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A New Role for DNA Virus Early Proteins in Viral Carcinogenesis

Andrew M. Lewis, Jr., and James L. Cook

Summary. The T antigen proteins encoded by DNA tumor virus early genes are involved in the transformation of normal cells to immortalized neoplastic cells that may or may not be tumorigenic in immunocompetent animals. Studies have been made of the tumorigenicity of DNA virus-transformed cells and the interactions of these cells in vivo and in vitro with immunologically nonspecific host effector cells such as natural killer cells and macrophages. The results imply that the T proteins determine the capacity of transformed cells to induce tumors by governing the level of susceptibility that transformed cells express to destruction by such host cellular defenses.

The capacity of certain DNA viruses to induce tumors in animals and transform cells in tissue culture was documented 20 to 30 years ago. Polyoma virus (PyV), simian virus 40 (SV40), and some serotypes of human adenoviruses were found to be oncogenic when injected into hamsters and certain strains of mice or rats. When normal cells from these and other species were grown in tissue culture, the viruses could convert them to immortalized cells that closely resembled tumor cells (*1, 2*). During the characterization of the oncogenic capacities of these viruses, it was noted that cells from virus-induced tumors expressed virus-specific T (tumor) antigens that were not associated with virion structural proteins (*2*). These T antigens are immunologic domains present on proteins encoded by virus genes that function early (prior to viral DNA synthesis) during the infectious cycle and are involved in initiating viral replication. Subsequent investigators found that, during the conversion of normal cells to neoplastic cells, those segments of DNA tumor virus genomes that encode the early T antigen–expressing viral proteins (T proteins) integrate into cellular chromosomes and become inheritable genetic elements within these cells. Initially, the role of these early T proteins in inducing the neoplastic process was unknown and their presence served only as diagnostic indicators of the tumor viruses that initiated cellular transformation. That specific segments of the viral genome that encode the proteins expressing the T antigen specificities could transform normal cells to neoplastic cells was documented by means of mutant viruses and restriction endonuclease-cleaved fragments of viral DNA (*3*). Thus the ability of the early viral genes and their proteins that are expressed as T antigens to convert normal cells to neoplastic cells seems to be firmly established.

A number of DNA viruses that are nononcogenic in one or more species express a more subtle oncogenic potential in that they can transform tissue culture–grown, normal cells from that species to neoplastic cells. These transformed cells express virus-specific T proteins and share a number of properties with tumor cells including immortality, disruption of the cytoskeleton that results in alterations in cell morphology, growth to high saturation densities, growth in low concentrations of serum, and growth in semisolid agar (anchorage independence). In spite of their similarities with tumor cells, these virus-transformed cells do not produce tumors when injected into immunocompetent syngeneic animals of the strain from which they were derived. However, virus-transformed cells of this type usually produce tumors when injected into immunoincompetent or immunosuppressed hosts (*4*).

Such data demonstrate that transformation (as currently defined) of normal cells in vitro by DNA viruses to immortal neoplastic cells is insufficient to convert these cells to neoplastic cells that can produce tumors in immunocompetent syngeneic hosts and that the interaction between DNA virus–transformed cells and host immune response is the critical element that determines whether transformed cells are rejected by the host or evolve into fatal neoplasms. In studies of the tumor-inducing capacities (tumorigenic phenotypes) of Syrian hamster cells transformed by human adenovirus (Ad) types 2 and 12, SV40, and PyV, we have observed that these viruses interact with the cells they transform in vitro to effect the expression of different levels of susceptibility or resistance to rejection by the cellular immune system of the hamster. The level of susceptibility or resistance expressed by such DNA virus–transformed cells appears to determine their tumorigenic phenotype (*5, 6*). In this article we review and present data suggesting that one of the functions of the early T proteins of DNA tumor viruses is the regulation of the level of susceptibility or resistance of cells transformed by these agents to host cellular immune rejection. In this manner, we believe that these early T proteins play a critical role in determining the capacity of these virus-transformed cells to cause tumors in the immunocompetent host.

Andrew M. Lewis, Jr., is in the Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205, and James L. Cook is in the Robert W. Lisle Research Laboratory in Immunology and Tumor Cell Biology, Department of Medicine, National Jewish Hospital and Research Center, Denver, Colorado 80206.

