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This Week's Citation Classic®

Evans R & Alexander P. Mechanism of immunologically specific killing of tumor cells by macrophages. *Nature* **236**:168-70, 1972.
[Chester Beatty Research Institute, Belmont, Sutton, Surrey, England]

Although macrophages from tumor-immunized mice, or after treatment *in vitro* with lymphokine, appeared to be specifically cytotoxic, a two-stage mechanism was indicated. Following their interaction with lymphokine or immune T cells and the specific immunizing tumor cells, the macrophages were activated to become nonspecifically cytotoxic. [The *SCI*® indicates that this paper has been cited in over 455 publications since 1972.]

Robert Evans
Jackson Laboratory
Bar Harbor, ME 04609

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At the beginning of the 1970s, the role of the T cell in immunological reactions was coming into its own. The macrophage at that time was still an enigmatic cell type that was considered by many to be simply a scavenger having little to do with immunology. Despite the previous *in vitro* experiments on macrophages in allograft reactions,[1] little attention had been focused on the potential role of the macrophage in tumor immunology.

When I went to work with Peter Alexander in 1968, our mutual interest in macrophages and tumor biology led us to consider the possibility that the T cell might not act alone in defense against neoplasia. In 1970, we reported[2] that macrophages isolated from the peritoneal cavity of mice immunized against syngeneic lymphomas were able to inhibit growth *in vitro* in an apparently specific manner. Not having the range of anti-T-cell antibodies that became available much later, the role of contaminating T cells in this reaction was a moot point, although macrophage-depleted T-cell suspensions did not exert a cytostatic effect. The influence of T cells or their products became evident in 1971 when we demonstrated that lymphokines from immune T cells stimulated with specific tumor cells rendered normal macrophages cytostatic *in vitro*.[3] Two other groups[4,5] independently showed similar findings. The subsequent paper, the subject of this *Citation Classic*, suggested the mechanism whereby macrophages expressed their cytotoxicity. The data indicated that after contact with immune T cells or with lymphokines, the macrophages were armed or sensitized, as were those macrophages isolated from immunized mice, and, as a consequence, were able to recognize the specific tumor cells. Following this recognition, the macrophages were changed to become nonspecifically cytotoxic effectors, a process that we termed activation.

From then until now, it has become clear that the macrophage is more than just a scavenger and that it plays a pivotal role in immune and physiological responses.[6] It can be involved in antigen processing, antigen presentation to T-helper cells in the context of Class II antigens, activation of both T-helper and B cells by secreting interleukin-1, and, under some circumstances, suppression of immune responses. In addition, its pluripotential role in the physiology of the host, such as in wound healing, the complement system, and the production of several types of growth factors, illustrates the importance of the macrophage. We feel that this publication served to highlight the potential involvement of macrophages in immunobiological reactions. In particular, the finding that macrophages formed an integral part of progressing tumors added impetus to the attention afforded macrophages as antitumor effectors in the subsequent years.

1. **Granger G A & Weiser R S.** Homograft target cells: specific destruction in vitro by contact interaction with immune macrophages. *Science* **145**:1427-9, 1964. (Cited 240 times.)
2. **Evans R & Alexander P.** Cooperation of immune lymphoid cells with macrophages in tumour immunity. *Nature* **228**:620-2, 1970. (Cited 340 times.)
3. **----------.** Rendering macrophages specifically cytotoxic by a factor released from immune lymphoid cells. *Transplantation* **12**:227-9, 1971. (Cited 150 times.)
4. **Lohmann-Matthes M L, Ziegler F G & Fischer H.** Macrophage cytotoxicity factor. A product of *in vitro* sensitized thymus-dependent cells. *Eur. J. Immunol.* 3:56-8, 1973. (Cited 110 times.)
5. **Pels E & Den Otter W.** The role of a cytophilic factor from challenged immune peritoneal lymphocytes in specific macrophage cytotoxicity. *Cancer Res.* **34**:3089-94, 1974.
6. **Evans R.** Macrophages and neoplasms: new insights and their implication in tumor immunobiology. *Cancer Metast. Rev.* 1:227-39, 1982.

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