

Mechanisms in B-cell Neoplasia. Current Topics in Microbiology and Immunology Vol. 194; Edited by M. Potter and F. Melchers; Springer-Verlag; Berlin, Heidelberg, New York, 1994; xiii + 458 pp. DM 218.00. ISBN 3-540-58447-1

The 12th workshop on 'Mechanisms in B-cell Neoplasia' was held in Bethesda, MD, in June 1994, organised mainly by Dr. Alan Rabson at the National Cancer Institute. A book in the Current Topics in Microbiology and Immunology (CTMI) series (number 194) report from this meeting, edited by Michael Potter and Fritz Melchers.

The main topics covered were multiple myeloma (MM) plasmocytoma, human and mouse B-cell lymphomas, growth regulation (IL-6, *c-myc*, *Bcl-2*, cyclin D1 and ABL) and genomic instability

MM, which is becoming a more common malignant disease, was discussed from many different aspects, including pre-myeloma cells, expressing an Ig idiotype, as initially described by Mellstedt et al (Clin. Exp. Immunol., 17, 371, 1974). These cells were investigated by more sensitive techniques for clonality, including PCR and DNA fingerprinting. These pre-myeloma cells caused a problem in autologous bone-marrow transplantation, due to their ill-defined phenotype marker expression in relation to CD34 expression. An even earlier stage of MM may relate to a condition called Monoclonal Gamopathy of Undetermined Significance (MGUS), occurring of 3% of the population over 70 years of age. A large percentage of these MGUS patients were reported to develop into MM. Surface Ig on pre-myeloma cells may bind autoantigens and thereby upregulate surface molecules involved in B cell activation and differentiation.

The deregulation of *c-myc* is important in many types of B cell tumors in relation to the cellular control of mitotic cycling and apoptosis. Myc, and myc heterodimers, bind to regulatory motifs in DNA and thus regulate the expression of different genes. An increase in *c-myc* also leads to the accumulation of cells in G1/S for further progression to death by apoptosis.

IL-6 was implicated as a growth and maturation factor for plasma cell tumors. IL-6 was found to activate different transduction pathways

including immediate JAK-STAT and delayed, *ras*-dependent kinases and CD40-dependent signalling may induce autocrine IL-6 production. B cell regulation by IL-6 illustrate the complexity of signalling by cytokines that can modulate transcriptional factors important for terminal differentiation. The importance of IL-6 binding to the IL-6 receptor and signal transducer was approached by isolating a soluble form of the IL-6 receptor (sIL-6R) and analysing the effect of other growth factors that share the same signal transducer (gp130).

Genomic instability was studied in relation to VDJ rearrangements, and heavy chain isotope switching, and the translocation of other, non-Ig regions, including target genes, such as *c-myc*, *Bcl-2*, *pvt-1* and others. The PCR technique was used to further characterise chromosomal translocations in relation to the natural history of lymphoma development and the identification of some of these also in non-neoplastic tissues.

Growth regulation by the *Bcl-2* gene family was discussed. Heterodimerization with Bax was presented as a possible mechanism for *Bcl-2* to repress cell death. This information needs only to be completed with the latest descriptions of other survival genes, such as *BAG-1* and *Bad* (Takayama et al., Cell 80:229 and Yang et al., Cell 80:285). *Bcl-2* overexpression in B-CLL is associated with increased accumulation of B-CLL cells and apoptosis inhibition. *Bcl-2* was proposed to regulate calcium release and to have antioxidant activity to explain its protective potential against different conditions that induce apoptosis.

These are just a few of the many reports (54) written by leading workers in the field. The book focuses on important, 'hot' areas in mechanisms in B-cell neoplasia and is a rich source of information both for clinical and basic scientists.

M. Joudal

Alzheimer Disease: Therapeutic Strategies; Edited by E. Giacobini and R. Becker; Birkhauser; Boston, 1994; xiv + 509 pp. \$ 74.50. ISBN 0-8176-3757-5

Alzheimer's disease (AD) is major cause of dementia, and a major health problem, with suffering both for the affected and their relatives, and enormous costs for the society. The last years have also seen a wealth of studies to characterise the neurochemical pathology of AD. This knowledge forms the platform for therapeutic strategies and attempts to develop new drugs for the disorder. Indeed, *Alzheimer Disease Therapeutic Strategies*, the third publication in a series on Alzheimer therapy, edited by Giacobini and Becker, gives a welcome extensive update on these topics.