DNA Virus–Transformed Cell Tumorigenic Phenotypes

Syrian hamsters can discriminate between the oncogenic capacities of DNA tumor viruses. Random bred animals of this species were used to classify human adenoviruses into highly oncogenic (serotypes 12, 18, 31), weakly oncogenic (serotypes 3, 7, 11, 14, 21, 34, 35), and nononcogenic (the remaining serotypes) subgroups (*7*). SV40 is highly oncogenic only in Syrian hamsters. PyV is also highly oncogenic in hamsters; this virus is quite tumorigenic in certain strains of mice, but is either weakly tumorigenic or nontumorigenic in other strains of mice (*1*). Each of these viruses transforms hamster cells in vitro, and the tumorigenic phenotype of these transformed cells in the immunocompetent host reflects the tumor-inducing capacity of the transforming virus. For these reasons, we used Syrian hamsters as an animal model to evaluate the role of DNA tumor virus early T proteins in viral carcinogenesis. To initiate these studies, we obtained hamster embryo cells from the LSH strain of inbred Syrian hamsters and transformed these in tissue culture by Ad2, Ad12, SV40, and PyV. Clonally derived cell lines representing independent transformation events were thus produced, and these were characterized with respect to the presence of virus-specific early T proteins, growth characteristics, the absence of detectable commensals, and their tumor-inducing capacities in hamsters of different ages and different inbred strains as well as in congenitally athymic nude mice (*5*).

We then grouped Ad2- and Ad12-transformed LSH hamster embryo cells into three tumorigenic phenotypes (Fig. 1). Ad2-transformed LSH embryo cells that represent tumorigenic phenotype I failed to produce tumors in hamsters of any age when the animals were challenged subcutaneously with 10^8 cells; fewer than 10^6 of these cells induced tumors when they were injected into nude mice. Ad2-transformed cells that represent tumorigenic phenotype II produced tumors when transplanted into nude mice and newborn hamsters, but 10^8 cells failed to produce tumors when transplanted into syngeneic immunocompetent adult hamsters. Ad12-transformed LSH hamster embryo cells represent tumorigenic phenotype III; these cells produced tumors with similar efficiencies in nude mice and in syngeneic, newborn, and adult LSH hamsters.

During these experiments we made the unexpected observation that SV40-transformed LSH (haplotype Hml^a) hamster embryo cells would produce tumors in adult syngeneic and adult allogeneic CB (haplotype Hml^b) hamsters with almost equal efficiency (*8*) (Fig. 1). [For a review of the hamster major histocompatibility complex (MHC) see (*9*).] Hamster cells transformed by Ad2 and Ad12 were readily rejected by allogeneic CB hamsters. The ability of SV40-transformed LSH hamster cells to induce tumors across a major histocompatibility barrier could not be explained by a lack of immunogenicity of the transformed cells. The SV40-transformed cells used in these studies were highly immunogenic in that they conveyed high levels of protection (100-fold to greater than 1000-fold) to immunized hamsters in assays for SV40 transplantation antigens (*5*). This degree of protection is as good as, or better than, that observed with Ad2-transformed LSH hamster cells (Fig. 2). In addition, CB hamsters previously exposed to LSH alloantigens by immunization with LSH spleen cells rejected 10,000- to 100,000-fold more tumor-producing doses of SV40 LSH tumor cells than did nonimmune CB hamsters (*5*).

These results implied that the ability of SV40-transformed LSH hamster cells to produce tumors in immunocompetent adult CB hamsters was not due to the lack of expression of SV40 transplantation antigens or the absence of LSH histocompatibility antigens on transformed cells or tumor cells. The data permitted us to discriminate between highly oncogenic SV40-transformed LSH embryo cells and highly oncogenic Ad12-transformed LSH embryo cells that expressed tumorigenic phenotype III and allowed us to assign SV40-transformed LSH cells, and subsequently PyV-transformed LSH cells which also produced tumors with high efficiency in allogeneic CB hamsters, to tumorigenic phenotype IV. From these data we concluded that SV40- and PyV-transformed hamster cells possessed an inherent resistance to allograft rejection while Ad2- and Ad12-transformed hamster cells did not. These data further suggested that either the Ad2 and Ad12 early T proteins might be associated with the induction of different levels of susceptibility to cellular immune rejection or that SV40 and PyV early T proteins might be involved in the induction of resistance to allograft rejection in Syrian hamster cells transformed in vitro.

