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Review

Reflections on tumor origin, immunogenicity, and immunotherapy

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The antigenic and immunogenic properties of tumors, and hence the planning of immunotherapeutic approaches, must be considered in the light of tumor origin. Two broad categories of neoplasms can be distinguished in terms of etiology and immunologic behavior. In discussing these, the term 'tumor-associated antigen (TAA)' will be employed to subsume all constituents of neoplastic cells that incite, or serve as targets of, immunologic reactivity in the autochthonous (or syngeneic) host and that are demonstrably distinct from components of corresponding normal cells in kind, magnitude of expression, molecular arrangement, or appearance in ontogeny or tissue locality; designation of a TAA as 'immunogenic' indicates specifically that the determinant elicits immunologic responses of defensive import [25]; and a tumor is denoted as 'spontaneous' when it arises, whatever the cause, without intentional manipulation by the investigator.

Tumors that are inducible experimentally or that arise spontaneously only or predominantly when host immunologic capability has been severly compromised by factors other than the carcinogenic stimulus

Such tumors are seen in patients suffering from congenital or acquired immunodeficiency syndromes, viz., AIDS, or who have been subjected to intentional immunosuppression, as are recipients of kidney allotransplants. Tumor induction in the laboratory is conditioned on preceding experimental suppression of immunologic capacity. In subjects not immunologically compromised, immune resistance is adequate to guarantee destruction of nascent neoplastic variants.

The known instances of such tumors are those induced by ubiquitous oncogenic viruses. Protection against them accrues from host evolution of effective rejection responsiveness, when a large segment of the species has been exposed to the causative agents for a sufficiently long period of time [15]. Where the targets of the rejection responses are products of the viral transforming genes, i.e., the immunogenic TAA are a direct expression of the transformed state, as is the case for tumors induced by the oncogenic DNA viruses, tumor cell escape by antigen loss, depletion, or masking is not likely.

It may be that carcinogenic agents other than viruses also induce tumors that can develop progressively only in the face of strong extrinsic immunosuppression, where these neoplasms too would otherwise pose a serious survival threat to the species and where their rejection antigens are similarly an unexpendable aspect of the transformation even.

It can be said that immune surveillance is indeed highly effective against those tumors which do not (normally) occur.

Tumors that are inducible experimentally by chemical, physical, and viral agents, or that arise spontaneously, in subjects with no evident immunologic dyscrasia of extrinsic origin

The immunogenic properties of such tumors range from pronounced to absent [1, 10, 23], as indicated by tumorigenic capacity and immunizing potential in experimental subjects and, indirectly, by aspects of their behavior in the autochthonous host [29].

Various inciting agents have been incriminated in the etiology of spontaneous tumors in this category, for instance cigarette smoke derivatives in lung cancer, asbestos in mesothelioma and gastric carcinomas, UV irradiation in skin cancer, and the viruses of Marek's disease of chickens and of feline leukemia. The etiology of many other spontaneous growths is unknown.

The known, diverse inciting stimuli may have one or several identical modalities of action. One is activation of a limited number of oncogenes or proto-oncogenes leading to amplified expression of the normal product or to expression of a somewhat altered product. Such activation can be brought about by direct retroviral transformation, the oncogene being carried and transmitted by a transducing retrovirus; by insertion of a nontransforming retrovirus in the vicinity of c-oncs and their activation by the noncoding viral promotor and/or enhancer sequences; by relocation of c-oncs in the genome by chromosomal transposition; by chromosomal duplicatiation; and by point mutation. Another modality may be deletion of genes that control terminal differentiation, thereby making for ongoing cell replication [4]. Common mechanisms of transformation may be set in motion not only by discrete stimuli impinging from without, but also by inherent errors in DNA structure and organization.

