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This Week's Citation Classic™

Kay H D, Bonnard G D, West W H & Herberman R B. A functional comparison of human Fc-receptor-bearing lymphocytes active in natural cytotoxicity and antibody-dependent cellular cytotoxicity. *J. Immunology* **118**:2058-66, 1977
[Lab. Immunodiagnosis, Natl. Cancer Inst., Natl. Insts. Health, Bethesda, MD]

When simultaneously tested in parallel assays, human peripheral blood lymphocytes active in "spontaneous' or 'natural killer' (NK) cell lysis of cultured tumor cell lines were shown to be structurally and functionally similar to, if not identical to, Fc-receptor-bearing 'killer' (K) lymphocytes active *in vitro* in antibody-dependent cellular cytotoxicity (ADCC). [The *SCI*® indicates that this paper has been cited in over 320 publications since 1977.]

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"Often, major new developments in scientific understanding unfold when established 'dogma' is brought into question by unexpected but reproducible data. Such was the case in the early 1970s when it was found that lymphocytes from healthy donors frequently caused the lysis of tumor cells when cocultured in the same test vessel. This was unexpected, since at that time it was thought that cytolytic capacity was reserved for specifically 'sensitized' lymphocytes from patients with an active disease process. Strong *in vitro* reactivity by cells from normal donors was therefore viewed by many investigators as artifactual. However, during my postdoctoral training in 1972-1973 with Joseph G. Sinkovics in his tumor immunology laboratory at the M.D. Anderson Hospital and Tumor Institute in Houston, we found consistent evidence that the antitumor cytolytic activity of normal donor lymphocytes was a real phenomenon.[1-2] This independently corroborated earlier results from Ron Herberman's laboratory at the National Institutes of Health, reported by Rosenberg,[3] Oldham,[4] and McCoy,[5] who had also observed this *in vitro* cytotoxic phenomenon.

"In 1975, I had the very good fortune to continue my studies as a visiting scientist with Herberman's group at the National Cancer Institute. Because Herberman's lab was both active and crowded, I found my bench space was limited for some time to the work surface available inside an unused fume hood! This, however, had the advantage of keeping the next guy's books and beakers off my work area, and also added delightfully to my memories of a hardworking, productive environment, where ideas abounded and collaboration was easy. Working with Bill West (a physician/investigator already characterizing membrane receptors on 'natural killer' [NK] cells) and Guy Bonnard (a senior scientist in Herberman's group who was heading up the human NK studies unit), I began to explore the intriguing relationship between NK cells on the one hand, and 'killer' (K) cells on the other, which are identical to NK cells in every way, except that they require .the Fc receptors on their surface membranes to bind IgG-sensitized targets. The results of our studies were submitted to the *journal of Immunology* in November 1976.

"The popularity of this manuscript has been most surprising, and no doubt relates to: 1) the sound reputation established over the years by Herberman and his colleagues in NK cell studies; 2) the vigorous popularity which studies of NK cells have now cometp enjoy (e.g., when I began my NK studies, there may have been two or three papers a year reporting tumor cell killing by normal-donor lymphocytes; today, there are at least ten times that many appearing every month!); and 3) the interesting results we obtained while addressing the NK/K cell relationship. For example, the paper has been frequently cited for our descriptions of the protease-sensitivity of NK activity compared to antibody-dependent cellular cytotoxicity (ADCC); our use of staphylococcal protein A to block binding of effector-cell Fc receptors to immobilized IgG immune complexes; our comparison of NK/ADCC function in T cell and non-T cell fractions; and our use of unique celt lines to simultaneously measure NK and ADCC functions in parallel but separate assays. A comprehensive update of the NK field was recently edited by Herberman."[6]

1. **Kay H D**, **Cabiness J R, Ervin F, Virgil W & Sinkovics J G.** Do lymphocytes presensitized to tumor antigens occur in normal individuals? *Abstracts of the annual meeting of the American Society for Microbiology.* Washington, DC: American Society for Microbiology, 1973. p. 111. Abstract no. M227.
2. **Kay H D & Sinkovlcs J G**. Cytotoxic lymphocytes from normal donors. *Lancet* 2:296-7, 1974.
3. **Rosenberg E B, Herberman R B, Levlne P H, Halterman R H, McCoy J L & Wunderlich J R.** Lymphocyte cytotoxicity reactions to leukemia-associated antigens in identical twins. *Int. J. Cancer* **9**:648-58, 1972. (Cited 80 times.)
4. **Oldham R K, Siwarski D, McCoy J L, Plata E J & Herberman R B.** Evaluation of a cell-mediated cytotoxicity assay utilizing ^{125} iododeoxyuridine-labeled tissue-culture target cells. *Natl. Cancer Inst. Monogr.* **37**:49-58. 1973.
5. **McCoy J L, Herberman R B, Rosenberg E B, Donnelly F C, Levlne P H & Alford C.** ^{51} Chromium-release assay for cell-mediated cytotoxicity of human leukemia and lymphoid tissue-culture cells. *Natl. Cancer Inst. Monogr.* **37**:59-67. 1973.
6. **Herberman R B,** ed. *NK cells and other natural effector cells.* New York: Academic Press. 1982. 1.566 p.