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PATHOLOGY

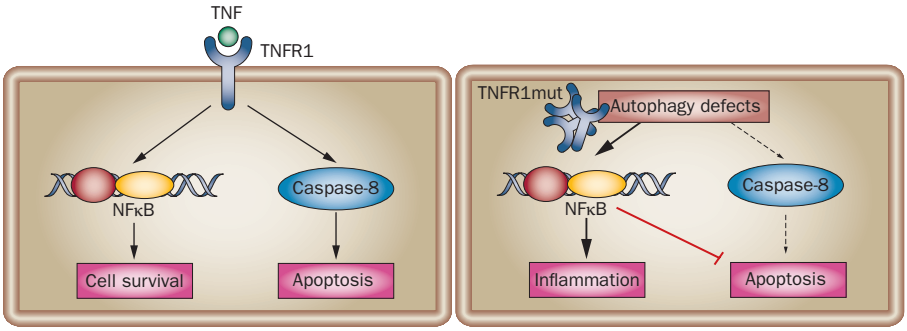
Autophagy defect traps mutant TNF receptor in TRAPS

The finding that an induced impairment in autophagy seems to participate in the pathogenesis of TNF receptor-associated periodic syndrome (TRAPS) will assist in "the identification of new druggable targets" in the disease, says Isabella Ceccherini, commenting on her group's work published in the *Annals of the Rheumatic Diseases*.

An autoinflammatory syndrome, TRAPS is caused by mutations in *TNFRSF1A*, which encodes TNF receptor 1 (TNFR1), but details of the pathologic mechanism are unclear. With TNF signalling being a target in many autoimmune rheumatic diseases, it might seem likely that TNFR1 defects would tend to inhibit inflammation. Nevertheless, periodic inflammation characterizes TRAPS, and "the most effective therapy is achieved by inhibiting the signalling cascade induced by IL-1β, rather than by the use of drugs counteracting the TNFR-mediated pathway," notes Ceccherini.

Ligation of normal TNFR1 induces either activation of nuclear factor κB (NFκB) signalling or apoptosis. The mutant receptor accumulates in the endoplasmic reticulum; immune cells from patients with TRAPS have higher levels of reactive oxygen species (ROS) than controls; and neutrophils from these patients have apoptotic defects. These observations, together with a known link between excessive IL-1β secretion and impairment of autophagy, as well as the implication of autophagic defects in various inflammatory disorders, prompted Ceccherini and colleagues to test for a role for autophagy in TRAPS pathogenesis.

In *ex vivo* work, the investigators isolated monocytes from 10 Italian patients with TRAPS, and the HEK-293T cell line was used for *in vitro* experiments. Cell-surface expression assays confirmed previous findings that TNFR1 mutations that affect cysteine residues have most effect on localization of the protein. Ultrastructural investigation of cells from a patient expressing one such mutation, Cys55Tyr, revealed abnormally large autophagic vacuoles. Next, inhibitors of the ubiquitin–proteasome system and of autophagy were used to examine the fate of transfected TNFR1 constructs, and showed that "autophagy plays a crucial role in the physiological balance of TNFR proteins within cells," says Ceccherini. Furthermore, autophagy was impaired in the presence of mutant TNFR1.



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"Before this work, we knew that structural TNFR1 mutants (like C55Y) were retained intracellularly and had a longer half-life than the wild-type protein," explains Richard Siegel, an expert in TRAPS and Chief of the Immunoregulation Section at the NIH, who was not involved in the study. "The advance here is in the proposal that autophagic, rather than proteasomal, degradation may govern the half-life of TNFR1, and that the mutant TNFR1 may avoid autophagy."

So how could mutant TNFR1, impaired autophagy, production of proinflammatory cytokines and ROS be linked in TRAPS? The authors suggest that the failure of autophagy to clear the mutant TNFR1 causes aggregation of the receptor, inducing a general autophagic defect and subsequent accumulation of the signalling adaptor p62. Sustained expression of p62 as a result of autophagy defects is known to alter the regulation of NFκB, and can lead to oxidative stress and inflammation.

The antibiotic geldanamycin, which affects the actions of chaperones, can induce autophagy. Treatment with this agent rescued the cell-surface localization of the cysteine mutant TNFR1, reduced the aberrant activation of NFκB in HEK-293T cells expressing the mutant protein, and reduced the lipopolysaccharide-induced secretion of IL-1β by monocytes. However, the latter effect was seen in cells from healthy controls as well as from patients with TRAPS.

"The proposal that geldanamycin or other chaperones might reduce inflammatory consequences of TNFR1 misfolding in TRAPS is intriguing, but must be interpreted cautiously in light of the fact that it is a known inhibitor of NFκB signalling," says Siegel, adding that *in vitro*, "the pathways of degradation may be different to when TNFR1 is not so dramatically overexpressed."

Ceccherini agrees that more work is needed and plans further investigation into crosstalk between intracellular pathways. "Fine characterization of pathogenic mechanisms in TRAPS will hopefully have not only a speculative fallout on our basic knowledge, but also impact on quite practical aspects of this disease," she concludes.

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Original article Bachetti, T. *et al.* Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS). *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2012-201952

Further reading Aksentijevich, I. & Kastner, D. L. Genetics of monogenic autoinflammatory diseases: past successes, future challenges. *Nat. Rev. Rheumatol.* **7**, 469–478 (2011) | Buckland, J. New insights into the pathogenesis of TRAPS. *Nat. Rev. Rheumatol.* **6**, 384 (2010)