Despite the likelihood that different transforming agents have common loci of action, the differential immunogenicity of the resultant tumors may well be related to the differential intensity of excitation [30]. Oncogene lesions or deletion of differentiation-inducing genes may be critical in transformation, but they are not the only requisite changes in the

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progression of normal cells to autonomous neoplastic deportment [16, 18]. Tumor progression may involve, moreover, the activation of a series of oncogenes [17, 22]. Where carcinogenesis is achieved with high doses of chemical and physical agents, or with viruses selected for efficient, rapid transforming capacity – the usual experimental situation – tumor progression is likely to be accelerated by the telescoping of sequential oncogene events and by the impelling of other stepwise, independent changes in multiple unit characteristics toward frank neoplasia [7, 21]. The acceleration of tumor progression curtails opportunities for selection of less immunogenic (or intrinsically more immunoresistant) clones. Intensive chemical or physical carcinogenesis frequently impairs immunologic ability and thereby also lessens immunoselective pressure on the neoplastic cells. It may lead, furthermore, to secondary molecular changes that are not central to transformation but can contribute to the cells' antigenic divergence and perhaps also facilitate their growth and progression. Retroviruses that lack oncogenes (v-oncs) and that transform because of their integration into the host genome in the vicinity of c-oncs frequently also make for the expression of antigenic viral components on the cell surface; although their presence is also not an indispensable aspect of the transforming process and although they can be lost or selected against, they act at times as protective immunogens.

Where carcinogenesis is moderate, on the other hand, as may be presumed to the case for most spontaneously arising neoplasms, undue quickening of tumor progression is not anticipated, nor is the occurrence of pronounced incidental alterations in molecular architecture thought to be likely.

Where transformation is actuated by an exaggerated or untimely elaboration of products within the normal genetic repertoire of the cell, distortions in antigenic profile from normal that directly reflect the transforming event will be quantitative, or in relation to the usual sequence of appearance of differentiation markers in the ontogenesis of cells and organism and to their usual distribution in tissues. Deviations from normal cell antigenicity in only the amount, or time and place of occurrence, of determinants may be recognizable by the host but they are not apt to generate strong, defensive immune reactions. They could, however, become the targets of immune reactions that have been provoked by *modified* TAA. Even very limited antigenic aberrations of a tumor cell might thus serve as a 'handle' for therapeutically intended immunologic manipulations.

Where transformation is effected by the production of altered cell constituents, viz. mutation in c-oncs or coding by v-oncs for somewhat different products, the resulting TAA may be immunogenic. However, selection of the host species for powerful resistance against them cannot be assumed where the ubiquity of the threat in early life is not such as to endanger the species.

Those tumors that are immunogenic may develop progressively in the primary host, despite their immunogenicity, for one or several additional reasons. The immunologic impairment that often accompanies intensive carcinogenesis may permit nascent neoplastic variants to establish a foothold. There may be an unrecognized, highly specific immunologic dyscrasia of extrinsic origin. And established tumors are proficient at various escape mechanisms from immunologic attack [27].

Where carcinogen-induced immunosuppression is transient, the later fate of the tumor will depend on the rapidity of immunologic recovery and on the ability of the heterogeneous neoplastic cell population to meet renewed immune reactivity by means of neutralization or avoidance, adaptively or through selection.

Immunologic intervention

Immunogenic tumors that arise in immunologically incompetent hosts may be susceptible, in principle, to intervention aimed at restoring immune capacity. It might prove valuable to identify the particular immunologic reactivities that most effectively hold such neoplasms in check in immunologically normal subjects, so that efforts at immunologic rehabilitation can be focused on restoring, and heightening, these capabilities.

For the commonly occurring cancers of man, the operative assumption must be that tumor-associated immunogenicity is in most instances absent or restricted. Their inability to evoke *defensive* immunologic responses does not, however, necessarily denote them as immunologically inert. As indicated above, some digressions from normal antigenic profile, even if not of qualitative nature, can be expected to accompany most if not all neoplastic transformations. Normal subjects often display a degree of immunologic reactivity against some normally represented self components and products [24], and their expression in unusual amounts, time, or tissue locality can be presumed generally to favor autoreactivity. Even where spontaneous autoreactivity does not occur, moreover, normal epitopes deviantly expressed on tumor cells may be the *targets* of reactivities artificially incited.

