BIOMEDICINE

A Cellular and Molecular Foundation for Understanding Cancer

George Klein

Around the middle of the last century, the image of cancer metamorphosed from an enigmatic disease to the multistep clonal-subclonal evolution of cell populations toward increased independence of growth control, a Darwinian process. The changes in cell phenotype (and, as they became known, in the corresponding genetic determinants) that accompanied cancer turned out to be relevant for understanding normal growth and development. Until then, cancer biology had been the junior partner or poor relative of cell biology. During the next two decades, their positions were reversed and cancer biology took center stage. The 1970s saw a panvirological interregnum, when most if not all tumors were attributed to manifest or cryptic viruses. But then the discovery of oncogenes and tumor suppressor genes, heralded by the chase for tumor viruses, displaced viruses from the limelight. While many virologists departed from the cancer field, an ever-increasing number of cell biologists entered. Robert Weinberg was among the most important pioneers in this reorienting of research. His pivotal discovery of the first oncogene mutation (ras) in a human tumor put an end to the notion that oncogenes could only be activated by viruses. It was one of the main starting points for the molecular analysis of the development and progression of tumors. Weinberg's work on the cooperativity between different oncogenes was another milestone. Now, in *The Biology of Cancer*, Weinberg offers students and researchers alike a comprehensive view of the field.

The book, unlike some by authors who have made far fewer original contributions, does not emphasize Weinberg's substantial role in the development of cancer biology. Like a medieval monk, he chose to hide his contributions within a nearly complete coverage of the field. It therefore seems appropriate to bring them up, if only to make the point that Weinberg's incessant publication of original research would appear incompatible with the production of this amazing, singly authored book

Weinberg, who is widely admired as a teacher, has taken great pains to be simultaneously comprehensible for the student and interesting for the expert. The book offers an abundance of didactic, and sometimes masterful, illustrations. Each chapter is followed by a list of key concepts, prospects, and "thought questions," designed to stimulate the active involvement of the reader. A CD-ROM included with the book contains all of the illustrations in PowerPoint format along with additional sidebars, mini-lectures, and movies. An accompanying poster summarizes key signaling pathways involved in tumor genesis and development in humans. The set offers a veritable gold mine for lecturers and students.

The Biology of Cancer
by Robert A. Weinberg
Garland Science, New York, 2006. 864 pp + CD-ROM. $140, £89.99. ISBN 0-8153-4078-8. Paper, $99, £41.99. ISBN 0-8153-4076-1.

The book covers an astounding breadth of material. Both descriptive and analytical, it amalgamates the historical background and modern developments. The text integrates cancer biology with gross and histopathology. If not solidly linked, laboratory research and epidemiology are at least juxtaposed. Weinberg gives detailed consideration to existing and prospective therapeutic approaches. He provides convincing examples of the value of high-throughput molecular approaches in diagnostic subclassification and prognostication. His analysis of the potential for a rational targeting, heralded by drugs such as Gleevec and Herceptin, includes explanations of when these and similar approaches are frustrated and offers clear guidelines for further progress. The author blends analytical detail with conceptual projections. The lucid text carries the reader forward at a steady pace, and there is never a boring moment.

One must look hard to find the book's shortcomings. In areas outside his direct experience, Weinberg occasionally favors hypotheses that have already been disproved. In contrast to Epstein-Barr virus–driven immunoblastomas, the development of Burkitt's lymphoma does not require immunosuppression. Epstein-Barr virus does not express its mitogenic program in Burkitt's lymphoma or nasopharyngeal carcinoma cells and does not drive their proliferation. The immunoglobulin gene–*MYC* translocations are accidents of normal immunoglobulin gene rearrangements or class switching. They occur in cancer-free people as well and do not require malaria-induced proliferations. Nor is the tumorigenic phenotype dominant in hybrids between virus-induced tumors and normal cells. (The recessiveness of tumorigenicity in tumor-normal hybrids also applies to most virus-induced tumors, with the exception of some mouse lymphoma-lymphocyte hybrids.) But it would be petty to belabor minor points like these.

Cancer colonies. Liver metastases (white) often arise in patients with advanced colon cancer, after cancer cells migrate through the portal vein.

CREDIT: FIG. 2.2B FROM *THE BIOLOGY OF CANCER*/COURTESY PETER ISAACSON

A more important critique may be directed against the relatively low profile Weinberg accords cancer epigenetics. As he and most cancer geneticists readily acknowledge, epigenetics has now emerged as a worthy partner of cancer genetics. But it is still often mentioned in parentheses—(methylation)—rather than on equal footing. In addition, there is more to epigenetics than changes in DNA methylation. Chromatin structure and the stringency of parental imprinting are emerging as important variables that can influence the likelihood of tumor development.

Another new and rapidly growing field, concerning the effect of the microenvironment on initiated precancerous or even fully fledged cancer cells, is discussed in detail. But some of the most remarkable cancer-related effects receive less attention than they deserve. For example, there are the "normalization" of tumor cells by contact with normal cells and the suppression of tumorigenicity by recreating three-dimensional tissue structure. That approach, pioneered

The reviewer is at the Microbiology and Tumor Biology Centre, Karolinska Institute, 17177 Stockholm, Sweden. E-mail: georg.klein@ki.se

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by Mina Bissell, shows that "phenotype can override genotype" (*1*), irrespective of the number of genetic changes in the tumor cells. The book does not even mention the most spectacular case, Beatrice Mintz's demonstration that highly malignant mouse teratoma cells can, if placed in an early embryonic environment, be induced to develop all normal tissues of the mouse (*2*). On the other hand, Weinberg provides a very interesting discussion on epithelial-mesenchymal transition during the development of invasive tumors and the reverse, mesenchymal-epithelial transition in late tumor progression. These transitions, which mimic certain stages of embryonic development, are very relevant for an understanding of interactions between cells and their normal or modified neighbors.

