

a guide to antigen processing and presentation

A Guide to Antigen Processing and Presentation: Implications for Immunology and Beyond

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Abstract: This comprehensive guide to antigen processing and presentation explores the intricate mechanisms by which the immune system recognizes and responds to foreign substances. We delve into the major pathways, including MHC class I and class II presentation, their significance in generating immune responses, and their crucial role in vaccine development, immunotherapy, and autoimmune disease research. The article also highlights the burgeoning industrial applications of this fundamental immunological process.

Introduction: Understanding the Fundamentals of "A Guide to Antigen Processing and Presentation"

The immune system's ability to distinguish "self" from "non-self" is paramount to maintaining health. Central to this process is antigen processing and presentation, a sophisticated mechanism enabling the recognition of foreign antigens (e.g., viruses, bacteria, and cancer cells) by T lymphocytes, key players in adaptive immunity. A thorough understanding of this intricate process, as detailed in this guide to antigen processing and presentation, is crucial for advancing research in numerous areas, including vaccine development, immunotherapy, and autoimmune disease treatment.

Antigen Processing: The Preparation Phase

Antigen processing is the initial step where complex antigens are broken down into smaller, manageable peptide fragments that can be presented to T cells. This process occurs primarily within antigen-presenting cells (APCs), including dendritic cells, macrophages, and B cells. There are two main pathways:

1. MHC Class I Pathway: This pathway primarily presents intracellular antigens, such as viral proteins or tumor-associated antigens, to cytotoxic T lymphocytes (CTLs). Infected or cancerous cells degrade intracellular proteins via the proteasome, and the resulting peptides are transported into the endoplasmic reticulum (ER) by transporter associated with antigen processing (TAP). In the ER, peptides bind to MHC class I molecules, and the complex is then transported to the cell surface for presentation to CTLs. Understanding this pathway is crucial for developing effective cancer immunotherapies targeting intracellular antigens. This aspect of "a guide to antigen processing and presentation" is fundamental to immunotherapy strategies.

1. MHC Class II Pathway: This pathway processes extracellular antigens, such as bacteria and their toxins, taken up by APCs through phagocytosis or endocytosis. The ingested antigens are degraded within endosomes and lysosomes, and the resulting peptides bind to MHC class II molecules synthesized in the ER. This complex is then transported to the cell surface for presentation to helper T lymphocytes (Th cells). This pathway is critical for initiating humoral immunity and regulating adaptive immune responses. A detailed understanding, as provided by this guide to antigen processing and presentation, helps us understand autoimmune diseases where the immune system mistakenly attacks self-antigens.

Antigen Presentation: Unveiling the Antigen to T Cells

Antigen presentation is the process by which MHC molecules on the surface of APCs display processed peptide antigens to T cells. The T cell receptor (TCR) on the T cell recognizes the specific peptide-MHC complex, initiating T cell activation. This interaction is highly specific; each TCR recognizes only a particular peptide-MHC combination. The binding triggers a cascade of signaling events leading to T cell proliferation, differentiation, and the subsequent elimination of the antigen. A guide to antigen processing and presentation must highlight the specificity and crucial nature of this interaction.

The Implications for Industry: Translating Knowledge into Applications

A thorough understanding of "a guide to antigen processing and presentation" has profound implications for various industries:

Vaccine Development: Modern vaccine design relies heavily on manipulating antigen processing and presentation pathways. Subunit vaccines, for example, utilize purified antigens or specific peptides to stimulate immune responses. By optimizing antigen presentation, vaccine efficacy can be significantly enhanced.

Immunotherapy: Cancer immunotherapy aims to harness the power of the immune system to fight cancer. Strategies, such as checkpoint inhibitors and adoptive cell therapies, target and manipulate different aspects of antigen processing and presentation to enhance anti-tumor immunity. This area greatly benefits from "a guide to antigen processing and

presentation".

Autoimmune Disease Treatment: In autoimmune diseases, the immune system mistakenly attacks self-antigens. Understanding antigen processing and presentation helps in developing therapies that suppress or redirect these aberrant immune responses.

Diagnostics: The ability to measure specific peptide-MHC complexes can be used for diagnostic purposes, allowing for early detection and monitoring of various diseases.

Drug Discovery: Identifying and targeting key molecules involved in antigen processing and presentation can lead to the development of novel therapeutic agents.