A primary task of tumor immunotherapy, accordingly, is the heightening of any anti-TAA responses that are mounted by the host and their modulation toward cytotoxic effector functions, and the initiation of such reactivities where they are wanting. One approach in this direction is sensitization with TAA preparations whose immunogenicity has been potentiated. Various methods have been suggested: chemical haptenization; chemical, physical, and enzymatic modification; and viral and genetic heterogenization [12, 29]. Other possibilities may be the utilization of tumor cells cultured under conditions that favor the expression of immunogenic determinants, and of tumor cell fractions that, in certain dose ranges, preferentially provoke cytotoxic, rather than suppressor, responses [14]. It could then be hoped that antitumor responses elicited by modified TAA might also be manifested against tumor cells remaining in host tissues: cytotoxic immune elements directed against modified antigens may cross-react with the unmodified determinants; sensitization with modified entities could abolish specific unresponsiveness; and the greater adjuvanticity of modified antigens could make for a responsiveness that epitopes lacking that property fail to elicit.

Another approach lies with the nonspecific stimulation of host immune capability by means of biologic response modifiers (BRMs). Even the crude, first-generation reagents employed in preceding years have been effective in heightening immunologic responsiveness to many antigens, and in steering reactivity toward preferential production of particular immunocytes, antibodies, and cytokines [29, 31]. It may be hoped that newer, characterized BRMs will prove to have still greater and more discriminatory immunopotentiating powers. Correction of any idiopathic or therapy-related immunodeficiency and elevation of desired reactivities above normal baselines may be of value not only in strengthening antitumor defenses, but also in affording cancer patients protection against microbial infections [32].

The possible uses of BRMs go beyond nonspecific potentiation and modulation of specific immunologic responses. Some such reagents create changes in tissue microenvironments, in some instances by provoking immunologic reactions against themselves that are nonspecifically inimical to neoplastic cells. Further work is indicated to explore the therapeutic potentials of BRM introduction into, or in the vicinity of, tumor niduses that cannot be wholly extirpated surgically or radiologically; recent observations on the efficacy of BCG in the treatment of cancers of the bladder [2] underline the validity of such efforts. Certain cytokines excite macrophages and families of lymphoid cells to nonspecific antitumor cytotoxicity, and may be directly toxic to transformed cells [5]. Such endeavors at tumor destruction entirely beg the question of TAA occurrence and proficiency.

Attempts at potentiating TAA immunogenicity and host reactivity against tumor cells may be active, in the tumor-bearing subject, or passive/adoptive, by producing in vitro the desired immunologic reagents and introducing them to the host in quantitites and under conditions deemed favorable on the basis of 'relevant' experimental models [28] and of preliminary clinical trials. (No animal tumor model is in fact relevant to human cancer. What can be done is to pose a question in diverse test models, in each of which prominent parameters of the human situation are simulated as far as possible. A highly contrived but nonetheless interesting system to which we have recently given attention is the testing of chemoimmunotherapy against freshly excised human tumors growing in athymic mice that also receive implants of autochthonous or allogeneic human lymphoid tissue.) The seeming advantages of passive/adoptive immunotherapy over active intervention, as well as the formidable obstacles to be anticipated, have been discussed extensively elsewhere [12].

One passive modality that deserves exploration is the use of monoclonal antibodies against TAA as specific carriers of agents toxic to tumor cells. Where autochthonous or allogeneic antibody formation cannot be attained, even under optimized tissue culture conditions, heterologous antibodies could be considered; and recourse to recombinant DNA techniques might be considered for the construction of antibodies with desired porperties [3]. Methods of genetic engineering could also be applied to the production of cytokines with particularly pronounced direct or indirect antitumor reactivities.

It must be strongly emphasized, however, that the mere provision of immunologic antitumor reagents, actively, adoptively, or passively, falls far short of promising any therapeutic success. This is evidenced by the refractoriness to immunotherapy of most known immunogenic animal tumors once they are entrenched in host tissues, even when strong concomitant immunity can be demonstrated and immunoprophylactic measures are effective. The task that confronts us, then, is far more difficult than a mere recruiting of immunologic weaponry; it is one of complex immunoengineering, and it is uncertain whether it can be accomplished.

