Two Competing Influences That May Explain Concomitant Tumor Resistance

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Abstract

A second tumor inoculum is often inhibited in its growth by the presence in the recipient animal of an earlier implanted, growing tumor. The tumor resulting from the first inoculum may, paradoxically, continue to grow despite the simultaneous inhibition of the growth of the second inoculum, a phenomenon usually called “concomitant immunity.” Evidence now suggests that the phenomenon can be observed in the absence of any recognizable type of immune reaction and might often be named more appropriately “concomitant tumor resistance.”

Consideration of a variety of probably related observations suggests that concomitant tumor resistance can best be explained by the competitive interaction of two opposing influences: a local diffusible, tumor-facilitating environment, produced by both tumor and normal tissues, that is counteracted by circulating inhibitors that are also produced by both tumor and by normal tissues. In an implanted small tumor, because of geometric considerations and diffusion, the action of the local facilitating environment is weak; in a larger tumor the local facilitating environment has a relatively greater influence and thus the larger tumor can continue to grow despite levels of circulating tumor inhibitors capable of inhibiting the smaller growth.

A second inoculum of a tumor is often inhibited in its growth if an earlier inoculum of tumor is growing in the animal; the larger primary growth inhibits the growth of the smaller secondary tumor (concomitant inhibition), but the larger tumor, paradoxically, often continues to grow (concomitant tumor resistance). Numerous authors, as I will now describe, have observed the phenomenon and have offered explanations for the seeming paradox, but none of these seems satisfactory.

Previous Explanations

Ehrlich (1) and Tyzzer (2) postulated that essential nutrients are consumed by the larger tumor, making it difficult for a second tumor to grow (the athrepsia hypothesis). It is not clear why the larger tumor would not also be inhibited by the lack of nutrients. Furthermore, it has been shown (3, 4) that the inhibition can be diminished by increasing the size of the secondary inoculum, an observation that is counter to the expectations of Ehrlich’s athrepsia hypothesis.

Bashford et al. (5) termed the phenomenon “concomitant immunity” and the idea that an immune reaction causes the inhibition of the smaller tumor has been the prevalent theory until comparatively recently. However, much persuasive evidence has now been gathered (3, 4, 6, 7) that shows that the phenomenon can be observed when using nonimmunogenic tumors; when using nude, immunologically deficient mice; and when using nude mice in which natural killer cell and macrophage activity is depressed by treatment with silica. Thus, the term “concomitant tumor resistance” is probably more generally appropriate than is “concomitant immunity” (3); however, immunity certainly enters the equation in those cases in which immunogenic tumors are grown in immunocompetent animals (8–10). The overlap-
larization; concomitant inhibition of the growth of a well-established secondary implant could be augmented by surgically reducing its size (3). However, induction of inflammatory cells in the vicinity of the secondary implant can diminish or eliminate the inhibition of the growth of the secondary implant (13).

The first experiment cited in the previous paragraph was made possible by the fact that concomitant tumor resistance, in contrast to the immunity produced by hydrocarbon-induced tumors, is relatively non-tumor specific (3, 4, 6, 14). It is possible that what specificity does exist is a specificity for some elements of organ- or tissue-type rather than for individual tumors. Consequently, it was possible to use two different tumors, with inherently different growth rates, together in the same animal in order to demonstrate that concomitant tumor resistance is not dependent upon the sequence of tumor transplantation.

Systemic Inhibition of Growth

Numerous lines of evidence, apart from concomitant tumor resistance per se, suggest the existence, in sera, of nonimmune, tumor-inhibiting ligands. Some of these data suggest that the inhibitory ligands are a product of tumor cell metabolism while others suggest that similar ligands may also be produced by normal tissues. Many of the observations could have other explanations or interpretations, but, collectively, they constitute a strong case for the existence of circulating, nonimmune, growth inhibitors.

Ruggiero et al. (11), as already discussed, have demonstrated tumor-produced nonimmunological "seric inhibitors" that cause tumor cytostasis and have shown that the resistance is transferable by parabiosis. Several authors have demonstrated, in experimental systems, that the presence of a large growing tumor inhibits the development of lung metastases (4, 6, 14–16). The sometimes explosive growth of distant metastases, after excision of the primary tumor, has been reported in both clinical and experimental contexts (12, 17); this phenomenon may be, at least in many of the human cases, nonimmunological inasmuch as the incidences of relatively few types of human cancer are modified by immunodepression (18). Perhaps also suggesting the existence of circulating tumor inhibitors is the observation that most circulating tumor cells do not establish metastases but perish in the blood stream (19).

