MILESTONE 3

Searching for the antibody producers

The importance of antibodies in protection against disease was established in the early 1900s, but their origin was less clear. Various theories were suggested, and the plasma cell theory evolved after it was noted that patients with higher concentrations of γ-globulin in their blood also had more plasma cells in tissues. In 1943, Mogens Bjørneboe and Harald Gormsen were the first to experimentally show that repeated immunization of rabbits with polyvalent vaccines leads to massive proliferation of plasma cells in most organs and that this proliferation correlates with antibody concentration.

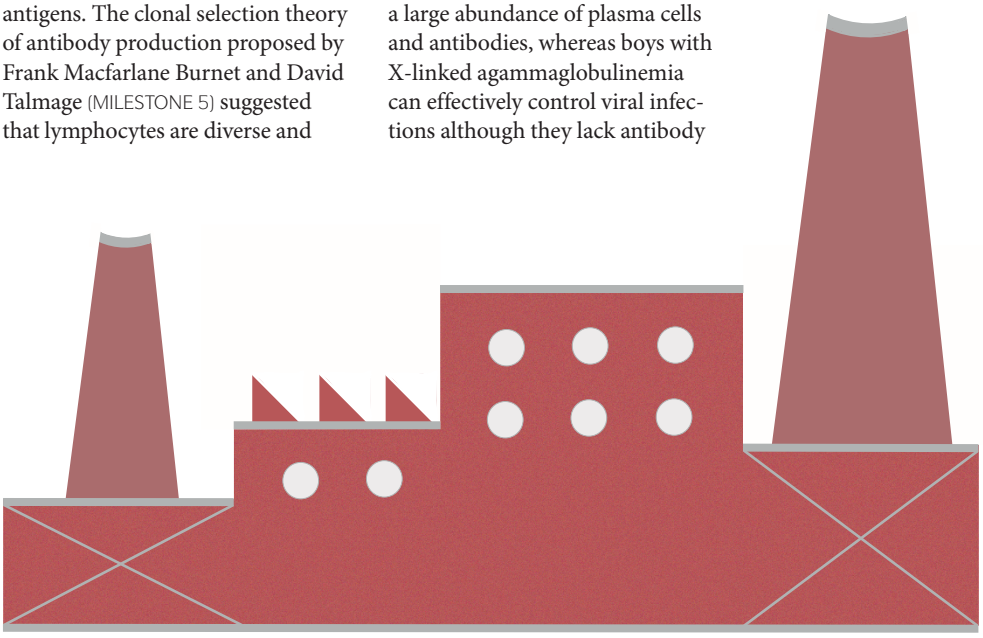
That finding was supported a few years later by Astrid Fagraeus, who reported that plasma cells produce antibodies *in vitro*. Tissue cultures of spleens from rabbits immunized with live bacteria showed abundant formation of plasma cells. Fagraeus concluded that plasma cells appear in connection with strong antigen stimulation.

Around that time, immunologists were fascinated by the structural nature and diversity of antibodies, as well as by how the immune system responds to the wide diversity of antigens. The clonal selection theory of antibody production proposed by Frank Macfarlane Burnet and David Talmage (MILESTONE 5) suggested that lymphocytes are diverse and that a specific antigen activates only its counter-specific lymphocyte. Gustav Nossal tried to challenge this theory, but he failed, and in 1958 he published, together with Joshua Lederberg, a study that provided the first experimental evidence supporting the proposal of clonal selection by showing that one plasma cell always produces only one antibody. The 'one cell–one antibody' discovery was crucial to the ground-breaking technique of generating cell lines that continuously produce monoclonal antibodies (MILESTONE 9).

Plasma cells were thus established as the antibody producers, but what was their origin? In 1961, Jacques Miller discovered that removing the thymus from neonatal mice leads to diminished antibody responses and the inability to reject skin grafts from different strains of mice. This suggested that the thymus is important for the development of the immune system, a conclusion confirmed in studies of rabbits by Robert Good and colleagues a year later. Around this time, Max Cooper was curious about the observation that boys with X-linked Wiscott-Aldrich syndrome cannot clear viral infections despite a large abundance of plasma cells and antibodies, whereas boys with X-linked agammaglobulinemia can effectively control viral infections although they lack antibody responses but have a normal number of lymphocytes. So, Cooper and colleagues hypothesized that plasma cell precursors might not belong to the thymus-dependent lymphocyte lineage. In 1965, they found that chickens lacking the bursa of Fabricius (a lymphoid organ unique to birds) lack plasma cells and antibodies but still have an abundance of lymphocytes. Through these studies, they had identified two lymphocyte lineages: one thymus dependent (T cells) and the other bursa dependent (B cells). In a follow-up study, they showed that B cells are required for antibody responses, whereas thymus-derived T cells mediate cellular immunity such as skin-graft rejection. Shortly after that, Miller and Graham Mitchell did cell-transfer experiments showing that the co-transfer of T cells and bone-marrow-derived B cells, but not the transfer of either cell type alone, leads to robust antibody responses in irradiated mice. Thus, T cells provide help to B cells to induce antibody production. Finally, Cooper and co-workers identified bone marrow as the mammalian 'bursa equivalent'.

The identification of plasma cells as antibody producers was a key discovery that paved the way for the development of monoclonal antibodies, which are crucial research tools as well as important therapeutics for cancer and autoimmune diseases (MILESTONES 13, 14).

Elisabeth Kugelberg, Associate Editor, *Nature Reviews Immunology*



A series of landmark papers in the 1940s and 1950s identified plasma cells as the 'antibody-producing factories' of the immune system. It was later shown that plasma cells develop from B cells and that this process requires help from T cells. Image credit: P. Guha/ Nature Publishing Group.

ORIGINAL RESEARCH PAPERS Bjørneboe, M. & Gormsen, H. Experimental studies on the role of plasma cells as antibody producers. *APMIS* **20**, 649–662 (1943) | Fagraeus, A. Plasma cellular reaction and its relation to the formation of antibodies *in vitro*. *Nature* **159**, 499 (1947) | Nossal, G. J. V. & Lederberg, J. Antibody production by single cells. *Nature* **181**, 1419–1420 (1958) | Cooper, M. D. *et al.* Delineation of the thymic and bursal lymphoid systems in the chicken. *Nature* **205**, 143–146 (1965) | Owen, J. J.T. *et al.* *In vitro* generation of B lymphocytes in mouse foetal liver, a mammalian 'bursa equivalent'. *Nature* **249**, 361–363 (1974)

FURTHER READING Gitlin, A.D. & Nussenzweig, M.C. Fifty years of B lymphocytes. *Nature* **517**, 139–141 (2015) | Cooper, M. D. The early history of B cells. *Nat. Rev. Immunol.* **15**, 191–197 (2015)