In a paper in this issue of the *Biochemical Journal* that questions the role of c-IAP1 (cellular inhibitor of apoptosis 1) in inflammation, new results from the Duckett laboratory remind us of the importance of truly knowing the mice we depend on. It turns out that c-IAP1 is tightly linked to caspase 11 and cannot be segregated by recombination. This disturbing result implies that immune functions ascribed to c-IAP1 may be due to the caspase 11 mutation that is co-inherited with the locus.

Key words: caspase 11, cellular inhibitor of apoptosis 1 (c-IAP1), genotype, inflammation, mouse knockout.

Scientists have employed mice for over a century in attempts to understand the fundamental processes that regulate and execute immune system programmes. Massive advances in our understanding have accrued from these studies. But, as we are told in *The Hitchhiker’s Guide to the Galaxy*, animal experiments on man” [1]. Some of these experiments test human scientists’ ability to correctly interpret the genotype/phenotype relationship upon which knowledge is built.

Laboratory mice strains have been produced by selective breeding and even by stochastic mutation of important genes. Thus, in the early days of immunology, much was learned by comparing the phenotypes of mice with different genetic backgrounds. For example, the discovery of histocompatibility genes involved in controlling transplant rejection [2,3]. Over the last three decades, technology for deleting and introducing specific genes into mice has become available and is now commonplace, rapidly accelerating the analysis of gene and protein function.

But there are two major technical issues that complicate gene ablation strategies. (i) Genes on a mouse chromosome are not nicely separated from each other by long stretches of DNA. This means that tightly linked genes cannot be easily separated during back-crossing on to a defined background strain. (ii) The mouse strain from which embryonic stem cells are generally obtained for gene ablations (129/Sv), like any other laboratory mouse strain, does not possess all genes in a functional format. Some genes in this mouse strain are mutated to a dysfunctional form.

Typically, the gene locus of interest is diluted, or transferred, into the test strain background by crossing on to that background for ten or more generations to create a congenic strain. But this only works if genes are far enough apart to be segregated by recombination. As a case in point, caspase 1 is considered to be a major pro-inflammatory mediator largely on the basis of genetic ablation. However, strain 129 embryonic stem cells are generally obtained for gene ablations (129/SvJ), like any other laboratory mouse strain, does not possess all genes in a functional format. Some genes in this mouse strain are mutated to a dysfunctional form.

Following up on this observation, in this issue of the *Biochemical Journal*, Kenneth et al. [5] examined the locus of mice targeted for deletion of c-IAP1 (cellular inhibitor of apoptosis 1), an intracellular protein implicated in several pathways including control of the innate immune response [6]. They show that c-IAP1 is tightly linked to caspase 11 and cannot easily be segregated by recombination, and that mice in which the c-IAP1 gene (*Birc2*) is ablated also carry the dysfunctional caspase 11 gene [5]. This disturbing result implies that immune functions previously ascribed to c-IAP1 cannot be separated from the caspase 11 mutation that is co-inherited with the locus.

Throughout the literature, there are examples of where specific mouse strains are deficient in specific proteins, and one-third of these involve genes with immunological functions [7]. Genome sequences of inbred strains of laboratory mice [8] provide a comprehensive database to validate whether strains used for genetic ablation carry functional genes in adjacent regions that may co-contribute to the outcome of the ablation. We hope that scientists carrying out specific gene ablations examine the available gene sequence databases of the mice from which they obtain embryonic stem cells, or they will fall into the trap nicely explained by Kenneth et al. [5]. The celebrated Scottish poet Robert Burns appeared to know of this when he wrote, “The best-laid schemes o’ mice an’ men gang aft agley, an’ lae’e us nought but grief an’ pain, for promis’d joy!”.