Several observations suggest that systemic growth inhibition is not a phenomenon confined to tumor systems but may be exhibited also by normal tissues. It has been claimed that endocrine organ transplantation is most successful when the corresponding host organ is either removed or diminished (Halsted's law) (20); however, when this phenomenon is seen, it is probably the result an increase in trophic hormones (21, 22). Regeneration of endocrine-dependent organs will, under the stimulus of the appropriate hormones, replace the size of the original organ; thereafter the organ will show no further growth, despite continued hormonal stimulation (23), suggesting a systemic inhibitor. Perhaps most persuasive is the observation that experimental embryomas, produced by syngeneic embryo transplantation, usually in contrast to the placenta-protected intrauterine fetus, show limited growth (24–26) unless malignant transformation occurs (27, 28). Compensatory hyperplasia in the liver (29–32) may be a further example of systemic inhibition. The ultimate inhibition of growth, both in regeneration and in ontogeny, is probably dependent upon a rising titer of systemic inhibitors since the entire organ must receive signals as to how much growth is appropriate (12). Although perhaps not directly relevant to the phenomenon of concomitant tumor resistance, it is worth noting that, in the compensatory hyperplasia of a normal tissue such as the liver, lymphoid elements have been shown to play a role as circulating growth regulators (33).

Local Facilitating Environment

The existence of local growth-facilitating influences is most dramatically shown by the effect of orthotopic tumor transplantation (transplantation into the same tissue- or organ-type as that in which the tumor had originated). Several authors, most notably Fidler et al. (34–39), have shown that certain human tumors that ordinarily grow poorly in the nude mouse may grow quite well if implanted orthotopically. It has also been observed that a capsule, as is seen around a smooth surfaced foreign body (40) or the tumor implantation site in the s.c. tissues of the nude mouse (34) or the artificial capsule provided by a small s.c. placed test tube (41), can sometimes facilitate tumor growth, perhaps by limiting the rate at which facilitating ligands can diffuse away from the site of tumor implantation. A possibly analogous phenomenon may be seen in the facilitation of the growth of a single cell, in tissue culture, when placed in the confining environment of a capillary tube (42). Facilitation of tumor growth can also be accomplished by modifying the local site of tumor implantation by the concurrent implantation of conditioned medium (43), fibroblasts (44), Matrigel (45, 46), or sponge (47); in some of these cases, an inflammatory response might, in addition to supplying growth-stimulating cytokines, limit the rate of diffusion. Conversely, an absence of a local inflammatory response, as produced by the phenomenon of counterirritation, augments the inhibition of the secondary tumor inoculum (13).

Further data, consistent with the idea of a local facilitating environment, come from the observation that the success of tumor transplantation is markedly, in most circumstances, correlated with the size of the tumor inoculum; a large inoculum, in addition to possibly providing a greater variety of genotypes for selection, may provide a local environment more conducive to tumor growth (3, 48, 49).

Although other explanations are possible, taken together, these varied observations are, at the least, consistent with the hypothesis of the existence of tumor-facilitating ligands, produced by both normal and by most tumor cells, that do not ordinarily enter the circulation in significant quantities but which diffuse slowly through the extravascular spaces and usually act locally. The exact nature of these ligands must, at this point, remain a matter of speculation, but it is probable that at least some may be already characterized growth factors. That diffusion of facilitating ligands, away from the local site, actually occurs is suggested by the importance, in some systems, of an apparently confining environment and, in the case of tumor systems, the importance of inoculum size; diffusion from the local site is a necessary condition for the explanation of concomitant tumor resistance that I am proposing.

Mechanism of Concomitant Tumor Resistance

If one grants the existence of circulating inhibitors and of slowly diffusible, largely local, facilitating ligands, concomitant tumor resistance becomes fully explicable. Whenever one of two tumors is large and the other is small, the titer of the circulating inhibitor will be large, because of its production by the large tumor, but the local titer of facilitating factors within the small tumor will be low because of the relatively high rate of loss, by diffusion, from the smaller tumor mass. Within the larger tumor, in contrast, the titer of local facilitators will be large because of the large number of cells producing them combined with the relatively low rate of loss that occurs from a larger mass; therefore, the smaller tumor will be inhibited at the same time that the larger tumor will be relatively protected from the effects of the circulating inhibitors and the larger may thus continue to grow. The same mechanism may also help explain the probable fact that larger
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may be, in general, more resistant to any tumor-inhibiting agent, dietary, chemotherapeutic, radiological, or immunological, than are smaller ones.

