IMMUNE RESPONSE

Supermouse 2

Following the recent report that mice with several genomic copies of *Trp53* are resistant to cancer formation, comes the discovery that a genetic trait can induce resistance to or regression of cancer in mice by soliciting an immune response. Amazingly, Zheng Cui and colleagues discovered this trait by accident, and have analysed it further.

In examining the response to intraperitoneal injection of S180 cells — which results in ascites fluid, metastasis and death within 3–4 weeks — the authors discovered a male mouse that was resistant to ascites formation. When bred with S180-sensitive mice, ~40% of the F1 progeny and later generations were also resistant, indicating that the trait was dominant to the wild type and only one locus is thought to be responsible. This was independent of sex, so the trait is presumably located on an autosome.

Interestingly, the response does vary according to age. Mice that are 6 weeks old on first injection of S180 cells are completely resistant to ascites formation; however, as mice age, their response changes from resistance to regression. If the mice are 22 weeks old on first injection, almost all have switched to a regression response — ascites fluid develops over the first two weeks, but then disappears within 24 hours. This indicates that the anticancer mechanism takes a longer time before it is engaged in older animals, but once it has been engaged, mice become completely resistant to tumour formation.

So how is this response manifested? The authors analysed peritoneal cavity washes following injection of S180 cells, and discovered that a resistant mouse was capable of destroying 20 million cancer cells within 12 hours. A large number of leukocytes migrate into the peritoneal cavity within 6–12 hours, but disappear after the cancer cells are destroyed. The immune cells seem to form rosettes around the cancer cells, and many of the cancer cells have ruptured membranes, indicative of a cytolytic event.

T cells have long been thought to mediate the anticancer immune response, but the resistance can be bred into athymic nude mice that do not possess mature T cells and remain ascites-free following injection of S180 cells. This indicates that resistance might require other immune components, and preliminary analysis reveals that these are likely to be part of the innate immune response, such as neutrophils, macrophages and natural-killer cells.

The ability of adoptively transferred leukocytes to mediate such a response in recipient mice looks promising, and suggests a strategy that could be translated into patients.

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References and links

ORIGINAL RESEARCH PAPER Cui, Z. *et al.* Spontaneous regression of advanced cancer: identification of a unique genetically determined, age-dependent trait in mice. *Proc. Natl Acad. Sci. USA* early edition 30 April 2003 (doi:10.1073/pnas.1031601100)

TRIAL WATCH

Pesticide exposure

The Agricultural Health Study (AHS) has been following nearly 90,000 people in North Carolina and Iowa since 1993, to assess the role of various environmental, occupational, dietary and genetic factors on the health of the agricultural population. Researchers from the three sponsoring organizations of the study — the National Cancer Institute, the National Institute of Environmental Health Sciences and the Environmental Protection Agency — and other collaborators, have evaluated the relationship between 45 pesticides and the incidence of prostate cancer in more than 55,000 men who use pesticides and participated in the AHS. These men are mostly farmers or nursery workers and had no history of prostate cancer.

Between 1993 and 1999, 566 new prostate cancers developed, compared with 495 that were predicted to occur in the general population — giving a standardized incidence ratio of 1.14. This ratio was higher (1.41) among the minority of men who work for commercial pest-control industries than among private users of pesticides (1.13).

Although farming has been the most consistent occupational risk factor for prostate cancer, the role of specific chemicals has not been established, largely because previous studies have not had the statistical power to draw firm conclusions. In this large study, one pesticide in particular, methyl bromide — which is used extensively in the United States to protect crops from pests in the soil and to fumigate grain bins — was associated with increased prostate cancer risk. The risk of cancer increased with frequency of use — men with the highest frequency of use had an odds ratio of 4.39. In addition, the risk of cancer increased with longer lifetime exposure to the chemical — men with the highest exposure to methyl bromide had an odds ratio of 2.63.

As expected, there was an association between age, family history and the incidence of prostate cancer. The authors also found a significant association between exposure to six specific pesticides — four of which belong to the thiophosphonate class of chemicals — and prostate cancer in those with a family history of the disease, but not among those with no family history. These data indicate that familial genes might enhance susceptibility or that family members are exposed to the same environment.

The AHS has so far had an average of 4.3 years follow-up — longer follow-up will help confirm these findings.

ORIGINAL RESEARCH PAPER Alavanja, M. C. R. *et al.* Use of agricultural pesticides and prostate cancer risk in the agricultural health study cohort. *Am. J. Epidemiol.* **157**, 800–814 (2003)