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The Inhibition of Tumor Growth by Tumor Mass

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ABSTRACT

Evidence suggests that a tumor behaves, in its pattern of growth, like an integrated organ rather than a collection of independently growing cells. Tumor growth tends to slow progressively as size increases and to undergo compensatory growth after partial resection. Consequently, therapies that reduce tumor mass may tend to accelerate the growth of the remaining tumor and tumor metastases. An approach to therapy based upon a simulated increase in tumor mass may be worthy of consideration.

Normal organ growth is obviously precisely controlled and regulated; each organ achieves its allotted size and no more. The older literature concerning the regulation of organ growth was reviewed by Paschkis (1). The mechanisms that regulate this process are largely unknown, but, despite hypotheses to the contrary, probably have little to do with the lymphoid system. Some organs, such as the liver, retain regenerative capacity in the adult; there is evidence that the lymphoid system may play a role in such regeneration (2, 3), and it may play a part in growth control generally (4), but it seems unlikely to be a primary role. Burch and Burwell (5, 6) formulated a theory in which growth was regulated by the lymphoid system and the yardstick by which organ size was measured was contained in that system. Although this theory has appealing aspects and has not been disproven, it has not gained widespread acceptance. Much is known about the critical role of hormones, and more recently of a variety of growth factors, in the regulation of organ growth. However, despite their critical role, these agents appear to be supporting rather than principal players; for example, although androgens are essential for the growth of the prostate, they cannot cause prostatic growth unless the organ is less than the normal adult size (7).

Although the mechanisms regulating the size of normal organs are largely unknown, some attributes of these mechanisms can be deduced. The regulation of organ growth depends upon intercellular communication over some distance; all parts of the organ are "aware" of the size to which other parts have grown. Also, it is obvious that the controls have some organ specificity because various organs grow to differing sizes and to differing schedules; however, it is also apparent that growth among organs is orchestrated since the proportional growth of various organs is much the same in mouse and elephant; thus, some degree of nonspecificity might be anticipated.

Burnet proposed that organs possess identity flags on their cell surfaces that would prevent autoimmune attack (8); from this concept, it was a small step to conceive of identity flags that would regulate organ growth and this led to the proposal of Burch and Burwell (5, 6), already mentioned, and to the proposal of Green (9) that cancer was the result of the loss of cell surface "antigens" (it is clear that Green did not mean antigens in the conventional sense but used that term for want of another) that were necessary to control growth. Many organ-specific molecules that seem to be deleted in cancer cells have been described (10–12), but it is not clear that any of them function as growth-regulating identity flags. Although these theories were rather loosely cast in terms of immune regulation, they can be generalized to encompass any scheme dependent upon cell surface flags that interact with any type of regulatory moiety. In modern terminology, the flags, if they exist, could be thought of as organ-specific and nonspecific receptors for positive and/or negative organ growth-regulating factors, the perturbation of any of which might result in neoplasia.

Whatever the mechanisms that control organ growth, the effect has been described precisely by Laird *et al.* (13, 14); organs, in their growth, follow a Gompertzian growth curve that approaches an asymptote. In other words, growth is exponential, but it is modified by an exponential decline in rate with the approach to full size. Some mechanism monitors the organ size and precisely regulates its growth along the typical Gompertzian curve toward an asymptotic plateau.

Laird *et al.* were further able to show that tumor growth, in a wide variety of examined cases, followed a similar Gompertzian curve (13, 14). This was not caused by failure of blood supply or any other artifact of increased size, but each tumor behaved intrinsically more like a normal organ, in the shape of its growth curve, than like a collection of independently growing tumor cells. The only difference between the growth pattern of a tumor and a normal organ, apart from the tendency of the tumor to metastasize, appeared to be that the plateau size of the tumor was often larger than was compatible with the viability of the host. However, while the host lived, the tumor followed the same shape of growth curve as a normal organ and, if extrapolated sufficiently, would slow and eventually stop growing. Perhaps one could say that a malignant tumor of the mouse simulates, in the pattern of its growth curve, a normal organ in a rabbit or possibly, in extreme cases, an elephant! According to this view, biological progression in a tumor clone merely resets the plateau size upward. It should be noted that the growth of the tumor returned to the starting point when the tumor was reduced in size by transplantation.

