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# This Week's Citation Classic

**Hellström K E & Hellström I.** Lymphocyte-mediated cytotoxicity and blocking serum activity to tumor antigens. *Advan. Immunol.* **18**:209-77, 1974. [Depts. Pathology, Microbiology, and Immunology, Univ. Washington Medical School, Seattle, WA]

**This paper reviews evidence that lymphocytes from animals and human patients with tumor are specifically reactive to cells from the same tumor *in vitro* and that their reactivity can be prevented by circulating 'blocking factors' such as tumor antigens and antigen-antibody complexes. [The *SCI*® indicates that this paper has been cited a total of 653 times of which 8 occurred in 1974, 74 in 1975, 119 in 1976, 113 in 1977, 126 in 1978, 87 in 1979, 66 in 1980, and 60 in 1981.]**

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"In 1966, we both started working at the University of Washington Medical School in Seattle, having left George Klein's group at the Karolinska Institute in Stockholm, where we got our training. The project on which we embarked concerned lymphocyte reactivity to tumor-associated antigens as assayed *in vitro*.

"We found, rather to our surprise, that lymphocytes from mice with growing, chemically induced sarcomas were often as reactive to cells from the same sarcomas *in vitro* as were lymphocytes from mice whose tumors had been removed. Similar findings were made with other experimentally induced tumors and with human neoplasms.

"In an attempt to learn why tumors can grow progressively *in vivo*, in spite of the fact that the tumor-bearing individuals' lymphocytes can kill plated tumor cells *in vitro*, we tested serum from the respective tumor-bearers for any adverse effect on the ability of the lymphocytes to react. We observed that tumor-bearer serum could suppress ('block') lymphocyte reactivity, and we attributed this to circulating 'specific blocking factors.'[1] These factors were able to bind to tumor cells from the donors of the respective sera and they disappeared shortly after tumor removal. In 1971, we obtained evidence that the circulating blocking factors were circulating antigen-antibody complexes and that free antigen could also serve as a blocking factor.[2]

"The findings that we had obtained were confirmed and extended in other laboratories.[3] They contradicted the prevailing view that lymphocyte clones that are reactive to a given tumor antigen are absent ('forbidden') from the tumor-bearing host. They indicated, instead, that lymphocyte reactivity must be regulated, and we proposed that the 'blocking factors' play an intricate part in this regulation. Further evidence supporting the view of regulation of lymphocyte activity rather than clonal loss came from studies which we performed on rats that had been made tolerant to skin allografts. These rats had lymphocytes that were reactive *in vitro* to the tolerated tissue, and they also had circulating blocking factors, inhibiting this reactivity.[4]

"Our 1974 paper in *Advances in Immunology* reviewed these findings. We believe that the reason our paper has been much cited reflects both the great amount of interest and the considerable controversy which our rather unexpected observations caused. Today, it is generally accepted that reactive lymphocytes occur in tumor-bearing animals, that their activity is subject to close regulation, that blocking factors in the form of tumor antigens and complexes turn on suppressor T cells, and that other blocking factors are the products of such cells.[5] The greatest advancement since 1973 is that it has become possible, using proper cell surface markers, to dissect subsets of lymphocytes with distinct functions, while in 1974 we did not know of NK cells and of various types of T killer, helper, and suppressor cells. Thus, the phenomenological framework in which we and others were then working is gradually being replaced by knowledge at the cellular and even at the molecular level."

1. **Hellström I, Hellström K E, Evans C A, Heppner G, Pierce G E & Yang J P S.** Serum mediated protection of neoplastic cells from inhibition by lymphocytes immune to their tumor specific antigens. *Proc. Nat. Acad. Sci. US* **62**:362-9, 1969.
2. **Sjögren H O, Hellström I, Bansal S C & Hellström K E.** Suggesting evidence that the 'blocking antibodies' of tumor-bearing individuals may be antigen-antibody complexes. *Proc. Nat. Acad. Sci. US* **68**:1372-5, 1971.
3. **Baldwin R W, Price M R & Robins R A.** Inhibition of hepatoma-immune lymph node cell cytotoxicity by tumor-bearer serum, and solubilized hepatoma antigen. *Int. J. Cancer* **11**:527-35, 1973.
4. **Bansal S C, Hellström K E, Hellström I & Sjögren H O.** Cell-mediated immunity and blocking serum activity to tolerated allografts in rats. *J. Exp. Med.* **137**:590-602, 1973.
5. **Hellström K E & Brown J P.** Tumor antigens. (Sela M, ed.) *The antigens.* New York: Academic Press, 1979. Vol. 5. p. 1-82.