Grappling with Cancer

ONE OF THE GREATEST CHALLENGES IN THE STUDY OF CANCER HAS BEEN CONFRONTING THE mindset that the disease is too complex to address effectively: too many tissue types, too many etiologies, too much genetic chaos. In the 1970s, the oncogene concept provided temporary relief from this angst, because it was thought that a limited number of genes (proto-oncogenes), when activated through mutations, might turn a normal cell into a cancerous one. But what briefly seemed tidy quickly became messy again with the discovery of other classes of genes that normally protect against cancer. Most recently, advanced genome sequencing technologies have revealed a surprising fact: Every tumor contains hundreds to thousands of mutations, most of which affect only a small percentage of the cancers in any tumor type (see the Review by B. Vogelstein et al., p. 1546). In addition, the high degree of cancer cell heterogeneity in each tumor suggests that we are studying a moving target that can readily dodge treatments through continual mutation. And the genetic uniqueness of every cancer raises the question of whether standardized cancer treatment protocols can ever achieve broad efficacy.

The good news is that we are now armed with dramatically more information and substantially more powerful tools to grapple with cancer’s complicated nature. By necessity, past research focused on one gene at a time, and so our mindsets were necessarily restricted. Now that we can access the complete, precise genomic information about any cancer, future advances will depend on exploiting the natural genetic complexity of this disease. This will require much more than annotating lists of mutations. What is needed is the ability to detect all of the relevant components of a system and describe the complexity observed in a mathematical manner so that models can be computed. We then need to reconstruct this complexity in experimental systems and perturb those systems to test their characteristics. Ultimately, this could reveal higher-order rules that explain the possible actions of each particular cancer in terms of its gene networks.

Going forward, a transition to a systems dynamics view requires a different empiricism. A major change will be viewing each type of cancer as an experimental system by itself. Rather than analyzing many thousands of tumors somewhat superficially, we may need very deep analyses of a few well-characterized tumors, using multiple approaches for which diverse data sets can be integrated (complete DNA and RNA sequences, whole-genome epigenetic information, etc.). The tumors to be analyzed can be selected on the basis of their exceptional differences in behavior, such as sensitivity versus resistance to chemotherapy, and aggressiveness versus latency. The analyses required to validate the behavior of that cancer could be aided by using genetically engineered mouse models and patient-derived xenografts. The goal would be to generate a “whole-system” understanding of each cancer and provide a more nuanced approach to developing therapies.

But perhaps this view of each type of cancer as a unified but static unit is too simplistic. Instead, each cancer could be considered an evolutionary experiment involving a genetically plastic population of cells undergoing selection within a tumor. The genomic composition of single cells in an individual cancer before and after treatment may best uncover the genetic fluxes that lead to therapeutic resistance. Thus, a small group of individuals entering a “proof-of-concept” study could have their tumors genomically analyzed, the tumors’ therapeutic sensitivity tested in patient-derived xenografts, and the in vivo tumor clonal response to a tailored anticancer treatment monitored by detailed analyses of circulating tumor DNA.

Which experimental approach will be the best for advancing understanding of cancer biology and improving clinical outcomes is, of course, debatable. But we are very fortunate to be in a position today to test each of the many possibilities.

— Edison T. Liu

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