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This Week's Citation Classic

Sell S & Gell P G H. Studies on rabbit lymphocytes *in vitro*. I. Stimulation of blast transformation with an antiallotype serum. *J. Exp. Med.* **122**:423-40, 1965. [Dept. Experimental Pathology, Univ. Birmingham Med. Sch., England]

This paper describes the ability of antibodies to rabbit immunoglobulin allotypes to stimulate small resting peripheral blood lymphocytes to undergo 'blast' transformation, synthesize DNA, and divide It is the first demonstration that some lymphocytes have surface immunoglobulin (sIg) and that this sIg can serve as a receptor for activation of the cell. [The *SCI*® indicates that this paper has been cited in over 435 publications since 1965]

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"In 1964, when I went to work with Philip Gell in Birmingham, England, studies in several laboratories that would lead to two decades of intensive exploration of cellular immunology were just beginning. Immunoglobulin antibody structure was being decoded, but the key question as to how lymphocytes recognized antigen was completely open. No one had been able to come up with a better idea than that proposed by Ehrlich's side chain theory at the turn of the century.[1] In 1961, Möller[2] described immunoglobulin on the surface of lymphocytes by immunofluorescence, but the technique used was not reproducible and it would only be later that vital staining procedures would give consistent results. Nowell[3,4] demonstrated that an extract of kidney beans, termed 'phytohemagglutinin,' stimulated peripheral blood lymphocytes to divide *in vitro.* George and Vaughan[5] described the phenomenon of inhibition of macrophage *in vitro* when antigen was added to cells from immunized animals and Pearmain *et al.*[6] reported that tuberculin could induce mitosis in peripheral blood cells from humans with positive tuberculin skin tests. Dutton and Eady[7] were in the process of showing that cells from immunized rabbits could respond to antigen exposure *in vitro* by proliferation, and Ada and Nossal[8] were carrying out experiments to show that some lymphocytes from immunized animals would bind radiolabeled antigen.

"I had proposed to Gell that we try to develop better assays for studying delayed hypersensitivity *in vitro* based on lymphocyte activation. Before we were able to work out antigen specific stimulation, the phenomenon of anti-immunoglobulin activation of lymphocytes was observed and led our studies in a different direction. One day, I added an antiallotype serum to a culture of lymphocytes from a rabbit bearing that allotype. Two days later, a large number of cells had 'transformed' into blasts.

"During the next 20 years (for a review see reference 9), this system was used to describe a number of other original observations. A partial list includes: 1) The process of lymphocyte activation is reversible. Enlarged 'blast' cells change back to small cells when the stimulus for activation is removed. 2) Cross-linking is not absolutely required for activation, but cross-linking can enhance the activation process. 3) Single lymphocytes may bear more than one surface immunoglobulin (sIg) class at a time. 4) Single immature lymphocytes may express more than one light chain or VH region allelic marker (allelic inclusion). 5) Activation of lymphocytes by anti-immunoglobulin or lectin is associated with endocytosis of reactive surface markers. 6) Activation of proliferation of sIg positive cells is not necessarily followed by differentiation into immunoglobulin synthesizing cells. 7) There is a population of normal cells with an apparent overlap of T- and B-cell properties. Many of these observations have recently been verified with human and mouse lymphocytes but some remain controversial."

1. **Ehrilch P.** Croonian lecture. On immunity with special reference to cell life. *Proc. Roy. Soc. London Ser. B* **66**:424-48. 1900. (Cited 135 times since 1955.)
2 **Möller G.** Demonstration of mouse isoantigens at the cellular level by the fluorescent antibody technique. *J. Exp. Med.* **114**:415-34. 1961. (Cited 530 times.)
3. **Nowell P C**. Phylohemagglutinin: an initiator of mitosis in cultures of normal human leukocytes. *Cancer Res.* **20**:462-6. 1960.
4..... Citation Classic. Commentary on *Cancer Res* **20:** 462-6. 1960. *Current Contents* (421:13. P October 1977.
5. **George M & Vaughan J H.** *In vitro* cell migration as a model for delayed hypersensitiwty. *Proc. Soc. Exp. Biol Med.* **111**:514-21. 1962. (Cited 645 times.)
6. **Pearmain G, Lycette R R & Fitzgerald P H.** Tuberculin-induced mitosis in peripheral blood leucocytes. *Lancet* **1**:637-8. 1963. (Cited 440 times.)
7. **Dutton R W & Eady J D.** An in *vitro* system for the study of the mechanism of antigenic stimulation in the secondary response. *Immunology* **7**:40-64, 1964. (Ciled 205 times.)
8. **Ada G L, Nossal G J V & Austin C M.** Antigens in immunity. V. The ability of cells in lymphoid follicles to recognize foreignness. *Aust. J. Exp. Biol Med. Sci.* **42**:331-46. 1964. (Cited 65 times.)
9 **Sell S, Skaletsky E, Holdbrook R, Linthicum D S & Raffel C.** Alternative hypotheses of lymphocyte surface immunoglobulin expression. B lymphocyte activation and B lymphocyte differentiation. *Immunol Rev.* **52**:141-79, 1980.