A number of observations in the literature support the idea that a tumor is an integrated, organ-like entity rather than a collection of independent cells. Most noteworthy is the work of Heppner and her collaborators (15–17) who showed that, in mouse mammary tumors, mixtures of identifiable subclones tended, in the resulting tumors, to approach reproducible proportions, characteristic for that array of subclones, and that these proportions were largely independent of the starting proportions or of selective pressures favoring particular subclones. The growth of each subclone within the tumor was apparently regulated by the other clones. A similar observation has been reported in a different tumor system by Korn and Downie (18).

An observation of my own, in retrospect, may be analogous to those just described. It was noted that tumors composed of

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mixtures of sublines of differing immunogenicities tended to retain the same overall immunogenicity through many transplant generations (19). This could hardly have been possible were the individual subclones not in some sort of communication that tended to maintain them in rather constant proportions despite varied selective pressures.

Much work directly examining the effect of partial organ or tumor ablation on growth of the residual tumor or of the effect of one tumor upon the growth of the same tumor at a second site ("concomitant immunity") is difficult to interpret, owing to the confounding effects of immune reactions, which are often present in experimental, transplanted-tumor systems, and the simultaneous presence of effects that may or may not be organ or tumor specific.

The most recent work with an apparently nonspecific mechanism is that of Fisher *et al.* (20, 21). These investigators noted that noncurative radiation or incomplete surgical removal of a mouse tumor resulted in a mitotic stimulus to the remaining tumor. Furthermore, they were able to show that the stimulation could be transferred by the serum to a second host and thus acted at a distance. Interestingly, the stimulating alteration in the serum could be prevented by prior treatment of either the donor or the recipient animal with cyclophosphamide, radiation, tamoxifen, or Xoladex. However, there was no evidence of either organ or tumor specificity.

It would seem, *a priori*, that the growth of hepatomas in partially hepatectomized mice or rats might provide information that would help to test the integrated organ hypothesis. However, although the results of this type of experiment are generally consistent with the hypothesis, the system is apparently too complex for easy analysis by presently available means. Lee (22) reported that reducing liver volume by partial hepatectomy did indeed stimulate the growth of s.c. inoculated syngeneic hepatomas, but inhibition of hepatoma growth has also been reported (23, 24). A wide variety of nonhepatoma tumors, both immunogenic and nonimmunogenic, have grown better after partial hepatectomy (25, 26), perhaps because of the increased level of growth hormone that hepatectomy induces (27). Partial hepatectomy also affects the immune system; it prolongs the survival of skin allografts (25) but has also been reported to enhance immune reactivity (23). Thus, partial hepatectomy may have too many and too diverse effects to be readily dissected.

Concomitant immunity, *i.e.*, the inhibitory effect of an existing large tumor upon the growth of a secondary implant of the same tumor, can exist in the apparent absence of lymphoid-mediated immunity, in which case the appellation "immunity" may be a misnomer. (For a discussion of immune mechanisms in concomitant immunity see Ref. 28.) Pasqualini and her associates (29, 30) have demonstrated the "concomitant resistance" phenomenon using nonimmunogenic tumors and in athymic nude mice. There was partial tumor specificity. They have also shown, in these cases, that the inhibition was innocent of any evidence of lymphoid infiltration; it was caused by cytostasis rather than cell death, a point also made by Gorelik (31). The magnitude of the observed effect was correlated with the size of the initial tumor.

These authors (29, 30) also addressed the question of whether or not the concomitant resistance they observed was an aspect of the Gompertzian type of growth described by Laird (14). They came to the conclusion that the two sets of observations were unrelated, because, in the concomitant resistance experiments, they observed evidence of inhibition only in the secondary challenge tumor. The integrated organ hypothesis would have been expected to produce growth inhibition in both tumors, the magnitude of the effect being proportional to the combined tumor mass.