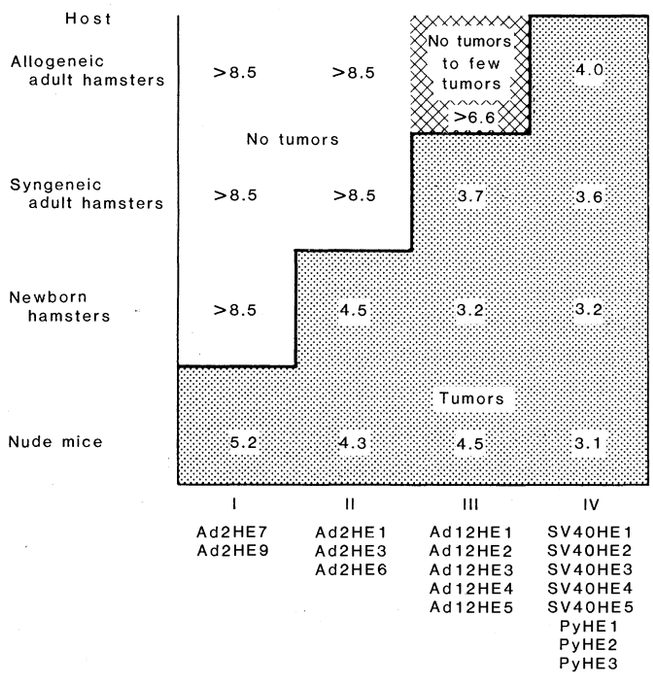

Fig. 1. Spectrum of four distinct tumor-inducing capacities (tumorigenic phenotypes) of LSH hamster embryo cells transformed by Ad2, Ad12, SV40, and PyV that was defined by the interactions between the transformed cells and the cellular immune response. Tenfold dilutions of transformed cells were injected subcutaneously into nude mice and hamsters, and the animals were observed for tumor development for 10 to 12 weeks. The number of transformed cells per tumor-producing dose at the 50 percent end point (TPD_{50}) was determined by the method of Karber (*21*). The numbers indicate the average number of cells (log_{10}) per TPD_{50}; the standard error of these mean values ranged from ±0.1 to 0.5. All cell lines were titrated in syngeneic and allogeneic adult hamsters; three or four cell lines from tumorigenic phenotypes III and IV, respectively, were titrated in nude mice or newborn hamsters.

Tumorigenicity Does Not Correlate with Immunogenicity

Cells transformed by DNA tumor viruses in vitro or derived from virus-induced tumors are highly immunogenic because of the expression of virus-specific T protein–determined transplantation antigens on their surfaces (*7, 10*). The potential to induce differences in the expression of these transformed-cell-sur-

face, transplantation antigens has been, heretofore, the accepted explanation for the differences in the tumor-inducing capacities of DNA tumor viruses and DNA tumor virus–transformed cells (*11*). The concept that differences in virus-specific transplantation antigens on the surfaces of transformed cells determine their tumor-inducing capacity suggests a theoretically proportional relation between the qualitative or quantitative expression of functional, cell-surface, transplantation antigens and the capacity of immunologically naïve animals to recognize and reject such transformed cells. Thus, DNA virus–transformed cells that are highly immunogenic (that is, they induce high levels of virus-specific transplantation immunity) should be theoretically less tumorigenic in immunocompetent animals than transformed cells that are weakly immunogenic (that is, they induce lower levels of virus-specific transplantation immunity). This concept has been particularly difficult to evaluate because of the problems of characterizing those virus-specific T proteins expressed on the surface of transformed cells that function as transplantation antigens. In spite of the general acceptance of this concept, it does not explain the paradox that highly immunogenic DNA virus–transformed cells and highly immunogenic neoplastic cells from DNA virus–induced tumors are highly tumorigenic for immunocompetent adult animals.

