Do Macrophages Destroy Nascent Tumors?  

The hypothesis of immune surveillance has been a powerful heuristic force in immunology over the past decades (1–3). This hypothesis suggests that the immune system protects the host from the development of spontaneous tumors (4–7). The reasons for postulating the existence of supracellular mechanisms to control the development and growth of neoplastic cells are many and have been discussed elsewhere (4–9). The supposition that this function is mediated by the immune system has, however, come under vigorous attack because many of its necessary postulates have not been experimentally borne out (10–17). The basis of these attacks lies in the implicit assumption by many that T-lymphocytes are the primary force mediating surveillance. In fact, multiple mechanisms of immune surveillance may exist (18, 19). The potential involvement of both natural killer cells (NK cells) and effector cells of antibody-dependent cell-mediated cytotoxicity (K-cells) has been raised elsewhere (18, 20–23). We here critically consider the proposition that macrophages effect a central role in immune surveillance.

Differentiation between immune rejection and surveillance is important. By immune rejection, we mean recognition and destruction by components of the immune system of neoplastic or allogeneic cells being present in large number or having left their site of origin by extending locally, metastasizing to another site, or being transplanted into a new environment. By immune surveillance, we mean recognition and destruction by components of the immune system of small numbers of neoplastically transformed cells developing in situ in their own natural microenvironment. At present we have no reason to believe the mechanism(s) mediating the two are necessarily synonymous. It then follows that experiments demonstrating the failure of tumors to evoke rejection or immunization do not necessarily indicate failures of surveillance.

MACROPHAGES AND REJECTION

Abundant evidence suggests that macrophages in collaboration with T- and B-lymphocytes can destroy neoplastic cells in vivo (24, 25). a) Macrophages constitute a significant proportion of the cells in tumors undergoing rejection (24, 25), and cytolytically activated macrophages can be isolated from rejecting tumors (26). b) Agents that depress or deplete macrophages prolong the survival of tumors (25). c) Agents that stimulate the function of macrophages promote the destruction of tumors (25). d) Macrophages are obligated in the destruction of some tumors (27–30). In rejection, macrophages appear to act as effectors after they have been attracted to the tumor and activated there by other components of the immune system (31). Immunotherapeutic models employing administration of tumor-specific antibody or of intralesional injections of immunostimulants such as BCG thus provide evidence that macrophages do destroy neoplasms in vivo if the macrophages can be attracted in large numbers and activated (24, 31, 32).

MACROPHAGES AND SURVEILLANCE

The biology of macrophages indicates they are admirably equipped to serve as effectors of surveillance. Macrophages heavily populate the tissues and are actively motile cells that move toward foreign substances and destroy syngeneic and allogeneic neoplastic cells efficiently in vitro by several mechanisms (33, 34). Macrophages are able to distinguish self from non-self without aid from other components of the immune system. For example, mammalian macrophages bind non-self by naturally occurring, nonspecific opsonins and, at least in the case of effete erythrocytes or denatured collagen, apparently do so in the absence of opsonins (35–40). A phylogenetic basis for this function exists in that phagocytes of invertebrates recognize non-self without the aid of immunoglobulins (41–44).

Of most importance, macrophages can selectively recognize and destroy neoplastic cells in vitro (45–50). Although activated macrophages are most efficient at this selective lysis of tumor cells, resident peritoneal macrophages also can selectively destroy tumor cells (47, 48). Furthermore, these resident cells lyse neoplastic targets to a considerable degree if previously cultured with those or other tumor cells for 2 days (Adams DO: Unpublished observations). The
mechanism by which macrophages selectively recognize and lyse neoplastic cells is not known (24). It does not depend on immunization of the macrophage donor against the tumor cells, and the presence of strong neotumors on untransformed cells does not uniformly lead to cytolysis by activated macrophages (30). Recognition for cytolysis appears to correlate with tumor genicity of the targets (45, 47, 49, 50), though this conclusion has been challenged (51). In any event, activated macrophages can bind tumor cells to their surface more than they bind normal cells or than non-activated macrophages bind either normal or neoplastic cells (52); Marino PA, Adams DO: Manuscript in preparation). This binding leads to selective lysis of the neoplastic cells and promotes that lysis (Marino PA, Adams DO: Manuscript in preparation). The possibility that macrophages recognize an altered surface component on neoplastic cells, perhaps by detecting an alteration of molecular complementarity, is an intriguing but unproved hypothesis.

MODEL FOR MACROPHAGE-MEDIATED SURVEILLANCE

We envision this model: Tissue macrophages recognize small clones of newly developed tumor cells, cluster about them, and destroy the nascent tumor to effect surveillance. One can further hypothesize that the extremely small burden of tumor cells is recognized and destroyed by the macrophages without need of amplification by other components of the immune system. What evidence actually supports this hypothetical model?