Conclusion

This guide to antigen processing and presentation provides a comprehensive overview of this fundamental immunological process. A deep understanding of the MHC class I and class II pathways, along with the critical interaction between APCs and T cells, is crucial for advancing research and developing new therapeutic strategies in various fields. The implications of this knowledge extend beyond basic science, directly impacting the development of innovative vaccines, immunotherapies, diagnostics, and drug discovery, driving significant advancements within the biotechnology and pharmaceutical industries.

FAQs

1. What are the main differences between MHC class I and class II presentation? MHC class I presents intracellular antigens to CD8+ T cells, while MHC class II presents extracellular antigens to CD4+ T cells.

1. What is the role of the proteasome in antigen processing? The proteasome degrades intracellular proteins into peptides for MHC class I presentation.

1. How do APCs capture and process antigens? APCs utilize phagocytosis, endocytosis, and pinocytosis to capture antigens, followed by lysosomal degradation.

1. What is the significance of TAP in MHC class I presentation? TAP transports peptides from the cytosol into the ER for MHC class I binding.

1. How can antigen processing and presentation be manipulated for therapeutic purposes? This can be achieved through various methods including peptide vaccines, checkpoint inhibitors, and adoptive cell therapies.
1. What are some examples of autoimmune diseases affected by antigen processing and presentation? Rheumatoid arthritis, type 1 diabetes, and multiple sclerosis.
1. How does antigen presentation contribute to vaccine efficacy? Effective antigen presentation leads to a stronger and more robust immune response.
1. What are the challenges in developing effective cancer immunotherapies based on antigen processing? Identifying tumor-specific antigens and overcoming immune evasion mechanisms.
1. What are the future directions in research on antigen processing and presentation? Exploring novel antigen presentation pathways, developing more effective delivery systems for vaccines and immunotherapies, and identifying new therapeutic targets.

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a guide to antigen processing and presentation: Antigen Processing and Presentation

Robert Edward Humphreys, Susan K. Pierce, 1994 One of the few volumes dedicated to antigen processing, this unique text is not only especially current but also valuable for its description of potentially hot areas with its Future Directions sections. * Current, important topics covered by this text include: Processing and presentation of foreign and self protein antigens to T lymphocytes Intracellular assembly and transport of MHC proteins Regulation of the assembly and expression of processed antigen-MHC complexes

a guide to antigen processing and presentation: Avian Immunology Bernd Kaspers, Karel A. Schat, 2012-12-02 The second edition of Avian Immunology provides an up-to-date overview of the current knowledge of avian immunology. From the ontogeny of the avian immune system to practical

application in vaccinology, the book encompasses all aspects of innate and adaptive immunity in chickens. In addition, chapters are devoted to the immunology of other commercially important species such as turkeys and ducks, and to ecoimmunology summarizing the knowledge of immune responses in free-living birds often in relation to reproductive success. The book contains a detailed description of the avian innate immune system, encompassing the mucosal, enteric, respiratory and reproductive systems. The diseases and disorders it covers include immunodepressive diseases and immune evasion, autoimmune diseases, and tumors of the immune system. Practical aspects of vaccination are examined as well. Extensive appendices summarize resources for scientists including cell lines, inbred chicken lines, cytokines, chemokines, and monoclonal antibodies. The world-wide importance of poultry protein for the human diet, as well as the threat of avian influenza pandemics like H5N1 and heavy reliance on vaccination to protect commercial flocks makes this book a vital resource. This book provides crucial information not only for poultry health professionals and avian biologists, but also for comparative and veterinary immunologists, graduate students and veterinary students with an interest in avian immunology. - With contributions from 33 of the foremost international experts in the field, this book provides the most up-to-date review of avian immunology so far - Contains a detailed description of the avian innate immune system reviewing constitutive barriers, chemical and cellular responses; it includes a comprehensive review of avian Toll-like receptors - Contains a wide-ranging review of the ecoimmunology of free-living avian species, as applied to studies of population dynamics, and reviews methods and resources available for carrying out such research

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Tamas Fulop, Claudio Franceschi, Katsuki Hirokawa, Graham Pawelec, 2009-02-27 This authoritative handbook covers all aspects of immunosenescence, with contributions from experts in the research and clinical areas. It examines methods and models for studying immunosenescence; genetics; mechanisms including receptors and signal transduction; clinical relevance in disease states including infections, autoimmunity, cancer, metabolic syndrome, neurodegenerative diseases, frailty and osteoporosis; and much more.