We evaluated the possible role of the immunogenic, virus T proteins expressed on the surfaces of our DNA virus–transformed cells by comparing the expression of functional, virus-specific, transplantation antigens in bioassays (Fig. 2). These results were assessed within the context of the possible theoretical relation between the immunogenicity of DNA virus–transformed cells and their tumor-inducing capacity. For this comparison, we studied the virus-specific immunogenicities of eight cell lines derived from hamster embryo cells transformed by Ad2, Ad12, and SV40 (Fig. 2). These cell lines represented each of the four tumorigenic phenotypes that were described above. Each of these cell lines was highly immunogenic in that each conveyed greater than 100-fold levels of protection to tumor cell challenge in immunized hamsters compared to nonimmunized controls. With the exception of the two Ad12-transformed cell lines, which completely protected immune animals against a tumor cell challenge in these assays, there was remarkably little difference in the capacity of the nontumorigenic (for hamsters) Ad2-transformed hamster embryo cell lines (Ad2HE7 and Ad2HE9) that expressed tumorigenic phenotype I to protect immune hamsters (resistance index, RI, 107 ± 59 and 563 ± 94, respectively) compared to the two highly tumorigenic SV40-transformed hamster embryo cell lines (SV40HE1 and SV40HE2) that expressed tumorigenic phenotype IV (RI, 439 ± 87 and 562 ± 0, respectively). Among these cell lines there was little or no correlation between tumor-inducing capacity and immunogenicity. On the basis of these data, we concluded that the T protein–determined, virus-specific immunogenicity of DNA virus–transformed LSH hamster embryo cells plays little or no role in determining their tumor-inducing capacities in hamsters. Our data agree with the findings of others who have also been unable to associate differences in the immunogenicities of DNA virus–transformed mouse and rat cells with differences in their tumor-inducing capacities (*10, 12*).

Tumorigenicity Correlates with Cytolytic Susceptibility

The results of histopathological studies performed during the course of rejection of Ad2-transformed hamster cells by immunocompetent animals suggested that host mononuclear inflammatory cells (lymphocytes and macrophages) appearing at the tumor site within less than 3 days were responsible for transformed cell destruction (*13*). The rapidity of this protective host inflammatory cell response in immunologically naïve animals suggested that it was not composed of specifically sensitized host effector cells. This host mononuclear cell response, which was observed in both Ad2 and Ad12 tumor sites, had a differential effect on Ad2-transformed cells that were destroyed and Ad12-transformed cells that were resistant to destruction and that induced progressive malignancies. These findings also indicated that the nature of this response was different from the immunologically specific cellular immune response induced in specifically immunized animals which led to the efficient rejection of all types of transformed hamster cells tested (Fig. 2). These observations suggested the possibility that these DNA virus–transformed hamster cells differ in their susceptibilities to destruction by host cellular defenses. Such defenses include the mononuclear cells that appear at the tumor site prior to the induction of the immunologically specific host cellular response directed at virus-specific, cell-surface antigens.

To test the hypothesis that the tumorigenic phenotypes of these transformed cell lines were associated with differences in susceptibility to lysis by immunologically nonspecific host effector cells, we used cell lines from the different tumorigenic phenotypes and exposed

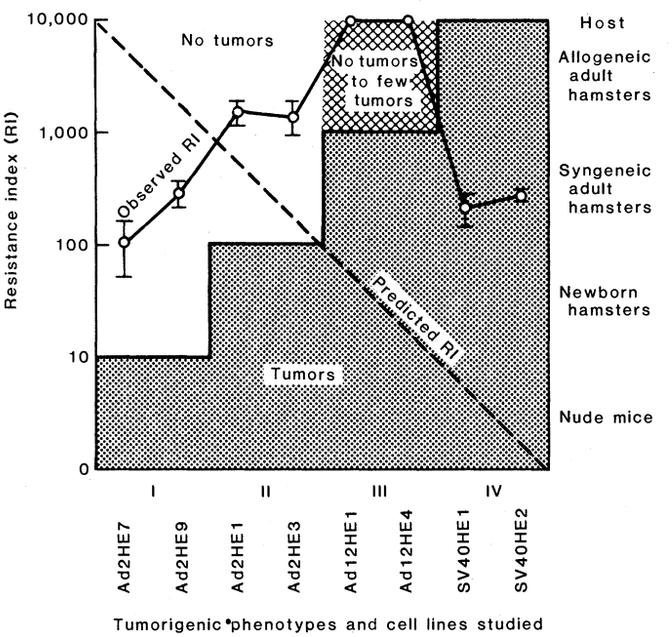

Fig. 2. Comparison of tumorigenic phenotypes of DNA virus–transformed hamster embryo cells with their virus-specific immunogenicities. Adult LSH hamsters were immunized with the transformed cell lines shown on the abscissa for each of the groups. The immunization schedule consisted of an intraperitoneal injection of 3×10^6 irradiated (3000 R) cells per week for 3 weeks. One week after the last immunization, immune and nonimmune hamsters were challenged with graded doses of viable tumor-producing cells. Over the next 3 months the animals were observed weekly for tumor development. At the end of this period the number of cells per TPD_{50} in the immune and nonimmune animals were compared and expressed as the resistance index (RI) calculated from the total number of cells per TPD_{50} in the immune animals divided by the number of cells per TPD_{50} in the nonimmune animals. The predicted RI line reflects the theoretical relation that should exist between the tumorigenic phenotypes of transformed cells and their virus-specific immunogenicities if immunogenicity plays a determining role in the tumor-inducing capacity.

