For Tissue Organization Theory of Cancer,
A Difficult Road to Acceptance

For the past 30 years, molecular biology has been the old reliable workhorse of cancer research. Its reductionist, cut-through-the-complexity approach to biology has played a leading role in a number of research breakthroughs and has helped to establish what many consider to be an air-tight case for the somatic mutation theory of cancer, the dominant paradigm and model of the disease.

But in recent years, a few scientists have begun quietly publishing essays that ask, has oncology’s heavy reliance on molecular biology become a liability in the race for a cure? As they note, not only has molecular biology narrowly defined much of the conceptual language of cancer research, it has also set its own self-fulfilling terms for victory, from hitting molecular targets to healing mutated genes.

Among the most steadfast of these editorialists are Carlos Sonnenschein, M.D., and Ana Soto, M.D., cancer researchers at Tufts University in Boston. They argue that cancer is not a consequence of a normal cell gone bad by reason of mutation, the essence of the somatic mutation theory. Instead, they suggest neoplasia arises from a more general and far more dynamic breakdown in communication among the various layers of a tissue.

In the tradition of cancer research in the early 20th century, Sonnenschein and Soto have tried for years to engage their fellow cancer researchers in a critical reevaluation of the somatic mutation theory. Starting with a review article in JNCI more than two decades ago, the scientists have since written a book on the subject and have published numerous essays and reports, the latest of which appeared in the April issue of the Journal of Cell Science, documenting the crucial role of the stroma in rat mammary carcinogenesis.

What they have discovered is the power of the paradigm can be enormously difficult to budge. “With any new idea, people have three choices: consider, attack, or ignore,” said Sonnenschein, who, along with Soto, studies the role of sex hormones on cell proliferation. “What we’re finding is, because most people already have their minds made up about the nature of cancer, the easiest thing for them to do is ignore us.”

Uncertain Path

Sonnenschein and Soto readily admit that they never set out to buck the somatic mutation theory. What led them down this uncertain path was an experimental oddity that arose in Sonnenschein’s laboratory during the late 1970s. “Carlos noticed at the time that estrogen target cells in the body proliferated in response to estrogen, but they also proliferated on their own in culture without any outside stimulation,” said Soto, who had just arrived in Boston from her native Argentina. As both knew, the latter wasn’t supposed to happen. According to every biology textbook, the default state of animal (metazoan) cells is quiescence, meaning that only after the estrogen was introduced into the culture medium were the cells supposed to be adequately stimulated to re-enter their cycles and replicate.

“We thought that this was surprising,” Soto recalled. “So, we did all kinds of things to work through the problem. It took us a while to realize it, but we finally concluded that maybe the cells were proliferating on their own because that is their true default state.”

The idea had evolutionary merit. Microbiologists have long recognized that the default state of bacteria is proliferation, and it seemed unlikely to Sonnenschein and Soto that single-celled organisms could completely rewire their default state to quiescence while evolving into specialized cells in multicellular animals.

After publishing their initial thoughts on the subject in JNCI in 1980, the two forged ahead with their research and kept quiet about their alternative views. “We didn’t know how to articulate it very well at [that] point,” said Soto. “We just decided that if we turned the paradigm around, probably our research would move ahead more smoothly.”

The two began to dig deeper into the default state of metazoan cells and soon discovered additional reasons to doubt the quiescence dogma. “When you take any bacterial cell and expose them to nutrients, they proliferate,” said Soto. “But when nutrients are depleted, cells
either die or sporulate, but they don’t have a true, long-lasting quiescent state. We wondered about unicellular eukaryotes. A similar story. Plants? Again, the same story.”

Assuming the default state of metazoan cells is proliferation, Sonnenschein and Soto came to the doubly unorthodox conclusion that animals must have evolved intricate biochemical systems to repress—not stimulate—proliferation. Thus, growth factors weren’t really engaged in growth-regulating biochemical feedback loops, a fundamental premise of somatic mutation theory and a huge area of research.

