Looking at Cancer Through an Evolutionary Lens

By Karyn Hede

Over the centuries, physicians have conceptualized cancer in many ways. Hippocrates viewed it as a malfunction of black bile. In India it was treated as an imbalance of Ayurvedic principles of dosha. Modern medicine has viewed cancer in terms of genetic mutations. Now some researchers are saying we should step back and view cancer through the lens of evolution and ecology to better understand how tumors form and spread. Doing so, they say, is consistent with the current genomic view but adds dimension. Conceptualizing cancer cells as a dynamic, interacting population provides new avenues for understanding and controlling the disease.

“[Evolutionary theory] is consistent with the way we understand cancer; it just describes the dynamics of that process, which people haven’t been paying that much attention to,” said Carlos Maley, Ph.D., assistant professor of molecular and cellular oncology at the Wistar Institute in Philadelphia. Maley has applied evolutionary principles to understanding how cells evolve from the precancerous Barrett esophagus to full-fledged esophageal carcinoma. He is a vocal proponent of incorporating evolutionary principles into cancer research.

“This understanding of cancer as an evolutionary theory is in a strange state, because when I give talks on it, there’s no objection to it,” he said. “Everyone agrees this seems to be true, and yet no one seems to be taking the next step in terms of what are the implications of that and how can we address it.”

To jump-start the discussion, the National Cancer Institute sponsored a February 2008 meeting in which interdisciplinary teams from the physical and biological sciences discussed ways to integrate new technologies and thinking into cancer research. Consensus emerged that cellular, or somatic, evolution has profound implications for cancer therapy. That is, the genetic instability of cancer cells, along with tumor microenvironment, leads to selection of the “fittest” cancer cells—much as natural selection leads to survival of the fittest in Darwinian theory but over a compressed time scale. The argument, laid out in a concept study that Maley co-authored in the February 2009 issue of Evolutionary Applications, suggests applying the analytical tools of evolutionary biology to studying cancer progression and acquired therapeutic resistance.

Most of the work in this area is still theoretical, with mathematical models playing a large role. Some researchers, however, are beginning to apply the models in the clinic as this approach to thinking about cancer gains ground.

Mathematical Models

The concept of applying evolutionary principles to the study of cancer first emerged in the 1970s. Peter Nowell, M.D., of the University of Pennsylvania, published an article in Science that combined the two-hit theory of carcinogenesis with observations of genetic instability and clonal variation and expansion. Since then, a few cadres of interdisciplinary researchers have applied well-established mathematical formulas, which describe clonal expansion, selection, and extinction, to the problem of cancer and have begun to develop computer simulations, or in silico models, that behave like tumors seen in the clinic.

One recent model, developed by Heiko Enderling, Ph.D., Lynn Hlatky, Ph.D., and Philip Hahnfeldt, Ph.D., of the Center of Cancer Systems Biology at Tufts University School of Medicine in Boston, aims not just to mimic tumor behavior but ultimately to predict it and assist physicians in choosing treatment options. The model, published in June in the British Journal of Cancer, suggests an explanation for recurrence of cancer after treatment with chemotherapy and radiation. The research team applied basic physical parameters of cell proliferation, migration, and death to show how physical constraints and interactions influence cell behavior. When cell proliferation is low and cell death is high, as in after treatment, tumor growth is paradoxically accelerated because space has been freed up for self-metastatic expansion.

Hlatky pointed out that the model closely mimics the well-documented phenomenon of posttreatment recurrence seen in the clinic. “A simple population-dynamical model like ours that accounts for the liberation and increased symmetric division of stem cells during cell killing, which is biased to nonstem cells, can explain many of the features of the phenomenon,” she said. Hlatky argues that posttreatment recurrence may be an effect attributed to the cells acting as a population rather than to any selectable quality of individual cells themselves.

“One could infer that a new, emergent property of cancer behavior arises specifically because the cells are interacting with one another in a population,” she said. “And when a property of a population affects tumor growth as a whole, it points to the need to look beyond the...
genes, and even individual cells, to gain a more complete picture of cancer development.”