them in vitro to hamster natural killer (NK) cells and activated hamster macrophages (*6, 14*). There was a direct correlation between the resistance of transformed cell lines to lysis by NK cells and their ability to induce tumors in immunocompetent animals (Fig. 3). Thus, Ad12- and SV40-transformed hamster cell lines were relatively resistant to NK cell–mediated lysis, whereas Ad2-transformed cell lines, which induced tumors only in immunodeficient hosts, were highly susceptible to lysis.

These data, obtained by using NK effector cells, are compatible with the hypothesis that DNA virus–transformed hamster cells that express increased tumor-inducing capacity in this spectrum of hosts should exhibit decreased susceptibility to rejection when confronted with immunologically nonspecific host effector cells. Raska and Gallimore (*15*) have obtained similar results from their studies of the susceptibility of Ad2- and Ad12-transformed rat cells to lysis by rat NK cells. As opposed to their resistance to lysis by hamster NK cells, Ad12-transformed hamster cell lines were found to be highly susceptible to lysis by bacillus Calmette-Guérin (BCG)–activated hamster macrophages, whereas SV40-transformed hamster cell lines were resistant to macrophage-mediated lysis. Thus, these highly activated macrophage populations were able to discriminate between transformed cells expressing tumorigenic phenotypes III and IV.

Since the cytolytic activity of both NK cells and macrophages may be stimulated as a result of exposure to alloantigen (*16*), it is possible that the increased susceptibility of Ad12-transformed hamster cells to lysis by activated hamster macrophages reflects the inability of these transformed cells to survive in the allogeneic host. In contrast, the resistance of SV40-transformed cells to these activated macrophages may explain their increased tumor-inducing capacity in such an environment. It is unlikely that macrophages infiltrating early tumor sites in immunologically naïve, syngeneic hosts exhibit cytolytic activity as potent as that observed with BCG-elicited macrophages. We now have evidence that nonspecific macrophage activation in vivo in response to exposure to DNA virus–transformed cells results in a macrophage cytolytic activity similar to that observed with hamster NK cells and significantly lower than that expressed by BCG-activated macrophages. Specifically, we have observed that Ad12- and SV40-transformed hamster cell lines are relatively resistant to lysis by such macrophage populations when compared to Ad2-transformed cell lines (Fig. 3) (*17*).

