Discovering lymphocyte subsets

A role for the thymus

In the early 1960s, Miller noticed that mice thymectomized at birth developed a wasting syndrome and died prematurely. These mice were found to lack the small circulating lymphocytes that had been identified not long before by Jim Gowans as the cells responsible for initiating immune responses to antigen. Miller’s mice also failed to reject foreign skin transplants—a phenomenon shown by Gowans and others to be mediated by lymphocytes. Miller thus proposed that the thymus was the source of immunocompetent lymphocytes (1), although most in the field regarded the thymus as an evolutionarily defunct organ that served as little more than a lymphocyte graveyard.

Miller was frustrated. “They couldn’t quarrel with the data,” he says, “but they quarreled with the interpretation.” In 1963, Miller finally answered the primary criticisms by repeating the transplant experiments using different strains of mice in a germ-free facility, thus ruling out concerns about strain-specific effects or confounding infections (2).

Two cell types

The thymus was now thought to give rise to a single population of lymphocytes capable of initiating both humoral and cellular immune responses. This was the next theory that Miller and others were to debunk. The first hints about lymphocyte diversity came from Frank Macfarlane Burnet’s group, who showed that elimination of the bursa of Fabricius in chickens caused a defect in antibody responses, whereas thymectomy crippled cellular immune responses (3). But were these findings applicable to mice and men, who don’t have a bursa? In 1966, Henry Claman published a crucial paper showing that irradiated mice given a mixture of bone marrow and thymus cells produced more antibody after immunization than those given either cell type alone (4). The differences Claman saw were not simply additive effects of the single populations, implying that some cooperation must be occurring. With no way to distinguish the populations of cells—since no immune cell markers existed—Claman was unable to extend these results.

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Miller, meanwhile, had shown that mice lacking a thymus did not make antibody-producing cells in response to immunization, despite having intact bone marrow (5). But mice reconstituted with thymus or thoracic duct (lymph) cells were again able to produce specific antibodies, thus supporting Claman’s data and suggesting that the two cell types cooperated to generate an antibody response (6, 7).

There was a critical difference in the new experiments, however. Miller and Mitchell used F1 hybrid mice as the source of cells to be transferred. The genetic difference between the transferred cells and those of the recipient allowed selective depletion with strain-specific antibodies. Thus, Miller and Mitchell could determine whether the antibody-producing cells arose from the donor (thymus derived) or host (nonthymus derived).

Miller was betting on the thymus. “I had discovered the function of the thymus, so I wanted everything to be thymus derived,” he admits. Miller lost his bet, since the depletion of the donor cells after immunization had very little effect on antibody production, whereas depletion of the host cells eliminated it almost completely (7). Thus, antibody-producing cells were coming from somewhere other than the thymus. In later studies, he used the same depletion techniques in adult-thymectomized, irradiated, and bone marrow–protected mice to prove that the antibody-producing cells came from the bone marrow (8).

“These studies changed the course of immunology,” Miller points out, “because all immune functions now had to be reassessed in terms of a possible role for two different kinds of cells.” In terms of complexity, immunology never looked back.

REFERENCES

1. Miller, J.F.A.P. 1961. Lancet. 2:748–749.
2. McIntyre, K.R., S. Sell, and J.F.A.P. Miller. 1964. Nature. 204:151–155.
3. Warner, N.L., A. Szenberg, and F.M. Burnet. 1962. Aust. J. Exp. Biol. Med. Sci. 40:373–387.
4. Claman, H.N., E.A. Chaperon, and R.F. Triplett. 1966. Proc. Soc. Exp. Biol. Med. 122:1167–1171.
5. Miller, J.F.A.P. 1962. Proc. R. Soc. Lond. B. Biol. Sci. 156:415–428.
6. Mitchell, G.F., and J.F.A.P. Miller. 1968. Proc. Natl. Acad. Sci. USA. 59:296–303.
7. Miller, J.F.A.P., and G.F. Mitchell. 1968. J. Exp. Med. 128:801–820.
8. Miller, J.F.A.P., and G.F. Mitchell. 1968. J. Exp. Med. 128:821–837.