Antitumor Drug Resistance

Editors: B. W. Fox and M. Fox

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Preface

The study of tumour resistance to anticancer drugs has been the subject of many publications since the initial discovery of the phenomenon by J. H. Burchenal and colleagues in 1950. Many papers have been published since then reporting development of resistance to most of the well-known anticancer agents in many different animal tumour systems, both in vivo and in vitro. Many different mechanisms of resistance have been described, and it is clear that the tumour cell has a wide diversity of options in overcoming the cell-killing activity of these agents.

Definition of the magnitude of the phenomenon in the clinic is, however, much more problematical, and it is with this in mind that the initial chapter, seeks to outline the problem as the clinicians see it. It appears that the phenomenon of true resistance to a drug, as the biochemist would recognise it, is an important cause of the failure which clinicians experience in treating the disease. The extent of the contribution of this phenomenon to the failure of treatment cannot easily be evaluated at the present time, but it is hoped that the development and application of new and more sophisticated techniques for the analysis of cellular subpopulations may help to give a more exact estimate and to shed some light on the causes of failure of many of the present therapeutic techniques.

The purpose of this book is to bring together in a single volume the results of many years' work by key people in this field. The different studies of the mechanisms of resistance are considered; in a separate section, the ways in which tumours adapt to different drug groups, taken primarily from the experimental field, but also – where recognised – from the clinical field, are described. The armoury of experimental techniques is rapidly expanding; along with improved methods of measuring drug transport and DNA repair, monoclonal and polyclonal antibodies are being employed in different ways. One of the main aims has been to identify specific changes which take place in the biochemistry of the tumour cell, especially at the cell surface, when it exhibits resistance to an anticancer drug. We are already learning about the changing levels of specific proteins, e.g. enzymes and cell-surface glycoproteins; with the newer concepts in immunology and the application of powerful techniques such as flow cytometry, a better understanding of the depth and extent of the problem of resistance is being achieved. The greatest emphasis in this book has been placed on the individual mechanisms determined to be those by which tumours have become resistant to specific drugs, and on the experimental observations and arguments that have led to the present understanding of these mechanisms.

A detailed study of the origin of resistance is basic to further progress in the treatment of cancer. It could not only modify the course of treatment, but may also, as our knowledge of "intrinsic resistance" increases, modify the type of initial treatment used, based as it is on a rapid analysis of the spectrum of sensitivity of the tumour. Although, to some extent, clonogenic assays, xenografts and renal capsule implant systems are being used for the initial analysis, the need for speed is paramount in making the early decision required for effective therapy. It is clear that some indicator of drug sensitivity at the time of the pathological investigation would be ideal, and in order to arrive at this level of diagnostic efficiency, flow cytometry will be a necessary intermediate stage in the study of properties of tumour subpopulations. Identifying a spectrum of sensitive and resistant cells in a tumour will provide a more rational basis for the choice of a drug or drug combination. More detailed pharmacokinetic data in humans are also needed if we are to take advantage of the sensitivity pattern obtained by subpopulation studies at the pathological level.

A knowledge of the genetics of the tumour, as well as that of the host, is important to understanding the sensitivity spectrum of a new tumour, and a knowledge of these factors could ultimately provide a basis for optimising the therapeutic index of the drug. The flow cytometry analytical technique will, again, be a useful tool for the effective manipulation of these factors.

During the preparation of this book it has become clear that the word "resistance" requires further description. It seems to us that "resistance" is a word that can justifiably be related only to the property of a single cell. It could be defined as the ability of a single tumour cell to survive a local concentration of a damaging drug that would otherwise have been expected to kill it. This could be an innate property of the cell (intrinsic resistance) or could have been acquired by a rapid adaptive response (adaptive resistance). If a cell were to survive a low concentration of a damaging agent and divide, probably in the face of the loss of many similar cells within the population of which it is a part, it could form the basis of a new population of resistant cells through a series of divisions. These may be further selected for reduced sensitivity (selected resistance) or actively become adapted by expressing alternative biochemical pathways, enhanced protective group synthesis, etc. (acquired resistance). In all such cases the type of resistance would merely describe the property of a single cell within the system being studied.

The tumour mass, which includes the population of tumour cells within its matrix, exhibits an overall sensitivity – usually measured according to changes in volume, number or weight – part of which may be a reflection of the tumour cell population it contains. The overall response of the tumour-cell population depends on the average sensitivity of the cells within it. The acquisition of resistance by a whole tumour could thus be the result of a shift in the proportion of intrinsically sensitive and resistant cells, influencing the overall average sensitivity of the population. The term "resistant tumour" is so widely used, however, that to speak of the "population resistance" of a tumour or tumour-cell population in this context would seem to be more accurate. It must be recognised that this is an average property of the tissue, and may not involve anything other than a change in the proportion of existing cells.

This collection of chapters, we believe, achieves the interim aim of bringing together the many parameters that are presently considered to constitute the nature of resistance in tumour populations; we hope that they will provide a basis for further discussions to substantially improve the efficacy of drug treatment of cancer in humans.

We would like to thank the many authors who adhered very closely to the timetable for submission of their chapters; we regret the omission of two of the originally planned chapters from the latter half of the book at such a late date that alternatives could not be found. However, much of the material that was to be presented in these is well covered in other contributions.

In particular we thank the Chief Editor, Professor A. D. Welch, for his continued vigilance, Mr. Ric Swindell for the indexing and Ms. Gillian A. Simpson for the typing of the necessary correspondence. Finally, the courtesy and efficiency of Mrs. Doris Walker of Springer-Verlag is much appreciated.

Manchester

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