Guest Editorial Ronald B. Herberman [1] *and* Howard T. Holden [1]

Natural Killer Cells as Antitumor Effector Cells [2]

Immune resistance against tumors is a widely recognized phenomenon and forms the basis for most studies in tumor immunology. Immunologic factors are involved in the resistance against challenge with many syngeneic transplantable tumors in experimental animals. Furthermore, manipulation of the immune response of patients with leukemia and some carcinomas may result in prolonged survival (*1*). These in vivo observations have led to extensive research on the nature of the effector cells mediating this resistance. Until recently, most attention has been focused on cytotoxic T-cells (*2*) and on antibodies produced by B-cells (*3*), and the role of lymphokines produced by immune T-cells has been considered (*4*). There is abundant evidence for an important role of immune, mature T-cells in in vivo resistance to tumor challenge (*5–7*), and in some tumor systems antitumor antibodies confer protection (*3*). For a time, T-cell immunity was considered to be the main effector mechanism (*8*). However, it has become increasingly clear that immune T effector cells cannot account for all aspects of resistance against tumors. For example, evidence has been presented on resistance to transplanted tumor cells in animals with few if any mature T-cells (e.g., nude mice, neonatally thymectomized mice, or mice immunodepressed by drugs) or even in lethally irradiated mice (*9*). Also, in clinical studies of the effects of immunotherapy on T-cell responses and on antibody formation, few if any consistent changes could be measured by the available assays (*10, 11*).

A similar sequence of events occurred regarding the concept of immune surveillance. This theory, emphasizing the central importance of the immune system in prevention of spontaneous tumors (*12, 13*), initially was met with much enthusiasm. Later, the theory was modified to stress the key role of thymus-dependent immunity in immune surveillance (*8*). However, there was again an inability to account for a number of observations in T-cell-deficient mice. For example, much attention has been given to the decreased incidence of mouse mammary tumors in thymectomized mice and to the failure to observe more rapid tumor growth or even higher incidences of spontaneous or chemical carcinogen-induced tumors in nude mice (*9*). A further assault on the immune surveillance theory has come from the failure to find evidence for tumor-associated transplantation antigens on many spontaneous tumors.

The major exceptions to the central role of immune T-cells in resistance to tumor transplants and in immune surveillance has led several investigators to question the importance of the immune system in protection against most tumors and even to formulate theories of immunostimulation (*14*). Such concepts are diametrically opposed to the main tenets of immune surveillance, suggesting that the immune system may have mainly enhancing effects on tumor induction and growth.

Recent studies have provided much evidence for two other types of effector cells, i.e., macrophages and NK cells, which can have potent antitumor effects. Both macrophages (*15*) and NK cells have been shown in various tumor systems to mediate in vivo resistance against tumors. In addition, both these effector mechanisms have been found in nude and neonatally thymectomized mice, which indicates that both mechanisms can be functional in the absence of mature T-cells. Therefore, the issues regarding the role of the immune system in protection against tumor transplants, in immunotherapy, and in immune surveillance now need to be reconsidered in regard to the possible role of one or more different effector mechanisms. This should be a cause for renewed, albeit cautious, optimism regarding the role of the immune system in the defense against tumors. The concept of multiple potential antitumor effector mechanisms should also provide a strong impetus for research on the relative roles of each effector mechanism in various tumor systems. It is possible, and in fact quite likely, that in various situations and with various tumors, different effector cells will be found to be the main factors in resistance.

For the present discussion, we will focus on NK cells and their possible role as antitumor effector cells. The phenomenon of cytotoxicity against tumor cells and against cultured cell lines derived from tumors by lymphocytes of many normal individuals first became recognized during attempts to examine specific cytotoxic activity of lymphocytes of tumor-bearing individuals against their own tumors or against tumors of the same histologic or etiologic type. It was initially

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ABBREVIATIONS USED: E = erythrocyte(s); FcR = Fc receptor(s); NK = natural killer.

