Milestone 3

Discovery of T cell memory

The immune system has the ability to remember an antigen it has previously encountered and respond more rapidly and effectively after re-exposure to the same antigen. This immunological memory was recognized long before the discovery of T cells — one of the two lymphocyte subsets involved in immunological memory.

In the 1960s and early 1970s, the study of immunological memory was centred around secondary humoral immune responses. Antibody-forming cells (plasma cells) in secondary immune responses arise from dividing precursors. Gowans and Uhr aimed to determine the origin of these precursors, which formed during primary immune responses and carried immunological memory, giving rise to antibody-forming cells during secondary immune responses. They provided strong evidence that small lymphocytes were the precursors of antibody-forming cells and were responsible for the carriage of immunological memory. At the time, although it was clear that two subsets of lymphocytes (thymus-derived lymphocytes and bursa of Fabricius derived lymphocytes) existed in chickens, it was unclear whether there were two separate lineages of lymphocytes in other species, including mice and humans.

In 1967, Miller and Mitchell (Milestone 1) made the ground-breaking discovery that thymus-derived lymphocytes and bone marrow-derived lymphocytes existed in mice, which were later termed T cells and B cells, respectively, and that antibody-forming cell precursors were B cells. By then, we knew that small lymphocytes consisted of T cells and B cells. If B cells were the precursors of the cells that formed antibodies, were T cells involved in the secondary humoral immune responses? Raff used anti-theta (Thy-1) antiserum to deplete T cells, and showed that T cells were important in secondary humoral immune responses and helped B cells to produce antibodies. This raised the question of whether immunological memory was exclusively performed by B cells or whether T cells also carried immunological memory.

Two landmark studies published in 1971 addressed this issue. First, Miller and Sprent neonatally thymectomized CBA mice, reconstituted them with thymus-derived lymphocytes from (CBA × C57BL)F_1 mice and used anti-C57BL antibodies to deplete T cells — these experiments elegantly showed that both T cells and B cells, carried immunological memory and that they collaborated in secondary humoral immune responses. Second, Gershon et al. used ^{3}H-thymidine to label mitotic cells during the primary immune response and found that the labelled cells responded mitotically to secondary antigenic challenge and were limited to the white pulp of the spleen where T cells reside, providing direct evidence that a population of (possible) T cells generated in the primary response responded to the same antigen in the secondary response. These T cells by definition would be memory cells.

"... both T cells and B cells carried immunological memory"

Now, more than 50 years on from these pioneering experiments, researchers have made great progress in understanding the generation, function, maintenance and heterogeneity of memory T cell populations. Three main subsets have been defined based on their migratory properties (Milestone 7) — central memory T cells, effector memory T cells and resident memory T cells (Milestone 17). These subsets of memory cells are phenotypically, functionally, transcriptionally and metabolically distinct, and differ in their immunological effects. Although a lot is now known, future studies should help to uncover many more aspects of memory T cell biology.

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Milestone studies

Miller, J. F. A. P. & Sprent, J. Cell-to-cell interaction in the immune response. VI. Contribution of thymus-derived cells and antibody-forming cell precursors to immunological memory. *J. Exp. Med.* **134**, 66–82 (1971) | Gershon, R. K., Krüger, J., Naysmith, J. D. & Waksman, B. H. Cellular basis for immunologic memory. *Nature* **232**, 639–641 (1971)

Further reading

Please visit the online article for a full list of further reading.

***The Persistence of Memory* by Salvador Dalí (1931).**