The analogy to infectious diseases may be instructive. There, *immunotherapeutic* measures against overt disease have proven of little avail, barring the specialized instances of successful treatment with antitoxin and opsonizing antisera, usually early in the course of infection. It might be counterargued that immune defenses brought to bear by the host against the strongly immunogenic pathogenic entities often do, in fact, ultimately terminate the pathogenic process even where extrinsic immune therapeutic attempts have no impact, and that the advent of antibiotics brought development of these to a halt just as immunology came of age as a science. It could be contended, then, that more sophisticated immunotherapeutic measures might prove themselves in the realm of infectious diseases. That contention does not, however, alter the fact that the pathogenic entities of spontaneous neoplasia are not, on the whole, discernibly immunogenic and that even experimental immunogenic neoplasms are remarkably indifferent to immune attack.

Although there is little assurance that more skilled immunologic approaches than have been undertaken so far will come to make sweeping contributions to cancer treatment, the possibilities of some gains being made against some malignant diseases of man are sufficiently cogent to warrant continued effort.

Immunoengineering

That effort must be predicated on recognition of the lability of host – tumor relationships. Ongoing clonal diversification and heterogeneity [8] of tumor cell populations can be assumed in every case of neoplastic disease, and the antigenic and immunosusceptibility properties of primary and metastatic tumor foci are individually changeable. Host immune capacity can fluctuate widely, and immunologic idiosyncrasies could be of determinant significance; for instance, the point at which specific or nonspecific immune stimulation will lead to suppressor activation cannot be predicted in advance, and individual monitoring with time appears to be needed to prevent elicitation of counterproductive effects. The evolution of malignant pathogenetic processes presents continuously changing situations. Thus, for example, the route of administration must be appropriate to the anatomy of the disease; reagents may be best given IV in some circumstances, while intralesional or intralymphatic modes of administration or closed organ shunts may be more appropriate in others. Immunologic intervention must accordingly be focused, individualized, and modulated as disease progresses.

Careful intercalation of various treatment arms is another basic requirement, not only to prevent treatment antagonisms – as has most probably been the case in many of the trials in which chemotherapy and bacterial adjuvants were given simultaneously – but also with the aim of treatment syngergism. Thus, multiple immunotherapy might effect cumulative damage to neoplastic cells and slow the emergence of resistant clones; chemotherapeutic agents can act to modify tumor cell antigenicity and thereby afford new opportunities for immunologic attack [29], and immunologic *enhancement* of tumor growth could conceivably be beneficial if adjuvant chemotherapy is so timed as to hit at the growth-stimulated cells.

Tumor debulking may in itself facilitate host immune responsiveness [20] and could further the impact of extrinsic immunologic intervention. Debulking may have to be repeated, by chemotherapy and irradiation as well as surgically. Whatever the reason, successful immunotherapy in aminal tumor models is often conditional on responsiveness of the tumor to parallel, sequential chemotherapy [13].

A variety of 'auxilliary' measures may have to be taken to permit manifestation of desired host responses and to prevent tumor cell escape. Plasma exchange and purification have been found therapeutically useful [11, 26], presumably because of the removal of factors of tumor or host origin that block or neutralize, specifically or nonspecifically, immune attack on the tumor. Treatment of the host under specified conditions

with hormones, cyclophosphamide, radiation, and antisera directed at markers selectively expressed by certain T cell subsets could lower the level of immunologic suppressor activity [12]. In the future, it may also prove possible to harness immunologic reactivity more indirectly, for example antibody-mediated reduction of the physiologic shedding by tumor cells of antigenic determinants that can block immune elements [19] and antibody-mediated inhibition of tumor angiogenic activity [6].

The task of immunoengineering may be considered a phantasmagory [9], but then a simplicity of intention to intervene in the nightmarish immunologic complexity of host – tumor relationships appears to be hopelessly delusional.

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