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Shoba Ranganathan, Vladimir Brusic, 2007-11-21 In contrast to existing books on immunoinformatics, this volume presents a cross-section of immunoinformatics research. The contributions highlight the interdisciplinary nature of the field and how collaborative efforts among bioinformaticians and bench scientists result in innovative strategies for understanding the immune system. Immunoinformatics is ideal for scientists and students in immunology, bioinformatics, microbiology, and many other disciplines.

a guide to antigen processing and presentation: *Encyclopedia of Virology* , 2021-02-24

Encyclopedia of Virology, Fourth Edition, Five Volume Set builds on the solid foundation laid by the previous editions, expanding its reach with new and timely topics. In five volumes, the work provides comprehensive coverage of the whole virosphere, making this a unique resource. Content explores viruses present in the environment and the pathogenic viruses of humans, animals, plants and microorganisms. Key areas and concepts concerning virus classification, structure, epidemiology, pathogenesis, diagnosis, treatment and prevention are discussed, guiding the reader through chapters that are presented at an accessible level, and include further readings for those needing more specific information. More than ever now, with the Covid19 pandemic, we are seeing the huge impact viruses have on our life and society. This encyclopedia is a must-have resource for scientists and practitioners, and a great source of information for the wider public. Offers students and researchers a one-stop shop for information on virology not easily available elsewhere Fills a critical gap of information in a field that has seen significant progress in recent years Authored and edited by recognized experts in the field, with a range of different expertise, thus ensuring a high-quality standard

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Neuroscience Matt Carter, Rachel Essner, Nitsan Goldstein, Manasi Iyer, 2022-03-26 Modern

neuroscience research is inherently multidisciplinary, with a wide variety of cutting edge new techniques to explore multiple levels of investigation. This Third Edition of Guide to Research Techniques in Neuroscience provides a comprehensive overview of classical and cutting edge methods including their utility, limitations, and how data are presented in the literature. This book can be used as an introduction to neuroscience techniques for anyone new to the field or as a reference for any neuroscientist while reading papers or attending talks. - Nearly 200 updated full-color illustrations to clearly convey the theory and practice of neuroscience methods - Expands on techniques from previous editions and covers many new techniques including in vivo calcium imaging, fiber photometry, RNA-Seq, brain spheroids, CRISPR-Cas9 genome editing, and more - Clear, straightforward explanations of each technique for anyone new to the field - A broad scope of methods, from noninvasive brain imaging in human subjects, to electrophysiology in animal models, to recombinant DNA technology in test tubes, to transfection of neurons in cell culture - Detailed recommendations on where to find protocols and other resources for specific techniques - Walk-through boxes that guide readers through experiments step-by-step

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a guide to antigen processing and presentation: Cell Biology of the Major Histocompatibility Complex Benvenuto Pernis, 2012-12-02 Cell Biology of the Major Histocompatibility Complex documents the proceedings of a symposium on Cell Biology of the Major Histocompatibility Complex held at Arden House on the Harriman Campus of Columbia University from June 8 -10, 1984. The meeting was the ninth of the P & S Biomedical Sciences Symposia. The book is organized into five parts. Part I on the structure of MHC molecules includes papers on human histocompatibility antigens; the cloning of human MHC; and organization of the genes of the H-2 complex. Part II on alternate forms of MHC molecules includes studies on the expression of a secreted form of the MHC class I antigen and alternative splicing in the H-2 multigene family. Part III deals with MHC biosynthesis, intracellular transport, and membrane expression. It includes studies on the manipulation of glycans on antigens of the MHC and dynamics of MHC molecules in lymphoid cells. Part IV on homologues of class I MHC molecules covers topics such as Tla expression in normal and malignant cells and the Qa series of antigens. Part V on the association of MHC with antigens includes studies such as histocompatibility molecules as immune response gene products and molecular nature of T-cell recognition of antigen.