As Sonnenschein and Soto later learned, a historical case could be made for their doubts. The concept of growth factors stems from the experimental vagaries of early cell culture work, which was once described as “a mixture of science and witchcraft.” “We started reading papers that referenced another paper 5 years earlier,” said Soto. “That paper referenced another paper and so on until we eventually found the original citation. It became like a chain of Russian dolls. At the end of the chain, you only find what I would call, at best, circumstantial evidence. But, by citing it again and again, people accept it as fact.”

The Book

In 1996, both scientists took sabbaticals from Tufts to explore in greater historical detail the epistemology underlying the study of cell proliferation. The result 3 years later was their 154-page book, The Society of Cells.

By diving into the historical why’s of cancer theory, the two concluded that neoplasia results from a breakdown in communication between the different cellular layers of a tissue, as first postulated at the end of the 19th century by Boll, Cohnheim, and Ribbert. This tissue-based theory of cancer had largely fallen through the historical cracks since the introduction of the somatic mutation theory in 1914.

Incorporating a full century of publications on this theory, Sonnenschein and Soto believed that sporadic cancers arise when pathogens or carcinogens disrupt the normal biological interactions between, say, the epithelium and stroma. This breakdown in communication might prompt disoriented epithelial cells to mistakenly revert to pro-growth patterns of behavior. Because this reversion represents a switch in behavior, not a mutational meltdown, Sonnenschein and Soto contend the epithelium, at least initially, can be coaxed back to good behavior.

Buttressing their contention are years of independent laboratory and clinical data on spontaneously regressing tumors, a stubborn fact that doesn’t fit the somatic mutation theory. What about the ever-present mutations in tumor cells? Sonnenschein and Soto agree that carcinogens may produce mutations. But they contend these mutations are secondary occurrences, not the initiating event that gives rise to neoplasia.

“Development involves the interplay of many factors within an organism and with its environment,” said Soto. “But it’s not simply the genes that cause development, nor is it the genes that cause sporadic cancer. True, you can knock out or mutate genes to perturb a system and produce a phenotype. But you cannot say that the gene calls for the phenotype, as phenotypes are context dependent.”

Challenges

Richmond Prehn, M.D., who wrote a review of The Society of Cells in the New England Journal of Medicine a few years ago, said he enjoyed the book. “They make a big case out of the idea that the default state for cells is proliferation,” said Prehn, now retired from the University of Washington in Seattle. “I think that’s a compelling argument, and I’ve thought that for a long time.”

Prehn said he recognizes the challenges Sonnenschein and Soto face in simply being heard by their peers. “If you talk to post docs and so forth, they don’t even consider the idea that there could be something other than mutations,” he said. “It’s just never crossed their field of vision. When something gets ingrained, it’s difficult to introduce new ideas.”

Nor do many of their peers feel the somatic mutation theory has run its course. “It is clear that somatic mutations represent the prime driving force behind the runaway proliferation of cancer cells,” said Robert Weinberg, Ph.D., of the Whitehead Institute for Biomedical Research in Cambridge, Mass., who said he is unfamiliar with Sonnenschein’s and Soto’s publications.

“There can no longer be any residue of doubt about that,” he continued. “An unresolved question, however, is whether these somatic mutations, on their own, explain the complex biology of these human tumors. In fact, they don’t, simply because tumors are complex tissues. Indeed, [they] are as complex as normal tissues.”

Weinberg added that understanding the interactions between tumors and their microenvironment, including tissue layers, remains a major challenge. “In the case of carcinomas, the microenvironment is created by mesenchymal cells that form the tumor stroma,” Weinberg said. “Only when this understanding of these interactions of cancer cells with stroma is more developed will we truly understand the full biological complexity of human cancers.”

In October, Sonnenschein and Soto published in the journal BioEssays another of their articles on the need for a new cancer paradigm. They also have an upcoming guest editorial in the journal Endocrinology set for January. Both scientists say it’s tough to know how many people read their articles, but they feel compelled to keep writing and keep suggesting a different road ahead. As they wrote in The Society of Cells, “Our summarized message is this . . . Come to terms with the frustrating experience learned in the last three decades, let’s go back to the drawing board, and start again!”

—Robert Longtin