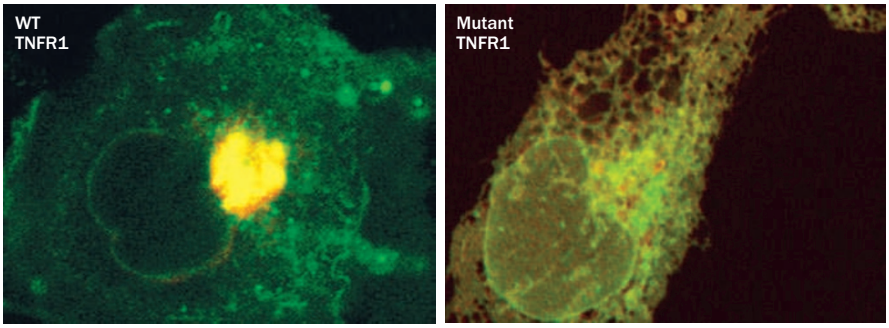
INFLAMMATION

New insights into the pathogenesis of TRAPS

Tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS) is an autosomal dominant recurrent febrile syndrome that is characterized by prolonged episodes of inflammation and fever. This syndrome is caused by mutations in the gene encoding TNFR superfamily member 1A (*TNFRSF1A*), which result in receptor misfolding and loss of receptor trafficking and function. Understanding the pathogenesis of this disease has, therefore, long been a puzzle: shouldn't blockade of signaling downstream of *TNFRSF1A* lead to a dampening down of the proinflammatory effects of tumor necrosis factor rather than result in excessive inflammation? Research from Richard Siegel *et al.* published in *PNAS* provides some clues as to the disease mechanisms in TRAPS, which have potential implications for our understanding of the pathogenesis of other autosomal dominant disorders.

The researchers generated knock-in mice expressing TRAPS-associated TNFR1 mutations and obtained peripheral blood mononuclear cells (PBMCs) from patients with TRAPS to investigate the behavior of the mutated TNFR1 proteins. They also generated embryonic fibroblasts from the knock-in mice to investigate the signaling pathways more closely. As expected, the mutant TNFR1 proteins failed to traffic to the cell surface, and were shown to accumulate intracellularly in PBMCs from the patients and in various cell types from lymphoid tissues of the mice. What effect did the TRAPS-associated TNFR1 mutations have on signal transduction? "We found aberrant activation of MAPK enzymes in cells expressing TNFR1 mutants, and showed that JNK and p38, two MAPK family members in T cells, were hyperactivated at steady state and even further after lipopolysaccharide treatment," says Siegel.

This led the authors to investigate the sensitivity of these mice to lipopolysaccharide-induced toxic shock: interestingly, heterozygous TRAPS-mutant TNFR1 mice were hypersensitive, but homozyygous mice were nearly as resistant as TNFR1-deficient mice. "To get the full phenotype of excessive inflammation, both the mutated TNFR1 and the normal TNFR1 need to be present. This is a unique situation, where you need both the mutated protein and its wild-type counterpart to get the full expression of a disease phenotype," Siegel explains. He concludes that "Co-operation between a protein altered by a genetic mutation and its wild-type counterpart is a newly-identified mechanism in human autosomal dominant disease."



Wildtype TNFR1 (green) colocalizes with a golgi marker (red) at the plasma membrane; mutant TNFR1 (green) colocalizes with the endoplasmic reticulum (red). Confocal images courtesy of Adrian Lobito.

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Original article Simon, A. *et al*. Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. *Proc. Natl Acad. Sci. USA* **107**, 9801–9806 (2010)