a guide to antigen processing and presentation: Natural History of the Major Histocompatibility Complex Jan Klein, 1986 This work is a natural history of the major histocompatibility complex written for anyone who is working on the MHC but wants to step back and review the complex in its entirety; for anyone who wants to be introduced to the MHC; or for anyone who is just curious about this much talked-about chromosomal region. By natural history is meant an all encompassing treatment of the MHC, both human and mouse, in its entire range and its details - but presented in a way that anybody can understand without consulting a variety of other sources. Most of the details are summarized in the form of tables whereas the text concentrates on generalizations and discussions. Thus, the book will be of interest to immunologists and geneticists seeking an overview of the subject and to graduate students in these disciplines. It will also be of value to technicians working in HLA-typing laboratories.

a guide to antigen processing and presentation: Fine Structure Immunocytochemistry Gareth Griffiths, 2012-12-06 Electron microscopy in the biological sciences can be divided into two

disciplines. The first, concerned with high resolution detail of particles or periodic structures, is mostly based on sound theoretical principles of physics. The second, by far the larger discipline, is interested in the information obtainable from thin sections. The theoretical background to those groups of techniques for preparing and looking at thin sections is often inexact and loose, for want of a better word. What should be chemistry is often closer to alchemy. This kind of electron microscopy is often enshrined with mystical recipes, handed down from generation to generation. Admittedly, many of the processes involved, such as those required to embed tissue in epoxy resins, involve multiple interconnected steps, which make it difficult to follow the details of any one of these steps. If all these steps are shrouded in some mystery, however, can one really trust the final image that emerges on the EM screen? When we present the data in some semi quantitative form is there really no better way to do it than to categorize the parameters with ++, +/-, etc? What happens when one labels the sections with antibodies? Does the whole business necessarily need to be more of an art than a science? Upon reflecting on these problems in 1981, I had the impression that many of the multi-authored textbooks that existed then (and that have appeared since) tended to exacerbate or at least perpetuate this

a guide to antigen processing and presentation: Immunobiology of Dendritic Cells Part A, 2019-10-04 Immunobiology of Dendritic Cells Part A, Volume 348 in the International Review of Cell and Molecular Biology series highlights new advances in the field, with this new volume presenting interesting chapters on the Origin and Development of Dendritic Cells, Dendritic Cell Subsets and Locations, Antigen Processing and Presentation, The Interaction of Dendritic Cells With Cancer Cells, The Role of Dendritic Cells in Human Diseases, and Dendritic Cells-based Vaccines for Cancer Therapy. - Provides the authority and expertise of leading contributors from an international board of authors - Presents the latest release in the International Review of Cell and Molecular Biology series - Includes the latest information on the Immunobiology of Dendritic Cells, Part A

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a guide to antigen processing and presentation: Immunization in Practice, 2015 This practical guide contains seven modules targeted at district and health facility staff. It intends to meet the demands to improve immunization services so as to reach more infants in a sustainable way, building upon the experiences of polio eradication. It includes materials adapted from polio on planning, monitoring and use of data to improve the service, that can be used at any level. Revising the manual has been a team exercise. There are contributions from a large number of experts, organizations and institutions. This new edition has seven modules. Several new vaccines that have become more readily available and used in recent years have been added. Also the section on integration with other health interventions has been expanded as exciting opportunities and experiences have become evident in the years following the previous edition. Module 1: Target diseases and vaccines Module 2: The vaccine cold chain Module 3: Ensuring safe injections Module 4: Microplanning for reaching every community Module 5: Managing an immunization session

Module 6: Monitoring and surveillance Module 7: Partnering with communities.