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Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.

assumed in those studies that lymphoid cells from normal individuals would be unreactive and thus would serve as good base-line controls for comparison. However, it gradually became apparent that lymphocytes from some normal controls were more cytotoxic against some target cells than were lymphocytes from the tumor-bearing individuals under study. Many investigators first attributed this anomalous control reactivity to a variety of in vitro artifacts [*see* Discussion in (*16*)]; however, much or all of this control reactivity was subsequently found to be due to NK cells, a particular subpopulation of small to medium-sized lymphocytes. On the basis of initial cell-separation studies, NK cells appeared to be null cells, i.e., lacking characteristic markers of either T-cells or B-cells. However, more recent data have indicated that mouse and human NK cells may be in the T-cell lineage. By use of optimal conditions for formation of E-rosettes with T-lymphocytes, most human NK cells were found to have low-affinity receptors for E (*17*). As a recent further confirmation that human NK cells reside in the T-cell lineage, treatment with specific anti-T-cell sera plus complement caused elimination of cytotoxic activity (*18*). In mice, high levels of NK activity were found in nude athymic mice, and this seemed to support the non-T-cell nature of NK cells. However, treatment with high concentrations of anti-Thy 1 serum plus complement, or repeated treatments, were recently shown to eliminate most mouse NK activity (*19*). Therefore, it now appears that mouse NK cells, although they are present with high cytolytic activity in nude and neonatally thymectomized mice, have a low density of Thy 1 antigen. Such low-density Thy 1+ cells have been described for nude mice, and such cells are probably pre-T-cells. To further support the concept that NK cells may be at an early phase of maturation along the T-cell lineage, we found that incubation of NK cells for 2 hours with some thymus hormone preparations, which are known to cause further differentiation and increased T-cell antigen expression, leads to decreased NK activity. Another cell surface marker on NK cells is the receptor for the Fc portion of IgG (FcR). FcR are readily detected on human NK cells, and methods that deplete FcR+ cells result in virtual elimination of NK activity. In mice and rats, NK cells initially appeared to lack FcR. However, when more sensitive procedures for depletion of FcR+ cells were used, more than half of the NK lytic units were removed (*20, 21*).

An important issue to be considered is the specificity of natural cytotoxicity. In most of the early studies of rodent NK cells, leukemia or lymphoma target cells were used; it was initially thought that only those cells were sensitive to NK activity. However, as mentioned above, many of the initial observations on human NK cells were made with monolayer cell lines derived from carcinomas. Such data suggested that NK cells might have a wide range of reactivity. This was confirmed by extensive studies of the susceptibility of a wide variety of cells to NK activity (*22*). In vitro cell lines of tumors have usually been more susceptible to lysis by NK cells, but some in vivo tumor cells have also been susceptible. Although it initially appeared that NK reactivity was restricted to target cells of the same species, mouse and rat NK cells have shown activity against some human cell lines (*23*). Reactivity of human NK cells against rodent target cells appears to occur less frequently. NK activity also was not restricted to tumor cells, with some types of normal cells having some sensitivity to lysis (*22*).