The space and detail Weinberg devotes to general and tumor immunology are somewhat surprising in view of his repeated emphasis of the "state of flux" of that particular field. We still lack a decisive answer to the original question: Does the immune system regard tumor cells as self or as nonself? Most of the observed nonself responses with an indisputable rejection potential have involved virus-transformed cells. The power of such responses can be demonstrated by the ability of immunocompetent T cells to bring even widely disseminated Epstein-Barr virus–driven immunoblastomas in immunodeficient patients to complete regression. Most nonviral tumors never have to face a comparable recognition. Although antibodies are (as the book shows) widely detected against many tumor proteins, this may be the symptom of a response rather than evidence of rejection-mediating effectors. Many ongoing efforts to mobilize tumor inhibitory immune responses may be akin to breaking tolerance to self. This approach is well presented in the book, but the question remains how far tumor inhibitory immune responses can be driven in the face of multifactorial protection against autoimmune reactions. Weinberg does not hesitate to reveal his own ambivalence, while doing justice to the current efforts that dominate the field.

The Biology of Cancer is no doubt the definitive statement on its topic today. But nothing remains definitive for too long in this field. An updated edition will be needed in a few years' time. By then, the RNA revolution and particularly the role of the regulatory microRNAs that can play both oncogene and tumor suppressor roles (*3*) will have delivered a vast body of new information. The concept of junk DNA may have been abandoned altogether. But however revolutionary these developments may be, they will stand on the solid foundation compiled in Weinberg's monumental book.

References

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HISTORY OF SCIENCE

On Smell and Scientific Practice

Miriam Solomon

A delightful book about the science of smell, *The Secret of Scent* takes the reader through a tour of the almost infinite range of human olfactory possibilities. Luca Turin also presents the recent history of theories of smell, culminating with his own frequency theory. Turin possesses an unusually sensitive nose and has the ability to detect and describe, like a wine expert, the character of individual odors and complex scents, natural and synthetic, pleasing and noxious. A perfume guide he wrote (*1*) became a best seller in France. His perfume reviews (*2*) contain such colorful lines as "This thing smells like an infant's breath mixed with his mother's hair spray.… What Rush can do, as all great art does, is create a yearning, then fill it with false memories of an invented past" and "Python … belongs in a tree shaped diffuser dangling from the rearview mirror of a Moscow taxi." The success of his perfume guide led to invitations to visit and consult with scent and perfume manufacturers, from which Turin learned much about the process of creation of scent.

In part because of this unusual access to perfumery materials and manufacture, Turin has found the leading theory of smell—that humans detect small volatile molecules by assessing the shape of the molecule or part of the molecule—unsatisfactory. Shape theories were originally proposed by Linus Pauling (*3*) and R. W. Moncrieff (*4*) in the 1940s and subsequently developed by John Amoore and others. Turin observes that research on creating new smell molecules is trial and error. Data mining for correlations between molecular shape and smell has not generated useful predictions. Scent manufacturers typically synthesize 1000 new molecules to get one that they can use. Turin observes that, contrary to the predictions of shape theories, molecules very different in shape can sometimes smell the same (e.g., boranes smell sulfurous) and molecules very similar in shape can smell different (e.g., isotopes of the same molecule such as acetophenone and deuterated acetophenone).

Turin has a Ph.D. in biophysics. At the time that he developed his theory of smell, he was a lecturer at University College

The Secret of Scent
Adventures in Perfume and the Science of Smell

by Luca Turin

Faber and Faber, London, 2006. 217 pp. £12.99. ISBN 0-571-21537-8. Forthcoming from Ecco, New York. ISBN 0-06-113383-3.

The reviewer is in the Department of Philosophy, Temple University, Philadelphia, PA 19122, USA. E-mail: msolomon@temple.edu

BROWSING

Strategies of Commitment and Other Essays. Thomas C. Schelling. Harvard University Press, Cambridge, MA, 2006. 355 pp. $39.95, £25.95, €36.90. ISBN 0-674-01929-6.
Schelling shared the 2005 Nobel Prize in Economic Sciences for use of game theory to understand the bases of conflict and cooperation. In this collection of previously published articles and excerpts, he offers informative perspectives on a wide range of topics. Some, such as the nature of commitment and the avoidance of nuclear war, have interested Schelling since early in his career. (A 1960 book review of his helped inspire *Dr. Strangelove.*) Others reflect more recent concerns, including end-of-life controversies, addictions, global warming, and using prices as regulatory instruments to protect the environment. One chapter reprints his 1971 "Dynamic Models of Segregation," which demonstrated a tipping point in the racial composition of neighborhoods. Several of the essays consider cases in which the usual assumptions of economists (e.g., rational decision-makers) do not hold. Anyone interested in the behaviors of individuals or societies will find many of the pieces thought-provoking; in one, Schelling even argues "that there are free lunches all over just waiting to be discovered or created."