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Demonstration of the physiological relevance of death receptor mediated apoptosis *(R Watanabe-Fukunaga, CI Brannan, NG Copeland, NA Jenkins, S Nagata. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature, 356: 314-317, 1992.*

Two morsels of wisdom that I have acquired are: (1) the study of spontaneously arisen mutant mice with spectacular phenotypes will inevitably lead to remarkable insight, and (2) outstanding scientific advances often result from the serendipitous convergence of previously independent lines of research. The 1992 Watanabe-Fukunaga *et al.* paper exemplifies both of these points.

Immunologists were for a long time fascinated by the progressive lymphadenopathy and systemic autoimmune disease that the *lpr* and *lpr^{cg}* (allelic) mutant mouse strains develop. Meanwhile, the groups of Krammer and Yonehara generated unintentionally monoclonal antibodies that induced apoptotic cell death in certain human tumour derived cell lines (Trauth *et al.*; Yonehara *et al.*). The cloning of the *Fas* gene (Itoh *et al.*) showed that FAS is related to the TNFR1 receptor, and (like TNFR1) can trigger apoptosis when stimulated.

The physiological function of FAS was revealed by the Watanabe-Fukunaga Nature paper, which showed that the *lpr* mice have an insertion in the 5' region of the *Fas* gene that dramatically reduced *Fas* mRNA expression. Conversely, *lpr^{cg}* mice have a point mutation that affects the so-called "death domain" in the intra-cellular part of FAS. This residue is highly conserved amongst so-called "death receptors" (e.g. TNFR1). Elegant biochemical studies demonstrated that the *lpr^{cg}* point mutation impaired FAS-mediated apoptosis signalling (Watanabe-Fukunaga *et al.*). Subsequent work by the laboratories of Wallach, Dixit and Krammer revealed that this residue is critical for the interaction of FAS with the adaptor protein FADD/MORT1, which in turn facilitates recruitment and activation of Caspase-8 to unleash cell demolition (Boldin *et al.*, Chinnaiyan *et al.*, Kischkel *et al*.).

An important practical outcome of the Watanabe-Fukunaga study was that whenever scientists hypothesised that a process involved FAS-mediated apoptosis, they could use *lpr* mice to check this. As such it was recently revealed that FAS-mediated apoptosis of infected intestinal epithelial cells constitutes a critical host defense against enteropathogenic and enterohaemorrhagic bacteria (Pearson *et al.*).

Translational studies by the groups of Fischer and Puck revealed that mutations in the *Fas* gene are the cause of autoimmune lymphoproliferative syndrome (ALPS) in children, which closely resembles the immune system abnormalities in the *lpr* mice (Rieux-Laucat *et al.*, Fisher *et al.*). Curiously, these inherited mutations act in a dominant manner but the parent carrying this mutation is usually healthy. This suggests that a polymorphism in an additional gene may contribute to pathogenesis. Notably loss of only one allele of *Bim* (acting in a parallel apoptotic pathway) synergises potently with the *lpr* mutation in causing lymphadenopathy and autoimmune disease (e.g. Hughes *et al.*). Thus many interesting questions in this area of research remain to be answered.

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ORIGINAL RESEARCH PAPERS

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