The cholinergic hypothesis still has a central role in AD therapeutics, receiving almost half the space in the book. The leading therapeutic approach aiming at increasing cholinergic neurotransmission in AD is by means of cholinesterase inhibitor (ChEI). Indeed, the only registered compound for treatment of the cognitive symptoms in AD is a ChEI, namely tetrahydroaminoacridine, or tacrine. Although 13 chapters go through ChEIs, also other compounds aiming at enhancing the cholinergic system are covered, including several chapters on nicotinic and muscarinic agonists.

However, it is clear that multiple neurotransmitter systems are disturbed in AD. One of these is the serotonergic system, reviewed in the chapter by Gottfries. Patients with AD suffer not only from memory disturbances and other cognitive symptoms, but also from emotional disturbances. Treatment with selective serotonin re-uptake inhibitors, such as citalopram, reduce emotional disturbances such as irritability, anxiety, and depression. These symptoms may, in the earlier stages of the disorder, often cause more discomfort than the cognitive symptoms.

Other therapeutic approaches in AD includes nootropic, antioxidant and anti-inflammatory agents. In the chapters by McGeer and co-workers and by Webster and Rogers, evidence for an inflammatory component in the pathogenesis is reviewed. Interestingly, also a preliminary clinical trial using the non-steroidal anti-inflammatory

drug indomethacin, support that anti-inflammatory agents may be beneficial for the treatment of AD.

Several chapters discuss therapeutic strategies aiming at arresting the deposition of amyloid in the brain. The pros and cons concerning the amyloid cascade hypothesis are weighed in the chapter by Hardy and Duff. According to the hypothesis, $\beta A4$ protein deposition is the central event in the pathogenesis of AD, which is regarded an amyloid storage disease of the brain. Amyloid deposition is regarded to start a cascade of events that finally results in the dementia that brings the patient to the physician. The essential prediction in the amyloid cascade hypothesis is that $\beta A4$ protein, or aggregates of $\beta A4$ protein, is neurotoxic. This has been both extensively tested (in animal experiments and cell culture systems), and debated (in a whole issue of *Neurobiology of Aging*). In fact, a book on therapeutic strategies for AD is an excellent forum to discuss the amyloid cascade hypothesis, since the real challenge for the amyloid cascade hypothesis will not come until drugs that (in cell culture or animal models) arrest amyloid deposition can be tested in living patients with AD, to see if they also arrest the progression of the disease.

Nine chapters are devoted to the issue of monitoring the drug by different imaging techniques (e.g. SPECT and PET) and by clinical testing (using different rating scales). However, although evidence is accumulating that what today is called 'Alzheimer's disease' actually is a heterogeneous syndrome, no chapter discuss whether the drug effect may vary between AD patients with different aetiology (e.g. rare genetic forms vs. common sporadic forms) and pathogenesis (e.g. patients with or without risk-factors such as the ApoE4 allele or concomitant vascular diseases). Moreover, it is also logical to assume that the pathogenesis in the rare cases with early-onset sporadic AD (with onset 40-65 years of age) is not identical to that in elderly patients 80-90 years of age (where AD pathology is found in almost all individuals, and 25-40% has dementia). Thus, also the clinical response to different drugs may vary between these patients. Consequently, a clinical

response to a drug may be overshadowed, if it is tested without considering subgroups of AD. This problem is only considered in the chapter by Svennerholm and Toffano, in which a study is presented where ganglioside GM1, a glycosphingolipid with neuroprotective and neurotrophic effects, is given by continuous intracerebroventricular infusion to patients with the classical, early onset, form of AD.

Anyhow, *Alzheimer Disease: Therapeutic Strategies* encapsulates the present knowledge in AD therapeutics, as well as the underlying

neurochemical pathology for compounds that today are clinically available (e.g. tacrine, citalopram) or under clinical trials (e.g. anti-inflammatory agents), and also reviews potential future therapeutic approaches (e.g. agents aiming at arresting amyloid deposition), a concept which must interest both scientists involved in AD research and clinicians.

K. Blennow

Dictionary of Gene Technology; Edited by G. Khal; VCH; Weinheim New York, 1995; xii + 550 pp. DM 184.00. ISBN 3-527-30005-8

The *Dictionary of Gene Technology* presents a large collection of terms and laboratory jargon used in the field of genetic engineering and related areas. In the preface the author states that gene technology is an extremely rapid growing science and anybody can agree with that. The book represents an immense piece of work and it is impressing that it has been possible to compile so many terms that are presented in a clear way and in general are explained and described in as much detail as is required to understand them. Each entry contains many cross references to other entries in the book and many of the descriptions are supported by good illustrations.

