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BIOLOGIC AND TECHNICAL CONSIDERATIONS FOR THE DESIGN OF SCREENING PROCEDURES FOR THE ASSESSMENT OF BIOLOGICAL RESPONSE MODIFIERS

In this chapter we present the rationale for the design of a meaningful test system for determining the potential value of biological response modifying agents for the treatment of cancer in general, and metastasis in particular. For the last two centuries, numerous efforts have focused on treating neoplastic diseases by the manipulation of the host with agents which we now classify as biological response modifiers (BRMs). An implicit assumption in these studies has been the belief that clinical cancer is the consequence of altered homeostasis, in which host responses to an oncogenic challenge are diminished or absent. Thus, it was reasoned that the successful awakening or boosting of a host's response to neoplasia should lead to tumor regression. However, clinical immunotherapeutic trials with a variety of agents have yielded discouraging results that are greatly inferior to those obtained in various animal models.

There are several possible reasons for these poor results. In general, animal tumor systems have relied upon the use of neoplasms transplanted into normal syngeneic recipients. In addition, many of these studies were actually investigating prophylaxis, since they involved stimulation of the host before or simultaneously with tumor implantation. Little data have been available on the ability of syngeneic animals to reject established metastases, and even less data are available on the outcome of immunotherapeutic studies of metastasis in animals bearing autochthonous metastatic neoplasms.

BIOLOGIC CONSIDERATIONS

Advances in surgical and radiotherapeutic techniques and improvements in supportive patient care have increased the success rate for treatment of primary neoplasms, but the lethality of most solid cancers can be attributed to their ability to produce metastases. Because metastasis has already occurred in the majority of cancer patients at the time of diagnosis, the main problem in cancer treatment and for BRMs is not the elimination of the primary tumor mass, but rather the elimination or control of disseminated metas-
tases. During the process of metastasis, tumor cells come into direct contact with the various components of the immune system (natural killer cells, B cells, T cells, suppressor cells, antibodies, and macrophages). Unlike the cells within a solid tumor mass, the progenitors of metastatic foci circulate as single cells or small cell clumps and are, therefore, initially highly accessible for interaction with both immunologic and nonimmunologic host factors. Thus, on theoretical grounds, it is reasonable to predict that the immune system could be manipulated by BRMs to become highly efficient in not only inhibiting metastatic spread, but in eradicating established micrometastatic foci. In fact, BRMs may prove useful in this role without being strikingly effective against clinically apparent ("bulky") disease.

Central to the identification of BRMs useful for clinical oncology is the recognition that, in the main, the challenge is the eradication of metastases that occur in the primary host. In this regard, two important facts must be kept in mind. First, metastases do not result from the random proliferation of tumor cells shed into the circulation from the primary tumor. Rather, metastases are produced by minor subpopulations of malignant cells which preexist in the parental neoplasm. Some metastases may actually have a clonal origin, but different metastases can result from the proliferation of different progenitor metastatic cells. However, even within a metastasis of a proven clonal origin, biological heterogeneity can develop very rapidly. This, in part, may be due to the fact that highly metastatic cells exhibit an increased rate of spontaneous mutation as compared with nonmetastatic cells isolated from the same neoplasm. These data may explain the findings that cells populating a metastasis can be antigenically distinct from their parental tumor or from various other metastases. The implications of such findings as they relate to the outcome of specific immunotherapy are quite obvious. Second, normal animals are not, and should not be assumed to be, comparable to animals bearing autochthonous neoplasms. Specific or nonspecific defects may exist in animals, and correction of such defects may require a totally different form of biological modification than that required to assist the normal host in control-