EDITORIAL

Tumor Cell Societies

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Over the past decade there has been growing recognition that cellular heterogeneity is a fundamental property of neoplasia. Diversity in cellular characteristics within tumors has been demonstrated repeatedly in a wide range of phenotypes. These characteristics include growth rate, ability to metastasize, immunogenicity, sensitivity to therapy, and phenotypic stability (1-3).

Even though the concept of tumor cell heterogeneity is now widely accepted, it is clearly too simplistic to explain fully the population biology of neoplasia. In fact, the very ability to isolate, from even advanced cancers, tumor cell clones that differ widely in growth properties suggests that something else must be going on. Otherwise, only the most aggressive and rapidly growing subpopulations should be found. The behavior of tumors, like that of other mixed populations, may not be governed simply by the behavior of the most deviant members. Instead, tumors may be cell societies, ecosystems in which the various members (clones) interact to produce a group dynamic that defines the overall behavior (1,3). Several experimental systems have demonstrated that tumor cell subpopulations can interact (4). Using a mouse mammary tumor model, Drs. Fred and Bonnie Miller and I have shown interactions that modify growth rate, immunogenicity, ability to metastasize, and sensitivity to chemotherapy.

One of the most intriguing interactions involves the stability of clonal phenotype. Poste and associates (5) and Miner et al. (6) reported that, although clones of the murine B16 melanoma changed over time in their ability to metastasize, the metastatic behavior of mixtures of the clones was stable. "Stabilization" was independent of the metastatic phenotypes of the mixed clones; that is, mixtures of highly metastatic clones, as well as mixtures of clones expressing high and low rates of metastasis, could be stabilized for metastasis.

Itaya and co-workers, in this issue of the journal, report experiments that (a) extend observations on interclonal stabilization to another phenotype—namely, one that expresses immunogenicity—and (b) give insight to the complexity of the associated molecular events. These investigators transfected the gene for a well-characterized antigen, the hemagglutinin of influenza virus, into cells of the CT-26 colorectal carcinoma line and then monitored tumor immunogenicity, antigen expression, mRNA production, and gene alterations. They compared the stability of these properties in an uncloned, heterogeneous HA-expressor population of CT-26 cells with that in four independent clones. They found that the uncloned parent population remained stable for all these properties over the 6 months in cell culture, while the clones, independently, underwent extensive variation. Three of the clones became less immunogenic, but to different degrees and at different times. Their molecular parameters also varied, but the level and type of variation differed among the clones in regard to antigen expression, mRNA production, and gene amplification or rearrangement. "Destabilization" of the immunogenic phenotype could not be associated with any one of the molecular changes measured.

What mechanisms could account for such striking results, for so many changes in so many properties? One possible explanation for these results cannot be ruled out. The cloned populations may be no less stable in isolation than they are as members of the parent line, but the stability of the parent population may be only apparent and, as the authors state, may "reflect a balance of the variations manifested by the individual clones." This possibility could perhaps be resolved by monitoring the outcome of prolonged culture of mixtures of the individual clones used, particularly if these clones were labeled in some way that would permit one to follow their individual fates within the mixtures. Other investigators, using methods that allow this type of monitoring, have presented evidence that individual populations do behave differently in a mixed population than when they are isolated (3,5). These results suggest that the behavior of the parent population is not due to some sort of "averaging.

We have used various approaches in attempting to understand the mechanisms of subpopulation interactions. One conclusion from our studies is that the mechanism of interaction seems to be highly dependent on the characteristics of the subpopulations in the mixture. In some experiments, the interactions have been shown to depend on a host response such as an immune reaction (7) or an alteration in drug metabolism (8); in other experiments, they have involved only the tumor subpopulations themselves (8,9). Interactions may depend on cell-to-cell contact (9) or, alternatively, may occur over a distance and be mediated by diffusable factors (8). Although it may be that we have not yet done the proper experiment to identify a mechanism common to all interactions, perhaps we have missed the point because of the reductionist impulse to search for a mechanism, which usually implies a "molecular" mechanism. Members of a society will interact; the mechanism is "any way they can."

As Itaya and colleagues point out, not all tumor cell interactions have the same outcome of "stabilizing" or "balancing" the population. In some cases, an equilibrium is reached gradually, after a period of instability that lasts until one member is maintained only at a low, albeit stable, level (10). In other cases, a heterogeneous tumor will develop into a ho-
mogeneous one, but the same clone will not always emerge the victor (11). In still other cases, a clearly dominant clone will consistently take over the mixture by “clonal dominance” (9,12). It has been suggested that this outcome, which has been described only recently, is characteristic of metastatic clones (12). This may be so, but clonal dominance is not an obligate hallmark of metastasis. We have reported on a tumor cell population in which the dominating subpopulation is not metastatic (9). Furthermore, although Itaya et al. speculate that clonal dominance may depend on host selection, in our tumor cell population, dominance occurred in vitro as well as in vivo.

Regardless of their biological significance and underlying mechanisms, tumor clonal interactions and clonal instability have important consequences. It seems that “nature abhors a clone.” Limitation of cellular variability, whether in the laboratory by cloning or in the clinic by noncurative chemotherapy, may provide a stimulus to diversity, resulting in a period of instability that lasts until a new equilibrium is reached. The results are unpredictable. Another, albeit less profound, consequence is that interpretation of cloning assays aimed at selection of chemotherapy may be problematic because of the disruption, by cloning, of subpopulation interactions that alter drug response. We have found that prediction of a tumor’s response to chemotherapy is not possible on the sole basis of knowledge about the sensitivity of its individual subpopulations (13).

The term cancer is applied to many of our society’s problems. Drugs, crime, and violence are often referred to as cancers of society by the popular press. As Itaya and associates suggest, the linking of cancer with society may be more than a journalistic metaphor.

References


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