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Book Review

Cancer Surveys Volume 22: Molecular Mechanisms of the Immune Response

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ISSUE 22 OF *Cancer Surveys* honoured Dr Mike Crumpton on the occasion of his retirement as Director of Research (Laboratories) at the Imperial Cancer Research Fund. It is based on a scientific symposium held at the Royal Society on 11th October 1993. The title of the symposium, The Lymphocyte Cell Surface, reflected Mike's major area of interest for much of his scientific life, and one to which he has made so many contributions.

For the latter part of his scientific career, Mike Crumpton was associated with two major areas of research: T cell activation and the biochemistry of lymphocyte surface molecules, in particular the class I and class II histocompatibility antigens. These areas, which are of course interlinked, form the major focus of the chapters in this book. Walter Bodmer, a long-term collaborator and colleague of Mike Crumpton, presents an evolutionary interpretation of the HLA region, speculating on its early evolution from a gene encoding an immunoglobulin domain with one encoding a peptide binding domain, such as Hsp70, followed by a series of duplications and divergence. These thoughts were extended to consider the different genes residing within the MHC region and the functions of these genes. These considerations provided a fascinating description of the potential history of the MHC, and beautifully illustrated why this complex of genes has provided such a paradigm for studies on genetics and immunology.

The structures of MHC class I antigens are discussed by Stan Nathenson. These molecules bind processed peptides that are recognised by T cell receptors. The recent crystal structure determination of class I molecules with single bound peptides has allowed us to understand the guidelines that govern peptide binding in a given MHC allele. From these studies, a picture has emerged in which the peptide binding cleft possesses a series of pockets that bind specific anchor residues of the peptide. The nature of the cleft varies between different alleles and dictates the set of peptides that can bind to a particular allele. This theme is elaborated in the chapter by Howard Grey and colleagues, who define the structural motifs that dictate the capacity of peptides to bind to five different HLA-A alleles. These motifs are, in general, very specific for the individual HLA-A alleles. Their definition permits the prediction of intermediate and high affinity binding peptides and the identification of epitopes within proteins that bind to class I alleles. Taken together, these structural and biochemical studies have greatly advanced our knowledge of the relationship between MHC binding of peptides and immunogenecity, and are important for the design of peptide based vaccines for prophylactic or therapeutic use.

Class I and II MHC antigens act as guidance systems for T cells, class II antigens presenting peptides derived from exogenous antigen, and class I antigens displaying peptides from proteins synthesised by the cell. The recognition of viral antigens by T cells is discussed by McMichael within the context of recognition of HIV by cytotoxic T lymphocytes (CTL). HIV-specific CTLs are readily demonstrated in infected individuals even within the initial asymptomatic period. CTL activity subsequently declines but remains detectable until the patient develops full blown AIDS. This ultimate failure of CTLs to control the infection may be due both to overstimulation of CTL activity, leading to T cell clonal exhaustion, and to virus variability, affecting epitope binding to MHC or presentation to T cells. Nonetheless, CTLs appear to play a critical role in controlling HIV infection, and an understanding of why they ultimately fail could lead to the design of improved therapies.

The interaction of the T cell receptor with antigen/MHC molecules is insufficient to activate T cells. Indeed, this interaction appears to lead to a state of anergy. Rather, a variety of accessory molecule interactions are necessary for full blown activation. One such molecule, called CD2, provides a powerful second signal, and the functional and biochemical interactions of CD2 and the TCR complex are considered in the chapter by Meuer. An understanding of the cross-communication between the TCR and costimulatory molecules provides a means for local immune intervention in diseases such as autoimmunity.

The intracellular events associated with T cell development and activation are unveiled in the chapters by Cantrell, Perlmutter and Crumpton. A number of protein kinases have been identified as being important in the signal transduction pathways that communicate signals from the cell surface. The serine/threonine protein kinase cascade that constitutes the MAP kinase pathway is regulated by the activity of $p21^{ras}$. Cantrell presented evidence that the activity $p21^{ras}$ is in turn regulated by the TCR, and that $p21^{ras}$ also cooperates with a calcium/calcineurin controlled system to stimulate the transcription factor, NF-AT, and hence the *IL-2* gene.

Compelling evidence for the role of the non-receptor protein tyrosine kinase, $p56^{lck}$, is presented by Perlmutter. This kinase is important early in T cell development, at the double negative to double positive thymocyte transition. It apparently acts as a means by which the thymocyte senses the presence of TCRβ protein, which promotes allelic exclusion at the TCRβ locus, initiation of TCRα gene rearrangement, cellular proliferation and differentiation. The regulation of $p56^{lck}$ activity thus has profound consequences for a developing T cell.

The consequences of the activation of multiple classes of kinases upon ligation of the TCR is described by Crumpton. A number of proteins phosphorylated on tyrosine residues have been identified. These include kinases themselves and components of the cytoskeletal network. The current challenge is to elucidate the biological consequences of these phosphorylation events, and their importance for the activation process.

Mike Crumpton has made fundamental contributions to studies on the MHC and on T cell activation, and these contributions have formed a platform for much of the subsequent work in the field. The articles that comprise this issue of *Cancer Surveys* provide ample evidence of the impact of Mike Crumpton's research, and emphasise the power of molecular approaches to the study of complex biological systems, such as the immune response.

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