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Book Review

The Molecular Pathology of Cancer

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MOLECULAR BIOLOGY has told us many interesting things about cancer, particularly about the involvement of various oncogenes and tumour suppressor genes in the process of cellular proliferation and differentiation. However, the understanding we have accumulated about the cancer cell is analogous to that which we might have about a Swiss watch that has been opened with a hammer and chisel. There are a large number of components with different sizes and structures which, when assembled in the correct combinations, enable the whole to exhibit much more than the sum of its parts. We can guess at the original locations and orientations of each component on the basis of physical characteristics, and we can make more informed guesses by breaking open other watches of contrasting appearance or behaviour and observing similarities and differences in the springs, cogs and bearings that fall out. But the real test is to build models with these components, testing which ones fit and where, which ones speed things up or slow things down, and which ones are essential or superfluous to the function of the structure. This is the role of the molecular pathologist. Pathologists are familiar with piecing together the evidence, the structural and functional characteristics of disease, through the study of cells, tissues and whole organisms. Molecular biology adds a new way of looking at the structure and functions of cancer cells, at the genetic rather than the microscopic level. Experimental pathologists have always built models of disease and now molecular biology has equipped them with a whole new tool kit and collection of components to make even more refined reconstructions. Molecular pathologists know what the models should look like and how they should function, and they are potentially in the best position to be the watchmakers of cancer biology.

This volume on the molecular pathology of cancer illustrates a series of models for cancer. Some of the contributors might describe themselves as molecular pathologists, others might offer other descriptions. All of them share a similarity of outlook, with an understanding that it is crucial to test each hypothesis and potential mechanism in a biologically relevant model. Our understanding of the molecular basis of colorectal and breast cancer is the most advanced, and many groups have made models designed to reconstruct these tumours. Those presented here are some of the best in terms of allowing accurate reconstruction of genetic events and, in the future, the design and testing of new approaches to prevention and treatment of these cancers.

The first chapter by Massimo Pignatelli examines parameters of differentiation in colorectal tumours and how far these can be studied in *in vitro* models and in immunocompromised mice. Ann Williams and colleagues further explore the relevance of *in vitro* models to tumour progression and to the genetic changes accompanying this.

The next four chapters illustrate the wide interest in laboratory investigations of breast cancer. Rosemary Walker and Jennifer Varley review the present knowledge of the molecular biology of human breast cancer. Joyce Taylor-Papadimitriou and colleagues show how normal and malignant human breast epithelial cells can be grown in culture and in nude mice and how such systems can best be exploited in the study of human breast cancer. Paul Edwards introduces tissue reconstruction models in which tissues are rebuilt from genetically manipulated cells. The advantages of these techniques are compared with those using transgenic mouse models. The latter are explored in more detail by Robert Cardiff and William Muller.

Thyroid cancer is a relatively rare malignancy, but its molecular modelling has helped to shed light onto the general design of genetic mechanisms of tumorigenesis. David Wynford-Thomas reviews the wide variety of models developed from thyroid tumours and compares those derived from spontaneous immortalisation with those induced by virus genes. Models of progression similar to those in colorectal cancer are suggested. Pancreatic cancer is a depressingly common malignancy, and a good model will be essential to our future progress in understanding and eliminating the disease. The chapter by Peter Hall and Nicholas Lemoine describes progress to date in developing such models. A range of animal models is available and so far these have been more promising than *in vitro* models. The histogenesis of human tumours is discussed and the conventional view of origin from ductal epithelium is challenged. The contribution by Finbarr Cotter shows the fascination of the biology of lymphomas. A wealth of detail is now known about which molecular switches have been thrown and when. This knowledge is power, and the future holds the promise of genetic intervention in controlling the process of tumorigenesis.

Metastasis is a key characteristic of malignant cells, but our comprehension of its underlying mechanisms is fragmentary, and advances have been hampered by the difficulties of making valid models of the phenomenon. A review of the state of this particular art by Nicholas MacDonald and Patricia Steeg covers this area of research with the aim of stimulating new approaches to the problem in the future. Renato Baserga outlines recent developments in our understanding of the control of the cell cycle and how this might lead to fundamentally new methods of controlling cancer cell growth. Gene therapy, or the use of selective gene transfer and expression, is also a realistic strategy for virus-associated cancers, which are a major health problem world wide. The development of vaccines to protect against cervical cancer associated with human papillomaviruses is critically reviewed by Crawford in the final chapter of this volume. This points the direction for the future, where intervention in cancer will be at the genetic level using informational drugs (nucleic acids and their derivatives) and where molecular pathologists will be active in the design and application of these new strategies.

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