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Journal club

THE PHYSIOLOGICAL RELEVANCE OF DEATH RECEPTOR-MEDIATED APOPTOSIS

Two morsels of wisdom that I have acquired are: first, the study of spontaneously arisen mutant mice that have spectacular phenotypes will inevitably lead to remarkable insights; and second, outstanding scientific advances often result from the serendipitous convergence of previously independent lines of research. The paper that was published in 1992 by Watanabe-Fukunaga *et al.* exemplifies both of these points.

For a long time immunologists had been 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 (Trauth *et al.*) and Yonehara (Yonehara *et al.*) had unintentionally generated monoclonal antibodies that induced apoptotic cell death in certain human tumour-derived cell lines. The cloning of the *Fas* gene by Itoh *et al.* showed that FAS (also known as CD95, APO1 and TNFRSF6) is related to tumour necrosis factor receptor 1 (TNFR1) and (similarly to TNFR1) can trigger apoptosis when stimulated.

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The physiological function of FAS was revealed by Watanabe-Fukunaga *et al.*, who showed that the *lpr* mice have an insertion in the 5′ region of the *Fas* gene that markedly decreases expression of *Fas* mRNA, and that *lpr*^{cg} mice have a point mutation that affects the ‘death domain’ in the intracellular region of FAS. This residue is highly conserved among ‘death receptors’ (such as TNFR1). Elegant biochemical studies showed that the *lpr*^{cg} point mutation impairs FAS-mediated apoptosis signalling. Subsequent work showed that this residue is crucial for the interaction of FAS with the adaptor protein FAS-associated death domain protein (FADD; also known as MORT1), which in turn facilitates the recruitment and activation of caspase 8 to unleash cell demolition. An important practical outcome of the study by Watanabe-Fukunaga *et al.* was that whenever scientists hypothesized that a process involved FAS-mediated apoptosis, they could use *lpr* mice to check this.

Within a few years of the paper by Watanabe-Fukunaga *et al.*, translational studies had shown that mutations in the *FAS* gene are the cause of autoimmune lymphoproliferative syndrome (ALPS) in children, which closely resembles the immune system abnormalities in *lpr* mice. Curiously, these inherited mutations function in a dominant manner, but the parent who carries the mutation is usually healthy, which indicates that a polymorphism in an additional gene might contribute to pathogenesis. Thus, many interesting questions in this area of research remain to be answered.

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