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Caspase-8 mutations cause autoimmunity

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Most cases of autoimmune lymphoproliferative syndrome (ALPS) are associated with heterozygous mutations in the genes encoding CD95 (Fas receptor), CD95 ligand and the apoptotic enzyme caspase-10. These mutations lead to defects in lymphocyte apoptosis, lymphadenopathy and autoimmunity. In the September 26 Nature, Hyung Chun and colleagues describe the first case of autoimmunity resulting from mutations in caspase-8 (*Nature*, **419:**395-399, September 26, 2002).

Chun *et al.* studied two patients who have ALPS-related disorders but lack mutations in the CD95, CD95L or caspase-10 genes. They identified a homozygous C to T mutation in the capsase-8 gene that reduced the protein's stability and destroyed its enzymatic activity. The mutation also affected T-cell activation and proliferation, natural killer cell activation and immunoglobulin production. They confirmed the role of caspase-8 in T cell functions using RNAi experiments in normal human lymphocytes and rescue experiments in the patient's cells.

The authors conclude that caspase-8 plays a broad role in regulating lymphocyte homeostasis and suggest that caspase-8 might be a useful target for immunosuppressive therapeutics.

References

1. ALPS: an autoimmune human lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis

2. H. J. Chun *et al.*, "Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency," *Nature*, 419:395-399, September 26, 2002., [http://www.nature.com]