I believe this conclusion, that the nonimmunological aspects of concomitant resistance represent a phenomenon distinct from the integrated organ hypothesis, may have been premature. While the reasons for the relative susceptibility of the secondary tumor to the inhibitory mechanism are completely unknown, I venture to suggest a hypothesis that, if true, would make it unnecessary to postulate a new mechanism distinct from that which accounts for the Gompertzian growth of tumors. I suggest that under the stress of transplantation, the putative tissue identity flags become more available; however, as the tumor grows and the stresses associated with transplantation recede, the flag presentation returns to normal levels. Thus, the secondary tumor, having been more recently transplanted, exhibits more flag and is thus tricked into behaving as though there were more tumor present than is actually the case; it is therefore relatively inhibited.

The idea that putative identity flags might be more available because of the stress of recent transplantation has some precedent. I have recently cited suggestive evidence that such a phenomenon may occur in relation to transplantation antigens (32).

Judging by the work already discussed, it appears that just as the normal liver responds to partial surgical removal by regeneration, so too does the tumor apparently undergo a "compensatory hyperplasia" when a portion is removed or destroyed. This conclusion stems, in part, from the observation of Laird (14) that tumor growth starts again at the beginning of the Gompertzian growth curve when the size of the tumor is reduced by transplantation.

Compensatory hyperplasia, on the part of residual tumor, may help to explain the observations of Noble. Working with hormone-dependent rat tumors, this investigator was able to show that tumor progression toward hormone independence was markedly accelerated by temporary tumor regression (33). It is not clear, at least to me, whether this acceleration was the simple result of the selection of previously existent variant cells or was due to an actual induction of variants; either process might be aided by a compensatory hyperplasia among the residual cells. Certainly the phenomenon of accelerated progression, toward hormone independence, during regression suggests that, in the absence of regression, there is an inhibition of progressor cell variants by the precursor population.

Related to the above, since a tumor and its tissue of origin probably share a common organ-regulatory mechanism, is the observation that regeneration of normal tissue, after partial ablation in the case of the liver or after wounding in the case of the skin, stimulates oncogenesis in those tissues (34–36).

The compensatory growth of residual tumor after therapy may account, at least in part, for otherwise inexplicable observations in the clinic. While hard figures are probably not available, the impression seems to be prevalent that patient survival is, in many cases, benefited little, if at all, by therapies that reduce the tumor burden. In melanoma, partial spontaneous regression is actually a bad prognostic sign (37)! I suggest, from what has been presented concerning the probable integrated, organ-like nature of tumor growth, that the all too often failure to affect survival, by producing partial regression, may be due, at least to some extent, to the compensatory hyperplasia and accelerated progression induced in the residual tumor. Of

course, growth-regulating mechanisms, other than those that are strictly organ specific, such as immunological or hormonal changes, may also be operative to a varying and unknown extent.

It has been suggested, in the cases of hormone-dependent tumors, that hormone deprivation be begun at or before the time of initial surgery or radiation, the rationale being that the tumor burden should be kept as low as possible to reduce the risk of the arisal of more aggressive variant cells (38). This is a logical approach if the tumor behaves like a collection of independently growing cells. However, if the integrated organ concept of tumor behavior is correct, it might be more efficacious to delay hormonal manipulation as long as possible; this is actually the course often followed, as for example in the treatment of prostate cancer, and the integrated organ concept provides a logical rationale for such a practice. A similar argument could be made concerning the simultaneous *versus* the sequential administration of different chemotherapeutic agents. The integrated organ concept also suggests that palliative therapy, instead of attempting to produce the maximal possible regression, might better be designed to keep the size of the tumor at the maximum consistent with the patient's optimal function and comfort.

This hypothesis, concerning the organ-like nature of tumor growth, suggests an even more radical approach to therapy. Since the tumor probably shares with its organ of origin common specificities in regulatory mechanisms, it follows that the tumor might be tricked into behaving as though there existed a lot more of it, or its organ of origin, than is really the fact. In such a case, the tumor might essentially stop growing. Parabiosis with an extracorporeal supply of tumor, or transplantation with an extra supply of the appropriate normal organ, might accomplish this trick. Since such procedures may be impractical, therapy based on this idea probably must await the identification and synthesis of the putative organ-specific control entities that probably circulate (see also Refs. 39, 40, 41).

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