**Beyond Theory**

“The problem is, how do you apply that beyond the theory?” said Ken Pienta, M.D., director of the urologic oncology program at the University of Michigan Comprehensive Cancer Center in Ann Arbor and associate dean for clinical and translational research.

Pienta posits that tumors are ecosystems in which cancer cells interact with normal host cells and with growth factors, oxygen, and other resources and factors in their environment. He and others, in the attempt to apply this idea to the clinic, are looking for ways to target factors that provide an environment conducive to cancer growth. For example, Pienta said, when prostate tumors metastasize to bone they subvert normal bone remodeling—the continual removal and replacement of bone. The result is a tumor ecosystem in which tumor cells cooperate with bone-forming osteoblasts and bone-destroying osteoclasts to accelerate bone remodeling to the benefit of tumor cells. Bisphosphonates, which disrupt bone remodeling, are an example of a tumor ecology-based treatment already in use as an adjunct to chemotherapy for advanced prostate cancer.

“You can’t think of Darwinian principles out of context of the environment they are in, and that gets into tumor ecology and ecosystems,” said Pienta, who outlined his approach in a review article in December in *Translational Oncology*.

In the clinic, Pienta is exploiting the cooperative relationship that metastatic cells develop with tumor associated macrophages (TAMS)—immune system cells that are recruited to the site of metastasis and provide secreted growth factors that cancer cells need to thrive. Because TAMs are not part of the normal bone microenvironment, they can be treated as an “invasive species,” said Pienta. He and others have shown that blocking TAM infiltration suppresses tumor growth in animal models. Several TAM inhibitors are under clinical investigation, including a proprietary receptor antibody developed by Millennium Pharmaceuticals. Pienta will soon begin testing the antibody in patients with bone metastases in a phase II clinical trial coordinated by the Southwest Oncology Group. (Pienta will also be testing an antibody against the ligand, in prostate cancer; see following news article.)

“What we in the cancer research community have come to realize is that targeting the cancer cells is not enough,” said Pienta. “We have to target their habitat. It’s easier to drain the swamp than it is to kill a million mosquitoes with a flyswatter.”

Another perspective comes from Alexander Anderson, Ph.D., codirector of H. Lee Moffitt Cancer Center’s mathematical oncology program in Tampa, Fla. He has been collaborating with Vito Quaranta, M.D., professor of cancer biology at Vanderbilt-Ingram Cancer Center in Nashville, Tenn., to determine basic phenotypic patterns of cancer cell behavior. With data on patterns such as doubling time, migration rate, and oxygen consumption, they will be able to test Anderson’s mathematical models.

“I think potentially experiments and models can talk to one another,” said Anderson. “You can quantify the time to resistance experimentally and we can quantify that in a model. So that then gives you a means to start tuning your model.”

Still another evolutionary approach gets at the problem of tracing cell lineage and thus which individual cancer clones are successful. Darryl Shibata, M.D., and his colleagues at the University of Southern California, Los Angeles, developed a method to use epigenetic tags to trace cancer cell dynamics. In March, they published a proof-of-concept report in the *Proceedings of the National Academy of Sciences* looking at clonal expansion in 12 male patients with colorectal cancers. They found that tumors arose from multiple, long-lived cancer stem cell lineages rather than from a few rare stem cell clones. The findings, they say, may provide a way to reconstruct the dynamics of growth for in situ human cancers.

Steven Frank, Ph.D., author of *Dynamics of Cancer: Incidence, Inheritance, and Evolution*, likened the state of understanding of evolution and cancer research to the early days of human immunodeficiency virus (HIV) research when researchers believed the virus had a latent period during which there was very little circulating virus and little or no replication. Frank said the problem was that no one thought to look at the rates of birth and death, which is a fundamental tool of ecologists. Once they looked at rates, it became clear that the virus was still replicating but was also being destroyed at a high rate, leaving little apparent circulating virus. “It was an ecology problem,” Frank said. Now, these principles are built into the study of HIV.

“I think that trying to push evolutionary biology as a discipline is not the way to go,” Frank added. “The way to go is to solve problems so that those [ecological] principles become inevitable and essential tools to everybody. That’s what happened in HIV and it worked, and it will happen in cancer research, because everybody can see that those principles must be important somehow.”

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