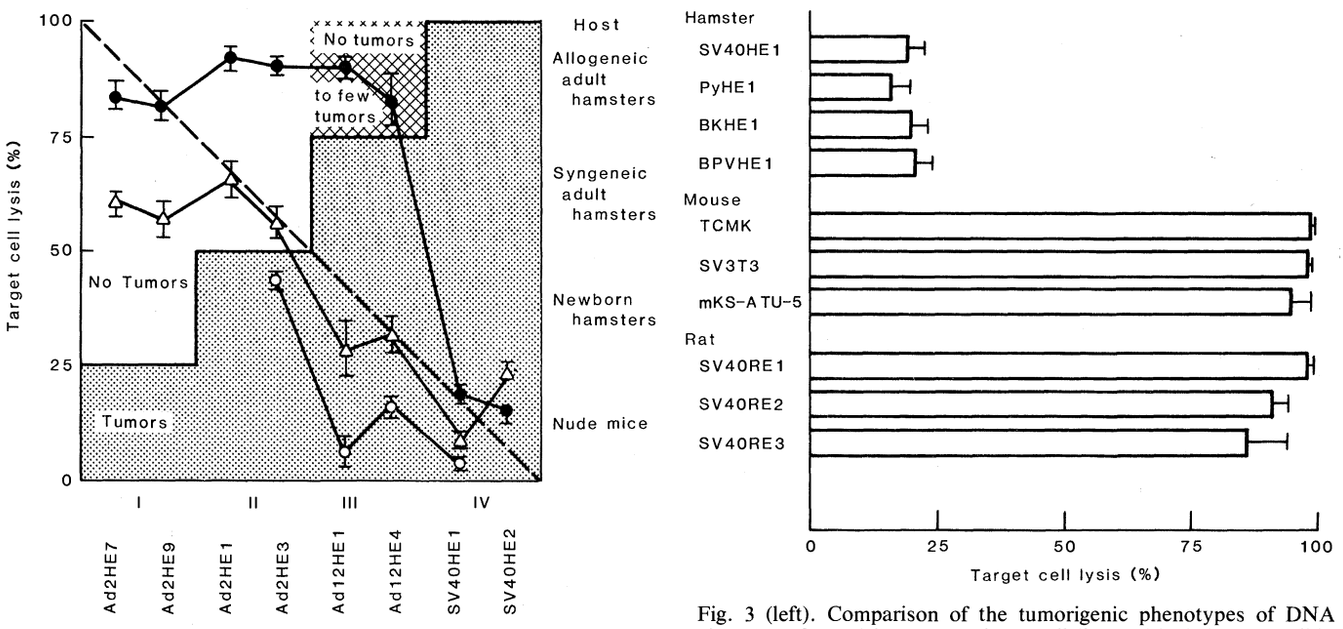

Fig. 3 (left). Comparison of the tumorigenic phenotypes of DNA virus–transformed hamster embryo cell lines with their susceptibilities to lysis by three different host effector cell populations. Transformed cells (target cells) were labeled with [^{3}H]thymidine and assayed for cytolytic susceptibility (as evidenced by release of ^{3}H from the nucleus after 48 hours) on monolayers of BCG-activated hamster peritoneal macrophages (●) or transformed cell-elicited hamster peritoneal macrophages (○) or in suspensions of spleen cells from nonimmune adult hamsters (△). Macrophage to target cell ratios were approximately 33:1. Spleen cell to target cell ratios were 100:1. BCG-activated macrophages and nonimmune spleen cells were prepared and assays were performed as described (*6*). Transformed cell–elicited macrophages were obtained by peritoneal lavage from adult hamsters 1 week after a single intraperitoneal inoculation of 1×10^7 irradiated (3000 R) Ad2HE3 cells. The same pattern of target cell lysis was obtained with macrophages elicited by irradiated SV40HE1 cells (data not shown). Washed macrophage monolayers always contained at least 95 percent macrophages as indicated by stained cell morphology, staining with nonspecific esterase, and phagocytosis of latex beads. Each point represents the mean ± standard error of the mean of the results of at least three experiments. The dashed line represents the theoretical relation that should exist between the tumorigenic phenotypes of transformed cells and their cytolytic susceptibilities if such putative host effector cells play a role in determining transformed cell tumor-inducing capacity. All of these cell lines were negative by anaerobic culture for mycoplasmas. Fig. 4 (right). Susceptibilities of papovavirus-transformed hamster, mouse, and rat cells to lysis by BCG-activated hamster macrophages. Lysis of target cells labeled with [^{3}H]thymidine after 48 hours on monolayers of BCG-activated hamster macrophages at macrophage to target cell ratios of approximately 33:1 was measured as described (*6, 14*). Identical patterns of target cell lysis were obtained for SV40HE1- and PyHE1-transformed hamster cells and for the SV40-transformed mouse and rat cell lines with the use of monolayers of BCG-activated mouse macrophages (data not shown). The hamster target cell lines were derived from clones of LSH strain hamster embryo (HE) cells transformed by SV40, murine polyoma (Py) virus, human BK virus, or bovine papilloma virus (BPV) as indicated. The mouse target cell lines were all transformed by SV40 and were derived from either the C3H/Mai (TCMK) or the BALB/c (SV3T3; mKS-A TU-5) strain (*22*). The rat target cell lines were derived from clones of Sprague-Dawley rat embryo (RE) cells transformed by SV40. All of these cell lines were negative by anaerobic culture for mycoplasmas. Each bar represents the mean ± standard error of the mean of the results of at least three experiments. All four papovavirus-transformed hamster cell lines were less susceptible to macrophage-mediated lysis than were the SV40-transformed mouse and rat cell lines.