Given this rather wide spectrum of reactivity for NK cells, the question then arises as to whether a single NK receptor reacts indiscriminately against all of the susceptible target cells or whether there are a variety of NK receptors with specificity for an array of possible antigens on target cells. Several lines of evidence support the latter possibility, i.e., that NK cells recognize at least several broad antigenic specificities. Many of the data in this regard were obtained by the cold-target inhibition assay. This assay consists of addition of various unlabeled target cells to the mixture of effector cells and ^{51}Cr-labeled target cells. Cells that can interact with the same NK cells mediating lysis of the labeled target cells will competitively inhibit ^{51}Cr release. When different labeled target cells were used in such studies, patterns of inhibition varied (*24*). Some cells that could strongly inhibit lysis of one target had little or no inhibitory activity for other target cells. In addition, there are some major differences in the reactivity of NK cells from different mouse strains against some target cells but not against others. Further insight into the nature of the interaction between NK cells and target cells has come from recent studies of rapid conjugate formation between the effectors and a mouse tumor cell line (*25*). Conjugate formation has been blocked by soluble extracts of tumor cells, and studies of the specificity of this inhibition have again indicated some heterogeneity in surface constituents of various tumor cell lines (*26*). Much work remains to be done on the details of the NK cell-target cell interaction and the actual mechanism of lysis. Spontaneous tumors with no detectable tumor-associated transplantation antigens, as measured by the usual test methods of comparison of resistance to growth in normal and immunized animals, need to be reexamined for their expression of NK-related antigens and their sensitivity to lysis by NK cells, because this may be the more relevant issue regarding the appearance of spontaneous tumors. Immunity of the autochthonous host to transplantation antigens on primary AKR thymomas has been difficult to detect. However, studies in our laboratory have indicated that some primary AKR thymomas are susceptible to lysis by NK cells and can inhibit cytotoxicity against more sensitive target cells. Similarly, some spontaneous human tumors were found to have NK-related antigens, inasmuch as they were able to inhibit the cytotoxicity of a sensitive target cell (*27*).

NK cell reactivity in mice and rats was initially thought to be restricted to young animals between 3 and 12 weeks of age, and some doubt was therefore raised regarding their possible role in adults. Recent studies, however, have indicated the possibility of

strong and rapid augmentation of NK activity by inoculation of a variety of agents, including tumor cells susceptible to NK activity, viruses, and immune adjuvants such as BCG and *Corynebacterium parvum* (*28–30*). Studies in both rodents and man have shown that interferon plays a major role in this augmentation (*31–33*). Very young and also older mice and rats, with little or no spontaneous NK activity, could rapidly develop high levels of NK activity after exposure to interferon or interferon inducers (*31*). The induction of augmented NK activity or the reappearance of such activity after inoculation of some tumor cells indicates that, in in vivo experiments involving challenge with tumor cells, the possibility of rapid boosting of NK activity should be considered a factor in resistance to tumor growth. The findings of interferon-mediated boosting of NK activity also have important implications for immunotherapy. In many tumor systems, nonspecific immunotherapeutic agents have considerable effects on tumor growth (*34*); in clinical immunotherapy trials, only nonspecific modalities, mainly BCG and *C. parvum*, have been clearly shown to decrease tumor growth and prolong survival (*1, 35–38*). The observations that NK activity is strongly and rapidly boosted by almost all of the nonspecific agents that have been successfully used for immunotherapy may provide an important clue to their mechanism of action. Previous immunotherapy trials, especially in man, have been almost or entirely empirical. It is therefore not too surprising that, in the absence of adequate or appropriate monitoring procedures and of the ability to rationally decide on dose and timing, most trials of immunotherapy at the clinical level have been unsuccessful or at best have provided modest benefits (*1, 38*). By monitoring effects on NK activity, and possibly on macrophage cytotoxic activity, of various doses, routes, and schedules of administration, it may be possible to rationally design immunotherapy protocols for optimal stimulation.

There have already been several suggestions or indications of mediation of in vivo resistance against tumors by NK cells. The findings of high NK activity in nude and neonatally thymectomized mice provide a plausible explanation for the observations of resistance to tumors in such animals. Most of the data available on the in vivo role of NK cells involve correlations between in vivo resistance and in vitro NK activity, and all of the studies have been on long-transplanted tumors in rodents. The main pieces of evidence for an in vivo role of NK cells are summarized in table 1. A major limitation of most of the studies has been that they involved challenge by tumor cells, and the only end points were survival time or growth rate. A complex situation exists in these experiments in which not only NK cells but also macrophages in addition to T-cells in mice with normal thymus-dependent functions could be activated. Recently, an in vivo assay has been developed in which within 4 hours of inoculation of tumor cells the degree of elimination of tumor cells can be measured (Riccardi C, Puccetti P, Santoni A, et al: Submitted for publication). Tumor cells prelabeled with [^{125}I]iododeoxyuridine are inoculated iv, and the amounts of isotope in various organs (mainly the lungs, spleen, and liver) are determined. This procedure is more likely to measure only the effects of existing levels of NK cells, because there would not be sufficient time for activation of macrophages or induction of sensitization of specific T-cell immunity. The possible effects of immune T-cells can be further eliminated by performing the assays in lethally irradiated recipients. The data obtained thus far by this assay have shown good correlation with available information on NK cells, with regard to strain differences, age, boosting, and inhibition by various treatments.

