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Journal club

T CELL–B CELL COLLABORATION

The field of T cell immunology began in 1961 with a landmark paper by Jacques Miller demonstrating the effects of neonatal thymectomy (NTx) in mice, which included a marked paucity of lymphocytes, signs of infection (hepatitis) and, remarkably, failure to reject allogeneic and even xenogeneic (rat) skin grafts. These findings evoked intense interest and were soon extended by several other groups. However, it was a 1968 paper from Miller's group that first showed that the thymus is a direct source of T helper cells for antibody production.

Although the early studies of NTx proved that the thymus controls cellular immunity, it remained possible that, rather than arising in the thymus per se, immunocompetent cells were generated elsewhere by 'hormones' released from the thymus. As a medical student, I heard Miller lecture in the mid-1960s and was so fascinated by the idea that the thymus might function as an endocrine organ that I later turned up in Miller's laboratory asking to do a Ph.D. on thymic hormones.

> "thymus-dependent antibody production reflected an interaction between thymus-derived and bone marrow-derived cells"

I was soon brought up-to-date on the recent work of Miller's graduate student, Graham Mitchell, who was investigating the notable observation of Claman *et al.* in 1966 that, in irradiated hosts, antibody responses to sheep red blood cells (SRCs) required both thymocytes and bone marrow cells. The key unresolved issue was which of these cell types made antibody. It should be noted that Mitchell only had crude alloantisera specific for two mouse strains (A and B) at his disposal. However, this was enough. Modifying the approach of Claman *et al.*, Mitchell and Miller developed a model in which anti-SRC responses were generated in adult thymectomized, irradiated (A × B) F1 mice that were injected with a mixture of strain A bone marrow cells and F1 thymocytes or thoracic duct lymphocytes plus SRCs. A week later, they tested whether anti-A or anti-B alloantiserum plus complement would abolish antibody formation by spleen cells *in vitro* in a plaque-forming cell (PFC) assay. The clear-cut finding was that only anti-A antiserum ablated PFC formation.

This simple yet elegant approach proved that thymus-dependent antibody production reflected an interaction between thymus-derived and bone marrow-derived cells (T and B cells, respectively), an observation that changed the face of immunology — and convinced me to forget about thymic hormones!

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