Regulation of Transformed Cell Cytolytic Susceptibility

The aforementioned data indicate that immunologically nonspecific lymphocyte and macrophage effector cells selectively recognize and destroy Ad2-transformed hamster cells (tumorigenic phenotypes I and II) but do not efficiently destroy Ad12- or SV40-transformed hamster cells (tumorigenic phenotypes III and IV) unless the effector cells are stimulated to a high level of cytolytic activity with an agent such as BCG, in which case Ad12-transformed (tumorigenic phenotype III) but not SV40-transformed (tumorigenic phenotype IV) cells are destroyed. Moreover, these data suggest that the immunologically specific host effector cells that mediate transplantation immunity in previously immunized animals do not discriminate between transformed cells from these four tumorigenic phenotypes, because all four types of cells are efficiently destroyed in vivo. Since NK cells and macrophages do not require previous sensitization to transformed cell-specific antigens for the expression of cytolytic activity, these nonspecific host effector cells may provide an initial barrier to neoplastic cell proliferation in vivo during the period of time required for the induction of specific cellular immunity. The reasons for the differences in the cytolytic susceptibilities of these DNA virus-transformed hamster cell lines exhibiting different tumorigenic phenotypes are unknown. A key component in the approach to this question is whether the regulation of cytolytic susceptibility and resistance in transformed cells is under viral genetic control.

We demonstrated recently that the increased cytolytic susceptibility of Ad2-infected hamster cells is associated with the expression of Ad2 T proteins (*18*). With Patch, Hauser, and Levine we also found that Ad2 early gene expression governs the cytolytic susceptibility of hybrid cells formed between Ad2- and SV40-transformed hamster embryo cells (*19*). These data imply that Ad2 T proteins actively induce a state of increased cytolytic susceptibility in hamster cells. This possibility raises interesting questions concerning the role of SV40 T proteins in the regulation of transformed hamster cell resistance to lysis by these effector cell populations. Do SV40 T proteins actively induce a state of cytolytic resistance in hamster cells or are SV40 T proteins simply unable to induce increased cytolytic susceptibility in hamster cells during transformation? Data from several experiments suggest a possible answer to this question. We have observed that nontransformed hamster cells, like SV40-transformed hamster cells, are highly resistant to lysis by both hamster NK cells and activated macrophages (*18, 19*). Nontransformed cells from other rodent species are also resistant to macrophage-mediated lysis (*20*); however, SV40-transformed cells from species other than hamsters are highly susceptible to destruction by activated macrophages (Fig. 4).

While these data do not rule out the possibility that SV40 T proteins actively induce or contribute to cytolytic resistance in hamster cells during transformation, the most conservative explanation of these observations is that, like Ad2 T proteins in hamster cells, SV40 T proteins induce increased cytolytic susceptibility during transformation of cells from other species but, unlike Ad2 T proteins, SV40 T proteins do not induce such increased susceptibility during transformation of hamster cells. A necessary corollary of this hypothesis is that the induction of transformation and the induction of cytolytic susceptibility are dissociable events, a conclusion that is justified on the basis of the observation that all of the cell lines described in these studies share generally accepted properties of transformed cells but differ greatly in cytolytic susceptibility.

In an attempt to determine whether the alteration of the expression of SV40 T proteins in transformed hamster cells results in increased cytolytic susceptibility, we studied hamster cell lines transformed by the viable SV40 deletion mutant 2005. Such cell lines express SV40 large T protein but lack SV40 small T protein and are equally resistant to macrophage-mediated lysis and equally tumorigenic in syngeneic and allogeneic adult hamsters compared to hamster cell lines transformed by wild-type SV40 (data not shown).

Therefore, SV40 small T protein expression does not appear to be required for cytolytic resistance in SV40-transformed hamster cells. To determine whether the cytolytic resistance of SV40-transformed hamster cells is unique to transformation by SV40, we also studied hamster cell lines transformed by PyV (PyHE1), human BK virus (BKHE1), and bovine papilloma virus (BPVHE1). These cell lines were found to be equally resistant to lysis by BCG-activated hamster macrophages compared to the SV40-transformed cell line, SV40HE1 (Fig. 4). These cell lines, transformed by four different papovaviruses, were also equally resistant to hamster NK cell-mediated lysis and induced tumors with equal efficiency in adult allogeneic CB hamsters (data not shown).

Cumulatively, the results of our studies suggest that the expression of early DNA viral gene products (that is, early T proteins) in rodent cells during infection and subsequent neoplastic transformation may determine the cytolytic susceptibility of the transformed cells when they are confronted by immunologically nonspecific host effector cells. The fact that SV40 induces a high level of susceptibility to lysis by activated macrophages in transformed mouse and rat cells but does not induce a similar increase in cytolytic susceptibility in transformed hamster cells compared to nontransformed cells is compatible with the observation that the oncogenic virulence of SV40 and the cells it transforms is unique to hamsters.