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a guide to antigen processing and presentation: Monoclonal Antibody Production National Research Council, Institute for Laboratory Animal Research, Committee on Methods of Producing Monoclonal Antibodies, 1999-05-06 The American Anti-Vivisection Society (AAVS) petitioned the National Institutes of Health (NIH) on April 23, 1997, to prohibit the use of animals in the production of mAb. On September 18, 1997, NIH declined to prohibit the use of mice in mAb production, stating that the ascites method of mAb production is scientifically appropriate for some research projects and cannot be replaced. On March 26, 1998, AAVS submitted a second petition, stating that NIH failed to provide valid scientific reasons for not supporting a proposed ban. The office of the NIH director asked the National Research Council to conduct a study of methods of producing mAb. In response to that request, the Research Council appointed the Committee on Methods of Producing Monoclonal Antibodies, to act on behalf of the Institute for Laboratory Animal Research of the Commission on Life Sciences, to conduct the study. The 11 expert members of the committee had extensive experience in biomedical research, laboratory animal medicine, animal welfare, pain research, and patient advocacy (Appendix B). The committee was asked to determine whether there was a scientific necessity for the mouse ascites method; if so, whether the method caused pain or distress; and, if so, what could be done to minimize the pain or distress. The committee was also asked to comment on available in vitro methods; to suggest what acceptable scientific rationale, if any, there was for using the mouse ascites method; and to identify regulatory requirements for the continued use of the mouse ascites method. The committee held an open data-gathering meeting during which its members summarized data bearing on those questions. A 1-day workshop (Appendix A) was attended by 34 participants, 14 of whom made formal presentations. A second meeting was held to finalize the report. The present report was written on the basis of information in the literature and information presented at the meeting and the workshop.

a guide to antigen processing and presentation: Strengthening Forensic Science in the United States National Research Council, Division on Engineering and Physical Sciences, Committee on Applied and Theoretical Statistics, Policy and Global Affairs, Committee on Science, Technology, and Law, Committee on Identifying the Needs of the Forensic Sciences Community, 2009-07-29 Scores of talented and dedicated people serve the forensic science community, performing vitally important work. However, they are often constrained by lack of adequate resources, sound policies, and national support. It is clear that change and advancements, both systematic and scientific, are needed in a number of forensic science disciplines to ensure the reliability of work, establish enforceable standards, and promote best practices with consistent application. Strengthening Forensic Science in the United States: A Path Forward provides a detailed plan for addressing these needs and suggests the creation of a new government entity, the

National Institute of Forensic Science, to establish and enforce standards within the forensic science community. The benefits of improving and regulating the forensic science disciplines are clear: assisting law enforcement officials, enhancing homeland security, and reducing the risk of wrongful conviction and exoneration. Strengthening Forensic Science in the United States gives a full account of what is needed to advance the forensic science disciplines, including upgrading of systems and organizational structures, better training, widespread adoption of uniform and enforceable best practices, and mandatory certification and accreditation programs. While this book provides an essential call-to-action for congress and policy makers, it also serves as a vital tool for law enforcement agencies, criminal prosecutors and attorneys, and forensic science educators.

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a guide to antigen processing and presentation: Quality Management and Accreditation in Hematopoietic Stem Cell Transplantation and Cellular Therapy Mahmoud Aljurf, John A. Snowden, Patrick Hayden, Kim H. Orchard, Eoin McGrath, 2021-02-19 This open access book provides a concise yet comprehensive overview on how to build a quality management program for hematopoietic stem cell transplantation (HSCT) and cellular therapy. The text reviews all the essential steps and elements necessary for establishing a quality management program and achieving accreditation in HSCT and cellular therapy. Specific areas of focus include document development and implementation, audits and validation, performance measurement, writing a quality management plan, the accreditation process, data management, and maintaining a quality management program. Written by experts in the field, Quality Management and Accreditation in Hematopoietic Stem Cell Transplantation and Cellular Therapy: A Practical Guide is a valuable resource for physicians, healthcare professionals, and laboratory staff involved in the creation and maintenance of a state-of-the-art HSCT and cellular therapy program.

a guide to antigen processing and presentation: Dendritic Cell Protocols Stephen P. Robinson, Andrew J. Stagg, 2008-02-02 Dendritic Cell Protocols provides chapter and verse for many useful practical approaches to the art of studying dendritic cells. The book gives information on the usual techniques for derivation of human dendritic cells from precursor stem cells, such as monocytes. In addition it provides data on the difficult tasks of isolating dendritic cells directly from different tissues; whether dendritic cells from precursor cells or from tissues of mouse or human are required, this book contributes practical information. The last section of the book is devoted to functional aspects of dendritic cells ranging from information relevant to cell migration to antigen uptake and T cell stimulation. But what is a dendritic cell? The explosion of studies on this cell type over the last few years is breathtaking. We now have so-called "myeloid" and "plasmacytoid" dendritic cells; are they of separate lineages or are they related? There are claims that dendritic cells can be

derived from B cells and from granulocytes, as well as from “monocytes.” Lymphocytes can be switched on or off by dendritic cells. Dendritic cells can preferentially cause Th1 or Th2 responses or some may stimulate B cells directly. When there is so much scope for exploring these new developments, it is particularly important that the data that are established and the practical basis for this work are clearly available, a task that this book fulfils.

