Lymphocytes: not useless after all

Half a century ago, an immunologist named N. Avrion Mitchison showed that lymphocytes—then thought to be useless—triggered tumor rejection in mice.

As recently as the 1940s, immunologists thought lymphocytes served no purpose. Antibodies, on the other hand, were all the rage. But this thinking started to change when a British group began to investigate the fate of tissue transplants.

One member of this group was Mitchison, a bright and independent-minded student whose work was inspired by his Oxford University mentor, Peter Medawar. Medawar had discovered that skin grafts given to patients with severe burns survived if derived from the patient's own body, but withered away if taken from a donor. A second graft from the same donor was rejected more quickly than the first. Medawar reproduced this phenomenon in rabbits and—as was customary at the time—believed antibodies to be responsible (1, 2).

Cells become suspects

Intrigued, Mitchison repeated the experiment in mice using tumor transplants instead of skin grafts, because tumors were easier to manipulate. His results were identical to Medawar's—secondary tumors were rejected more rapidly than first-time tumors—but his interpretation was different. Mitchison noticed that the transplanted mice had enlarged lymph nodes, and he recalled a similar observation by Karl Landsteiner and Melvin Chase in guinea pigs vaccinated with a bacterial antigen (3). In that study, the transfer of lymph node cells from vaccinated animals, but not antibody-containing serum, boosted the reaction of naive animals exposed to the antigen.

Mitchison thus wondered whether cells, rather than antibodies, were responsible for the accelerated tumor rejection in his mice. To distinguish between the two possibilities, he transferred either lymph node cells or serum from mice that had already rejected a tumor. Mice that received cells rejected tumors more quickly than both untreated mice and those that received serum, suggesting that the lymph node cells were doing the work (4, 5).

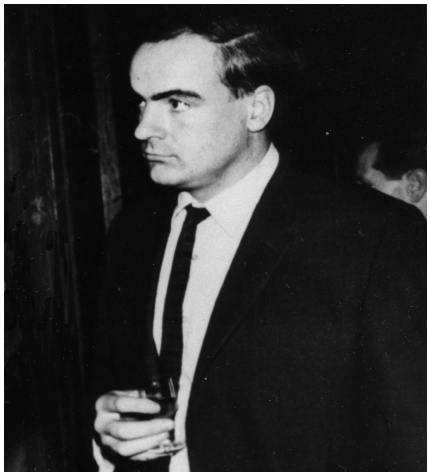
Inspired by Mitchison's finding, Medawar and colleagues Rupert Billingham and Leslie Brent found similar results in rabbits (6). Medawar had "never been that keen on antibodies," recalls Mitchison, "they were simply the only mechanism known at the time. He certainly accepted—gladly—my work".

But questions remained about how the transferred cells acted. Did they attack the tumor directly? Or did they carry tumor antigens with them that prompted a response in the host?

Immunology meets genetics

The effect of the transferred cells disappeared after 10 to 20 days. Mitchison guessed that the host immune system was rejecting the foreign cells and thus switched to a new set of tools—the inbred mice of geneticists Clarence Cook Little and George Snell (Jackson Laboratory, Maine). Bred over many generations, the strains were identical for genes now known as the major histocompatibility complex. This genetic parity allowed transferred lymph node cells to survive for many weeks after transfer without rejection.

Mitchison first confirmed that it was transferred lymphocytes, not antibodies, that led to the quicker tumor rejection in the hosts, as rejection occurred before the hosts could make their own antitumor antibodies. The effect was lost if the cells were killed by freezing before transfer, ruling out the possibility that transferred tumor antigens were the trigger. Mitchison later showed that only the lymph nodes closest to the tumors in donor mice—presumably those collecting and reacting to tumor fragments—contained the tumor-fighting cells.



Avrion Mitchison says cheers to lymphocytes (1957).

The already strong case against antibodies was further bolstered when Mitchison showed that serum antibodies, even if transferred with the lymphocytes, were unlikely to reach the tumor transplant. His results, published in three papers in the *Journal of Experimental Medicine* (7, 8, 9), helped bring immunology to a turning point: the recognition that lymphocytes were important.

The importance of lymphocytes was later solidified by Jim Gowans, who showed that lymphocytes circulated between blood and tissues and therefore could patrol the body (10). Jacques Miller then demonstrated that some lymphocytes developed in the thymus and were essential for fending off infections (11). Mitchison later returned to the UK where he was the first to show convincingly that T and B cells must cooperate to trigger antibody production (12).

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Text by Julie Clayton
Julie.p.clayton@blueyonder.co.uk