TABLE 1.—*Evidence for in vivo role of NK cells*

	Summary of evidence	Reference
1)	Poor growth of some NK-sensitive tumors in nude mice	(*24, 39*)
2)	Fewer transplantable tumors induced in 5- to 10-week-old mice, at the peak of NK activity, than in older mice	(*24, 40*)
3)	Correlation between NK activity and resistance to growth of an NK-sensitive tumor in various strains of mice	(*41, 42*)
4)	Close parallels between NK activity and genetically determined (*Hh*) bone marrow resistance in mice	(*43*)
5)	Close parallels between NK activity and radioresistant inhibition of tumor growth in mice	(*44*)
6)	Transfer of bone marrow precursor cells from high or low NK strains to lethally irradiated NK strain, producing high NK activity and increased resistance to tumor growth	(*45*)

Assuming that NK cells are involved in the in vivo antitumor response, one may speculate about their role relative to other effector mechanisms. It seems likely that NK cells are more effective in dealing with a small number of tumor cells rather than against a large tumor load. All the in vivo challenge experiments that suggest a role for NK cells (*see* table 1) were performed with the use of small tumor inocula. However, in tumor-bearing mice (*46, 47*) and patients (*48–50*) that had larger tumor loads, NK activity was depressed. Although this depression of NK activity in the spleen or peripheral blood of tumor-bearing individuals might be attributed to migration of these effector cells to the tumor site, this seems unlikely, because most studies have failed to detect NK cells within clinically detectable tumors [(*51*); Gerson J, Herberman R, Bonnard G: Unpublished observations]. In only one study did NK cells appear to be present within a tumor (*47*). However, there have not been many systematic studies on the presence of NK cells within the tumor.

Despite these indications of deficient or absent NK reactivity in tumor-bearing individuals, it seems unwarranted to conclude that NK cells are ineffective in

limiting tumor growth. Rather, the emphasis in future studies should probably be placed on the possible role of NK cells in the very early stages of tumor growth. Natural cell-mediated cytotoxicity may represent one of the first lines of defense against tumors but may also be somewhat inefficient and easily overwhelmed.

NK cells either have high spontaneous activity or can rapidly develop high activity in response to tumor cells or other stimuli. Macrophages may also have some spontaneous cytotoxic activity against tumor cells [(*52, 53*); Mantovani A, Jerrells T, Herberman R: Unpublished observations], but augmentation of macrophage cytotoxic activity by exposure to tumor cells or other stimuli usually takes at least 7 days. Immune T-cells with antitumor activity are generated only after a period of tumor growth and consequent sensitization to tumor-associated antigens. Therefore, T-cell immunity may come into play only as a relatively late event and may be more important in further resistance to progressive tumor growth. However, even at the time of detectable tumor burden, NK cells might also be induced to play some role if their activity was substantially augmented by interferon inducers or other immunotherapeutic manipulations.

Clearly, there is to date no conclusive evidence for a role of NK cells in the protection against primary tumors, in the incidence of spontaneous tumors, or in the induction of tumors by known carcinogenic agents like viruses, chemicals, or irradiation. This area will be a major and critical one for future research, to get some indications of the importance of NK cells for immune surveillance. Potentially useful experimental designs could include procedures to chronically and selectively augment or depress NK activity and to then determine the effects on spontaneous tumor incidence or on the incidence of tumors induced by carcinogenic agents. Until such information is available, NK cells can only be considered potential contributors to immune surveillance.

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