Our working hypothesis concerning the mechanisms by which these different levels of cytolytic susceptibility are induced during transformation is that early viral gene product expression in certain virus-cell combinations, such as Ad2-hamster and SV40-mouse or SV40-rat, causes increased cytolytic susceptibility of infected and transformed cells, whereas early viral gene product expression in other virus-cell combinations, such as Ad12-hamster and SV40-hamster, results in either a reduced level of cytolytic susceptibility or in no increased cytolytic susceptibility compared to nontransformed cells. If one assumes that nonspecific host effector cells play an important role in early host rejection of DNA virus–transformed cells, the ability of a transforming virus to immortalize cells, thus inducing unlimited growth potential without inducing an increased susceptibility to the lytic mechanisms of these effector cells, might result in a significant advantage for the neoplastic cell in the immunocompetent host. A further understanding of the mechanisms by which these differences in cytolytic susceptibility are induced during transformation might be achieved by defining the specific gene products responsible for induction of cytolytic susceptibility and exploring the functional properties of these proteins in the context of the interactions between transformed cells and host effector cells.

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The 1984 Nobel Prize in Economics

The Alfred Nobel Prize for Economics, on this 16th occasion of its award, goes to Sir Richard Stone of Cambridge University. Rather than divide the honor among scholars, as has often been done in the past, the Royal Swedish Academy of Sciences chose to stress the importance of Stone's work in formulating the system of integrated national-income accounts that have proved so useful in the post World War II era (*1*).

Economist peers will second this emphasis, while at the same time insisting that Stone has two other important achievements to his credit: innovations in econometric measurement of demands for groups of goods and services (*2*); and in linear matrix models permitting extrapolation and testing of growth relations (*3*). In framing his will, Alfred Nobel set a bad precedent for the physical sciences. A Lord Rayleigh could not win a Nobel Prize for a lifetime of deep and versatile work in all branches of theoretical physics, but fortunately could be fitted in under the rubric of being a discoverer of a new and rare component of the atmosphere. Arnold Sommerfeld, for all his innovations over an extended period of time, was not so lucky. Fortunately, committees know how to fudge on their own procedures, so that a Percy Bridgman as well as a lucky bystander could win the laurel leaves and lucre.

Social scientists, eager as always to ape the more exact sciences, can be counted on to take over the vices as well as virtues of their pace setters. Fortunately, though, the 1984 prize goes to a scholar prolific both in the empirical and theoretical sides of political economy and one recognized for having rung the bell of novel accomplishment several times.

The Anatomy of Social Accounts

First researches, like first loves, are important. J. R. N. Stone first gained world renown almost a half century ago for measurement of families' budget patterns with respect to spending and saving (*4*). Anyone who doubts that there is such a thing as economic law need only look at these well-documented ancient regularities. Stone's statistical investigations of the propensities to consume and save assumed an especial importance in the brave new dawn of John Maynard Keynes's revolutionary 1936 *General Theory of Employment, Interest and Money* (*5*).

During World War II itself, in the Offices of the War Cabinet's think tank attached to Keynes, Stone worked closely on setting up national-income accounts with James Meade (himself to share the 1977 Nobel Prize for innovation in international trade analysis). Those ideologically distanced from Lord Keynes—the late Lord Robbins and Sir Dennis Robertson for example—have testified to the exhilarating quality of that charmed circle. It was there that Stone and Meade made their first U.K. estimates, and forged the tools of interlocking accounts appropriate to a nation and, by extension, to a region or the whole world.

Cambridge University was not a friendly environment in the postwar years for a Department of Applied Economics in which people actually dirtied their hands manipulating empirical data. Stone fortunately wore the right tweeds, and as a Fellow of King's College and a protégé of Maynard Keynes was able to protect a revolving corps of able researchers. Not all of them spoke with top drawer accents and it must be admitted that many were colonials and Americans. But science, as we are told, recognizes no distinctions of class or race. Still it was considered rather much when a chair designated for finance and accounting went to a don (Stone himself) who had never met a payroll and whose double-entry items referred to societies and sectors and not to corporations and wholly owned subsidiaries.

Good wine travels far. What was good for the United Kingdom was found to be good for the United States and became the pattern for the United Nations community generally as the Stone square matrices of interlocking fund flows became the *lingua franca* of world statisticians: involved was a *production* account, and one each for *consumption, accumulation*, and *foreign finance*.

Physiology of the Circular Flow

Parallel with these accounts at the national level, there was being developed by Wassily Leontief at Harvard a