients with fever of unknown origin. “We have diagnosed and treated many patients with fever caused by different immune-related factors,” says Wang, “some of which have known autoinflammatory causes, and some of them are still unknown.” Clinically, the research provides a basis for potential treatment options, and it also furthers understanding of the complex immune mechanisms of febrile diseases, Wang explains.

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For Daniel Kastner, co-author of the second study, the publication represents the culmination of more than 20 years of clinical observation, as his group first encountered one of the affected families in 1999, at a time when the tools necessary to discover the genetic basis of the disease were not available. By the time they saw a second affected family, in 2010, sequencing technologies had advanced such that they were able to identify a *RIPK1* mutation in that family. “However, in order to be more confident that *RIPK1* was really the causative gene, we needed to find another family with similar clinical findings and a mutation in the same gene,” says Kastner. Genomic sequencing on stored DNA samples from the first family revealed this second mutation, and the group subsequently discovered a third in another family with a child with similar symptoms. “Much to our surprise, the affected individuals in all three families had a mutation affecting the same nucleotide of the *RIPK1* gene, resulting in three different amino acids at residue 324. It was as if lightning had struck three times in the same place!” recalls Kastner.

“We generated a large number of knockout animals and could definitively show that loss of RIPK1 cleavage, instead of leading to necroptosis as had been predicted by previous research, actually led to hyperactivation of caspase 8-mediated apoptosis,” explains Kastner’s co-author John Silke. “Thus, caspase 8 is primarily inhibiting its own activation by cleaving RIPK1 rather than RIPK3 activation.”

Together, the studies demonstrate that RIPK1 cleavage limits inflammation and TNF-induced cell death, and non-cleavable variants promote cell death as well as the production of pro-inflammatory cytokines.

“The combined genetic and functional analyses teach us that a very significant human autoinflammatory disease can be caused by genetic mutations that promote cell death,” notes Kastner. “The implications of these findings are profound, suggesting that unchecked cell death may play a very critical role in many other inflammatory conditions,” he adds.

Although many of the patients with disease caused by *RIPK1* mutations responded to treatment with tocilizumab, some did not respond as well or discontinued the treatment owing to adverse effects. Further studies are needed to understand how IL-6 inhibition modulates inflammation in these patients. Another important avenue to explore is the role of RIPK1 inhibitors, which are currently in development, in treating patients with disease caused by *RIPK1* mutations.

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ORIGINAL ARTICLES Tao, P. et al. A dominant autoinflammatory disease caused by non-cleavable variants of RIPK1. *Nature* **577**, 109–114 (2020) | Lalaoui, N. et al. Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. *Nature* **577**, 103–108 (2020)