a guide to antigen processing and presentation: Registries for Evaluating Patient Outcomes Agency for Healthcare Research and Quality/AHRQ, 2014-04-01 This User’s Guide is intended to support the design, implementation, analysis, interpretation, and quality evaluation of registries created to increase understanding of patient outcomes. For the purposes of this guide, a patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. A registry database is a file (or files) derived from the registry. Although registries can serve many purposes, this guide focuses on registries created for one or more of the following purposes: to describe the natural history of disease, to determine clinical effectiveness or cost-effectiveness of health care products and services, to measure or monitor safety and harm, and/or to measure quality of care. Registries are classified according to how their populations are defined. For example, product registries include patients who have been exposed to biopharmaceutical products or medical devices. Health services registries consist of patients who have had a common procedure, clinical encounter, or hospitalization. Disease or condition registries are defined by patients having the same diagnosis, such as cystic fibrosis or heart failure. The User’s Guide was created by researchers affiliated with AHRQ’s Effective Health Care Program, particularly those who participated in AHRQ’s DEcIDE (Developing Evidence to Inform Decisions About Effectiveness) program. Chapters were subject to multiple internal and external independent reviews.

a guide to antigen processing and presentation: Antigen Processing and Presentation Protocols Joyce C. Solheim, 2007-10-26 Antigen processing and presentation, as a field, explores a broad range of protein interactions and functions, both intracellular (in the cytoplasm and in the endoplasmic reticulum) and at the cell surface (between T cells and MHC molecules). To investigate such a diverse array, it is necessary that biochemical, cell biology, and immunological techniques all be employed. The purpose of Antigen Processing and Presentation Protocols is therefore to detail the most up-to-date techniques being used in this burgeoning field. Such techniques include those used to question how MHC-binding peptides are generated, to test how peptides are delivered to MHC molecules, to analyze MHC peptide-binding patterns, and to assay the T-cell response to MHC/peptide. Antigen Processing and Presentation Protocols should aid both those new and those experienced in this area of research in extending the questions that can be asked and answered by the application of these current methods. For editorial assistance, I would like to thank Angela Beninga and Rachael Turnquist.

a guide to antigen processing and presentation: Immunology Richard Coico, Geoffrey Sunshine, 2015-01-28 Immunology: A Short Course, 7th Edition introduces all the critical topics of modern immunology in a clear and succinct yet comprehensive fashion. The authors offer uniquely-balanced coverage of classical and contemporary approaches and basic and clinical aspects. The strength of Immunology: A Short Course is in providing a complete review of modern immunology without the burden of excessive data or theoretical discussions. Each chapter is divided into short, self-contained units that address key topics, illustrated by uniformly drawn, full-color illustrations and photographs. This new edition of Immunology: A Short Course: • Has been fully revised and updated, with a brand new art program to help reinforce learning • Includes a new chapter on Innate Immunity to reflect the growth in knowledge in this area • Highlights important therapeutic successes resulting from targeted antibody therapies • Includes end of chapter summaries and review questions, a companion website at www.wileyimmunology.com/coico featuring interactive flashcards, USMLE-style interactive MCQs, figures as PowerPoint slides, and

case-based material to help understand clinical applications

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presentation, and subsequent recognition of antigens by T cells. Topics discussed include the structure of MHC molecules, the nature and specificity of human class II molecule interactions with peptide antigens, the class II invariant chain, antigen processing and presentation by class I MHC molecules, the biology of antigen processing, and the presentation and role of accessory molecules in T cell recognition. Other chapters feature discussions about the T cell allorecognition of MHC molecules, the recognition of minor antigens, and the concept of superantigens. Color plates demonstrate the three-dimensional structure of MHC molecules and peptide antigen interaction with MHC molecules. Diagrams illustrate antigen presentation pathways, T cell receptor-MHC interaction and accessory molecule interactions. *Antigen Processing and Recognition* will be a valuable addition to the libraries of students and teachers of immunology, as well as cell biologists who are looking for a unified view of this rapidly expanding subject.

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