Although it is clear that concomitant tumor resistance has little tumor specificity, it is not entirely nonspecific (3, 11). The facilitation of tumor growth by orthotopic implantation may also lack complete organ specificity (50). The complex nature of the specificity may be illustrated by the “soil hypothesis” of metastasis distribution (51); prostate cancer, for example, is markedly facilitated by orthotopic transplantation (38) but metastasizes almost exclusively to bone (52). Many other tumors show a marked predilection to metastasize to particular organs (53). The existence of certain favorable “soils,” as well as the confusing patterns of specificities among circulating inhibitors, may be determined by many different factors that may vary from organ to organ and from tumor to tumor.

The specificities and cross-reactivities among various organs and their derived tumors may often be determined by the varied specificities of known or unknown stromal elements (52, 54), fibroblasts (55), or of factors, such as ELAM 1 (56). Most recently it has been shown that α-inhibin, of the transforming growth factor β family, is a secreted, circulating tumor suppressor protein with gonadal specificity in the mouse (57). However, in the mouse mammary fat pad, the local presence of normal mammary epithelium, but not of other epithelia, promotes the growth of implanted malignant mammary tumors (58).

If not all tumors exhibit the phenomenon of concomitant tumor resistance or exhibit it to differing degrees (3), the implication would seem to be that tumors that fail to exhibit the phenomenon, or show it in small degree, produce little of, and/or are insensitive to the action of, either the circulating inhibitors or the local facilitators or both. Concomitant tumor resistance, since it seems to be present in normal tissues as well as in tumors, probably evolved as a mechanism to help ensure that cells grow only in the appropriate organs and only to the proper extent. It seems reasonable to postulate that tumors grow and metastatize because they are less sensitive to this homeostatic mechanism than are normal tissues.

If life is sufficiently prolonged, there seems to be a significant slowing of tumor growth, a phenomenon that has been extensively documented (12, 59). The implication may be that, although most tumors apparently produce both growth inhibitors and locally acting growth facilitators, the titer of inhibitors within the tumor may usually, as the size of the tumor increases, gradually outstrip the rise in the titer of facilitators. One unusual, apparently nonimmunogenic, mouse tumor has been described that may exhibit an opposite effect, a relatively decreased production of inhibitors as tumor size increases; growth of this tumor produces concomitant tumor resistance but loses this property when the tumor reaches a rather large size (3). One possible explanation could be that this tumor produces so much local facilitator that, when the tumor becomes quite large, significant titers appear systemically, thus providing protection to the smaller tumor from the circulating inhibitors. All that would be necessary would be for the production of facilitator and inhibitor to be uncoupled and for this particular tumor to produce facilitator at a much higher rate than it produces inhibitor. It could be that such a mechanism might be operative in those rare instances in which metastases of human kidney carcinomas have been observed to regress, rather than to be stimulated, shortly after surgical removal of the primary lesion in the kidney (60, 61).

If the seric inhibitors, as I propose, also inhibit the growth of normal cells, a rising titer might, as some have suggested, contribute to the cachexia that is sometimes observed in patients with advanced cancer (62) (reviewed in Ref. 6); however, it must be noted that even large tumors often fail to produce cachexia (11). The possibility that some tumors may grow at a slower rate in older individuals (63–65) suggests the speculation that the titer of circulating inhibitors may rise with age; perhaps such a rise contributes to the debility that characterizes old age. I have previously suggested (12) that a rising titer of inhibitors, with the passage of time in young individuals, might account for the relative benign nature of neonatal tumors and the frequency of spontaneous regression among tumors of early childhood (66). Alternatively, the high incidence of neoplastic disease in old age may suggest that the circulating inhibitors, of the concomitant tumor resistance mechanism, become deficient in advanced age. I tend to favor the notion that neoplasia usually begins as an aberrant compensatory hyperplasia (67) and that one noxious element, contributing to the injury that results in compensatory growth, may be a rising level, with age, of seric inhibitors. Which among these speculations, if any, actually approaches reality is a question that only more work and ingenuity will answer.

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References


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