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BOOK REVIEW

Tumor Metastasis: Historical Perspective and Future Prospects

The Metastatic Cell: Behaviour and Biochemistry, *by C.W. Evans. Chapman and Hall, 555 pages, $115.00, 1991.*

Tumors could be treated much more successfully if they did not metastasize. That many tumors do metastasize complicates cancer therapy. There has been a great deal of research on biological and biochemical features of metastasis, with the aims of both understanding the process and identifying therapeutic strategies to either prevent or treat metastases. With the advent of recombinant DNA techniques, the field of metastasis has been taken into the realm of molecular mechanisms of metastasis, again with aims of both understanding and therapy. As this molecular genetic work proceeds, it is important to put these studies into the context of previous biological and biochemical research that has been done.

The Metastatic Cell: Behaviour and Biochemistry documents much work that has been done in the field of metastasis. As such, it is a useful volume. The author's stated audience includes "medical students who, despite a solid grounding in pathology and now molecular and cellular biology, nevertheless remain relatively ignorant of . . . fundamental aspects of cancer biology," as well as students contemplating a career in cancer biology. Certainly any student intending a research career in cancer biology would benefit from reading this book, as would current researchers in the field of metastasis.

Over the past twenty or so years, and especially since the experimental studies by Fidler in the early 1970s, there have been a very large number of investigations dealing with aspects of the biochemistry and biological behavior of metastatic cells. Every reader who works in the field will no doubt feel that some areas of this research have been neglected in this book, and others overemphasized. More than 50 pages are devoted to studies on B16 murine melanoma cells alone. This model is historically (and still) important, but perhaps is emphasized in this text at the expense of other informative models. In many cases, a great deal of detail is presented, often on studies that are then summarized as "needing more work." As a consequence, many important gems of concepts (e.g., "Clearly, an invasive cell that cannot grow at a distant site is not a metastatic cell. This possibility suggests that single steps in the metastatic cascade should not be studied completely in isolation. . . .") are tucked away in the text and get lost in the detail. A student would have an easier time if first introduced to the concepts, and then provided with the experimental details that led to the formulation of these concepts. In addition, many of these ideas (and some of the experimental details) could have been clarified by illustrations, diagrams, or photographs. There are very few figures or tables in the text; those that are included are often useful, and more would simplify reading this relatively long book.

My major disappointment with this text is that it stops in its review of the field in the late 1980s. I could find no references to work from the 1990s, and the majority of the references are from the mid-1980s or earlier. And—in a way—I find this disappointment to be very reassuring! In a field that, to many of us working in it, seems at times to be moving discouragingly slowly, that a book can appear to be out of date so quickly suggests that the field is indeed progressing! This progress has come from the application of the tools of molecular biology to the question of molecular mechanisms of metastasis, as well as to the more general questions of cancer development and progression. Progress in these areas has been rapid, with the promise of increasingly rapid growth. And I agree with Evans's premise, that future researchers in the field will benefit from knowing about the history of research in the field.

Ongoing work on oncogenes and tumor suppressor genes has given us a framework in which

Address reprint requests to Dr. Ann F. Chambers, London Regional Cancer Centre, 790 Commissioners Road East, London, Ontario N6A 4L6 Canada.

to study tumor biology and progression, including progression to metastatic behavior. We know that cancer is a disease of genes, either in the germ line or in somatic cells, and we know now what some of these genes are. There are the dominant-acting oncogenes, such as ras, which when mutated can positively influence the development and progression of tumors, as well as the "anti-oncogenes" or "suppressor" genes, whose absence or lack of normal function results in tumor development or progression. Studies on these two classes of genes are making major inroads into understanding the regulation of both normal cell growth and differentiation, as well the loss of regulation of these properties that is believed to result in cancer. Cancer involves the loss of normal controls on cell division and differentiation, and it is not surprising that the genes involved in cancer are those that, when behaving properly, govern these normal processes. Oncogenes, being regulatory and signal transducing genes, function by controlling other cellular functions. Studies on oncogenes are having an impact on our understanding of metastasis, by helping us to understand what genes are regulated by the expression of oncogenes. These "downstream effector genes," whose expression can be influenced by oncogenes, are likely candidates for genes whose expression is important in determining metastatic ability.

It is interesting (and satisfying) that processes implicated by earlier studies on the biochemistry and behavior of metastatic cells, as outlined in Evans's text, are in many cases identical to those implicated by studies on oncogenes. As an example, previous biochemical work has suggested that various proteolytic enzymes are likely contributors to the invasive and metastatic process. Studies on the ras oncogene and metastasis, from my laboratory as well as several others, have suggested that ras expression can induce expression of many of the same proteolytic enzymes. Future work with oncogenes will likely produce an understanding of the mechanisms by which oncogenes regulate expression of various "effector genes" that contribute to the metastatic phenotype. Along with helping us to understand the process of metastasis at a molecular level, these studies will then offer new molecular targets for possible therapeutic intervention.

Beyond a growing understanding of the functions of oncogenes and the ways in which they can generate increasingly malignant cells, molecular biological studies are contributing to the study of metastasis in other ways. The ability to put genes into cells (or mice), to (functionally or structurally) take genes out of cells (or mice), and to do all the other things one can do with molecular biology has given us new tools that are applicable to the study of many biological processes. The field of tumor metastasis is no exception. Biochemical and behavioral studies on metastatic cells, of the sort detailed in Evans's book, have pointed to several functions that appear to be required for metastasis. These studies now form the basis for hypotheses that can be tested using molecular biological techniques. The effects on metastatic ability of adding or subtracting a specific gene can be tested directly. For studies of this sort, an awareness of previous work on clonal heterogeneity and instability of the metastatic phenotype will offer cautions useful to the design and implementation of these experiments.

The next several years promise to be exciting, fruitful ones for the field of tumor metastasis. Tools and concepts are now coming into place that will permit rapid progress to be made in this complex and clinically important process. Two areas in which progress is needed are, first, a clarification of the molecular mechanisms of tumor progression, the process by which malignant cells are generated, and second, a similar clarification of the molecular mechanisms of the process of metastasis. Progress in these two areas will help us then to address the question of what can be done clinically about metastasis. There is a need for better clinical markers of tumors likely to metastasize (or to have already seeded occult metastases). In addition, there is a clear need for identification of molecular targets, responsible for functions important to metastasis, that will result in novel therapeutic strategies, either to prevent metastasis from occurring or, perhaps even more useful clinically, to block further growth of micrometastases already present in a patient. Molecular biological techniques, in combination with studies on oncogenes and tumor suppressor genes, have the potential to contribute to these areas. The ability to apply these techniques effectively to the study of metastasis will depend on a good understanding of the biology of the process.

Ann F. Chambers
London Regional Cancer Centre, and
Department of Oncology,
University of Western Ontario
London, Ontario
Canada