The areas covered go far beyond the broad field of gene technology, touching many related disciplines that include microbiology, genetics, chemistry and biochemistry. Although the dictionary comprises several thousand entries a certain selection seems to have taken place. For example, the book includes descriptions of several protein motifs like zinc fingers, leucine zippers, helix-turn-helix and helix-loop-helix motifs while other well known motifs, e.g. the RNA recognition motif and the EF-hand motif are left out. Perhaps this has to do with a predisposition to favour proteins that may interact with DNA. Furthermore, with such a huge dictionary it may be unavoidable that some terms are less adequately described. As stated in the preface the author is fully aware

of this. To mention a few, homology is defined as the extent of identity between two nucleotide or amino acid sequences. Although this interpretation is widely used in the literature the author misses the precise biological meaning, i.e. having a common evolutionary origin. Another entry, equilibrium dialysis, is rather clumsy defined as a method to determine protein-protein interaction with a description of a very special case, omitting the essence that it is a method to determine the binding strength of a low molecular mass ligand, that can pass through a dialysis membrane, to a high molecular mass macromolecule that cannot pass through the membrane. However, it would be out of proportion to highlight a few terms that clearly represent exceptions to the rule without emphasising that there are more than 4000 useful entries the great majority of which are adequately described.

The book is mainly addressed to students in the field of gene technology and scientists in related fields who are unfamiliar or only slightly familiar with recombinant DNA technology. Undoubtedly the dictionary will find a natural place in molecular biology laboratories that frequently host guests. The book provides information which is not easily perceived from other sources and it can be highly recommended.

Bent Honoré

Molecular and Cellular Enzymology. Progress in Molecular and Subcellular Biology; Edited by Ph. Jeanteur; Vol. 13; Springer-Verlag; Berlin, Heidelberg, 1994. x + 150 pp. DM 198.00. ISBN 0-387-57337-2

Enzymologists frequently suffer from the delusion that the enzyme properties that they observe *in vitro* are the same as those in the cell. This book will rapidly destroy such illusions but also suggests ways of studying the intracellular behaviour of enzymes. It is a collection of three very different articles on proteins within cells; the unifying theme is that proteins, particularly enzymes, will be affected by the microenvironment in the cell. All the articles are written by active workers in their fields but they differ in the commitment demanded of the reader.

The first chapter makes up more than half the book and is a detailed examination of the modelling of enzyme dynamics in cells. The approach is theoretical with many mathematical formulae which need to be grasped if the full thrust of the authors' argument is to be followed but the effort is very worthwhile. The foundation of the analysis is that the interior of a cell, particularly the membranes, can be regarded as a charged ionic matrix. The flow of charged particles through such a matrix is examined with particular reference to ATP-synthase. Examination of the effects of diffusion coupled to enzyme activity leads to the surprising finding that the activity of an enzyme under such conditions can vary, at the same concentration of substrate, according to whether substrate concentration is increasing or decreasing. The authors then discuss the effect on an enzyme of being inserted in a charged environment and conclude with a consideration of the

dynamics of feedback control and multi-enzyme systems. The theoretical ideas are illustrated by experimental examples.

The next chapter reviews microbial and genetic approaches to the study of proteins. Various approaches to point mutation of proteins are described, in particular the use of amber codons together with amber suppressor tRNAs to generate protein variants with up to 13 different amino acids at the same position. The authors' work on a cellulase is used as an illustration of the technique. Such multireplacement allows the sensitivity of protein function to the presence of particular residues to be determined. The use of inserted tryptophan residues to study conformational changes in calmodulin is also described.

The final chapter is an excellent review of fluorescence spectroscopy as applied to the study of single cells. The article ranges from details of fluorescence quenching, energy transfer, polarisation and anisotropy through to use of lifetimes and confocal microscopy. This is very much a quick tour around the experimental advantages and hazards of fluorescence techniques. It would form a suitable introduction for final year undergraduates.

Overall this book presents several perspectives on the effect of the cellular environment upon enzymes. It makes us stop and think what we are really trying to achieve when we study our enzymes outside the cell

Alan Thomson