Altered function of macrophages can be associated with an altered susceptibility to neoplasia (25). Three instances of increased incidence of tumors—youth, old age, and immunosuppression—are associated with deficient function of macrophages as well as lymphocytes (53-57). Further, stimulation of macrophages may reduce the emergence of tumors. Systemic administration of stimuli, such as BCG, Corynebacterium parvum, and polynucleotides, can delay the appearance of and reduce the incidence of spontaneous and chemically induced tumors (32, 58-61). Mice chronically infected with parasites such as Nippostrongylus or Toxoplasma gondii have a decreased incidence of spontaneous neoplasms (62, 63). Finally, the inherent, genetically defined ability of hosts to mobilize and activate macrophages effectively has been correlated with decreased incidence of spontaneous neoplasms. For example, strains of mice having reticuloendothelial systems that respond well to BCG also have a low incidence of spontaneous tumors, whereas poor responders have a high incidence (64). Lurie's (65) extensive studies of resistance to tuberculosis in inbred rabbits showed such resistance depended on rapid mobilization and activation of macrophages. The rabbits frequently developed adenocarcinomas of the uterus, and strains highly susceptible to tuberculosis had an almost doubled incidence of the tumor. The recent observations on genetic defects in C3H/Hej mice that include reduced activation of macrophages for cytolysis may provide a useful model for the examination of this problem (66). Though none of these examples represent an alteration of function that is specific to macrophages, together they support a protective role for macrophages against the development of spontaneous tumors.

In light of this model, it is also instructive to consider the arguments currently raised against immune surveillance as mediated by T-cells (table 1). Most arguments leveled at the classically formulated version of immune surveillance are not relevant when one considers the macrophage as the effector cell. The extant data support but do not controvert the hypothesis that macrophages exert surveillance. However, the experiments to test this proposition rigorously have not been performed. If macrophages play a role in surveillance, the following postulates are essential: a) Specific depression of macrophage function should be regularly associated with an increased incidence of induced and spontaneous neoplasms and a decreased latency period for these tumors. b) Primary deficiencies of macrophage function should be associated with an

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<th>Table 1.—Arguments frequently raised against the classically formulated concept of immune surveillance</th>
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<td><strong>Argument</strong></td>
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<td>1. Not all tumors are antigenic, and many, particularly spontaneously arising neoplasms, are only weakly antigenic.</td>
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<td>2. Tumors arising in vitro do not generally have &quot;stronger&quot; neoplastic antigens, and tumors arising in vivo do not have the &quot;weaker&quot; neoplastic antigens.</td>
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<td>3. Small tumors may grow in situ for long periods of time without inciting measurable systemic T- or B-cell response.</td>
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<td>4. Nude mice do not have an increased incidence of neoplasms.</td>
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<td>5. Antilymphocyte globulin and other suppressors of lymphocytes generally have no effect on carcinogenesis.</td>
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<td>6. Immunologically privileged sites do not have an increased incidence of neoplasms.</td>
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<td>7. The inherent immunodeficiency may not be associated with a high incidence of nonlymphoreticular tumors.</td>
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increased incidence of spontaneous or induced neoplasms. c) Macrophages should recognize and destroy all or at least most naturally occurring neoplastic cells. Two probable, though not essential, postulates are: 1) Specific stimulation of macrophage function should be associated with a decreased incidence of spontaneous and induced neoplasms with a prolonged latent period. 2) Clinically apparent tumors and effective carcinogens may depress macrophages and thereby subvert their surveillance function.

ESCAPE FROM SURVEILLANCE

We do not believe that the development of any neoplasm abrogates the idea of surveillance. Certainly, hosts occasionally develop extensive infections despite potent defenses that suppress most bacterial invasions. It is important to consider the existence of possible escape mechanisms from surveillance. Clinically apparent neoplasms may be those that have developed the means to subvert macrophage functions. Successful tumors, for example, might be composed of neoplastic cells that are either not recognized or not destroyed by macrophages or that alter macrophage function. Evidence in fact does exist that tumors and carcinogens directly depress the function of macrophages. The accumulation of macrophages at inflammatory sites is depressed in animals given tumor implants (71-77). The neoplastic cells in these animals contain and release a low-molecular-weight factor that specifically suppresses mononuclear chemotaxis in vivo and in vitro (74). Administration of this macrophage chemotaxis inhibitor in mice enhances the ability of small numbers of injected neoplastic cells to become progressive tumors and stimulates the growth rate of the tumors. Further, chemical carcinogens can suppress function of macrophages, such as the synthesis of complement in vitro (79). In vivo, carcinogens can depress the inflammatory accumulation, chemotaxis, and maturation of macrophages well before the carcinogen-induced tumors develop (Snyderman R, Adams DO: Manuscript in preparation). Many environmental pollutants and cocarcinogens also depress effector functions of macrophages (79, 80). All of the above examples represent systemic macrophage suppression. Only local, not systemic, suppression of macrophage function may be needed to hinder surveillance. Mice bearing tumors, for example, may have suppression of activated macrophages within the tumors but not systemically (81). Thus one can hypothesize that the complex transition of normal cells to neoplastic ones capable of forming progressive tumors includes acquisition of the ability to subvert host defenses. Likewise, the ability of chemical carcinogens and tumor promoters to suppress macrophage function may be necessary to their carcinogenic potential in addition to their ability to induce cell mutations. Subversion by tumor cells and carcinogens of the surveillance function of macrophages may be important in the establishment of tumors.

CODA

The purpose of this critique is not to attack or defend the immune surveillance hypothesis per se. Rather, it is to examine a modification of the classically formulated version. The modified version suggests that small groups of tumor cells in their native, unique microenvironment may be recognized by macrophages in situ and destroyed or held in check by them, unless the tumor or a carcinogen subverts the effector function of macrophages. Because many environmental pollutants also suppress the function of macrophages, the role of macrophages in host protection against spontaneous carcinogenesis needs to be established clearly.

This model is completely consistent with both the teleologic and direct evidence currently available and answers many arguments now raised against surveillance. However, the critical evidence necessary to establish or refute the idea is not now available, and the experiments necessary to validate or refute the hypothesis should be performed.

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