THE MOLECULAR BIOLOGY OF AUTOIMMUNE DISEASE pdf

1: Biology of Immune Cells in Health and Disease - Mayo Clinic Research

The application of molecular biology to elucidate the genes coding for the molecules paramount in eliciting the immune (or autoimmune) response and recently the cloning of the genes coding for the putative autoantigens of certain diseases may at last allow the autoimmune response to be dissected at the molecular level.

In Depth Tutorials and Information Autoimmune Diseases Molecular Biology Autoimmunity is not pathologic per se because natural autoantibodies, natural autoreactive T-cell clones, and the connected idiotypes and anti-idiotypes are part of the basic organization of the immune system. Autoimmune diseases AIDS are the consequence of a major failure in the regulation of the immune system, as the emergence of self-reactivity becomes aggressive and harmful to the organism. They represent a major cause of morbidity, and their incidence increases with aging. The primary causes of autoimmune diseases AIDS are still very poorly understood, and the precise target of the autoimmune reactions is not always known. In some cases, one organ, and eventually one target molecule, can be identified. Examples of these are myasthenia gravis, in which antibodies directed against the acetylcholine receptor have been identified, or autoimmune thyroiditis, where the presence of autoantibodies directed against receptors for thyroid stimulating hormone have been documented. Such antibodies may have very different impacts upon binding. Another example of an organ-specific AID is insulin-dependent diabetes mellitus, in which the cellular target is the b islets of the endocrine pancreas. Some AIDs appear to be not organ-specific, such as systemic lupus erythematosous, when a number of autoantibodies are directed against a large variety of antigens, including DNA and nucleoproteins. Several characteristics generally underline the occurrence of AIDs: It was postulated that this AID might be the consequence of an epitope mimicry, an infection with Klebsiella inducing an immune response that subsequently would cross-react with the HLA epitope of the host. A similar hypothesis was proposed for rheumatoid arthritis, a very common rheumatological disorder that may develop for years, because it was found to be associated with certain DR4 alleles expressing the Gln â€"Lysâ€"Argâ€"Alaâ€"Ala QKRAA sequence. A similar sequence was found in Hsp 70, which might provide another example of epitope mimicry as the starter for the initial immunization. The VH and VL regions of autoantibodies isolated from AID patients have been sequenced extensively, with the hope of detecting significant differences from natural, nonaggressive autoantibodies. In most occasions, but not always, these antibodies have mutated variable regions, as opposed to the germline sequences generally found in natural antibodies. The significance of this remains unclear, however, primarily because the autoantibodies developed by a rather large number of AID patients seem to be only passive witnesses of an autoimmune response, rather than being involved in pathogenesis, which is frequently attributed to cytotoxic T lymphocytes. Numerous animal models have been defined and extensively studied. Another example is the nonobese diabetic NOD mice that develop an autoimmune diabetes, which spontaneously develops an insulitis that becomes full insulin-dependent diabetes mellitus at 7 months of age. New Zealand black NZB mice and other strains that spontaneously develop a systemic lupus erythematosous-like syndrome are another example. These models are interesting because they provide a possible key to understanding the genetic basis for the equivalent human diseases. Other approaches are centered more on attempts to isolate antigens that might induce an AID-like syndrome. An example of this is experimental autoimmune encephalomyelitis, which is a possible model for multiple sclerosis; it can be induced upon injection of myelin basic protein, from which encephalitogenic peptides and precise epitopes have been described. This disease can also be transferred with lymphocytes but not by serum, pointing to the role of cell-mediated immunity in this AID. Interestingly, T cells with a suppressive activity have also been identified, offering the possibility of modulating the immune system negatively by this approach. Such a treatment is eagerly awaited for most AIDs, particularly multiple sclerosis. Thus far, primarily nonspecific immunosuppressive agents are used, with the obvious problem of generating severe secondary effects.

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2: The Molecular Biology of Autoimmune Disease : Alan M. McGregor :

Autoimmune diseases are common and often associated with considerable morbidity or - in diseases such as IDDM, myasthenia gravis and multiple sclerosis - mortality. In this volume, experts of international stature in basic science and clinical medicine with a common interest in understanding the normal and aberrant immune response present their.

This section does not cite any sources. Please help improve this section by adding citations to reliable sources. Unsourced material may be challenged and removed. February Learn how and when to remove this template message Classical immunology ties in with the fields of epidemiology and medicine. It studies the relationship between the body systems, pathogens , and immunity. The earliest written mention of immunity can be traced back to the plague of Athens in BCE. Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time. The study of the molecular and cellular components that comprise the immune system, including their function and interaction, is the central science of immunology. The immune system has been divided into a more primitive innate immune system and, in vertebrates , an acquired or adaptive immune system. The latter is further divided into humoral or antibody and cell-mediated components. The immune system has the capability of self and non-self-recognition. An antigen is a substance that ignites the immune response. The cells involved in recognizing the antigen are Lymphocytes. Once they recognize, they secrete antibodies. Antibodies are proteins that neutralize the disease-causing microorganisms. The humoral antibody response is defined as the interaction between antibodies and antigens. Immunology rests on an understanding of the properties of these two biological entities and the cellular response to both. Besides, there are direct implications of the immune system in the infectious diseases tuberculosis, malaria, hepatitis, pneumonia, dysentery, and helminth infestations as well. Hence, research in the field of immunology is of prime importance for the advancements in the fields of n the modern medicine, biomedical research, and biotechnology. February Learn how and when to remove this template message Clinical immunology is the study of diseases caused by disorders of the immune system failure, aberrant action, and malignant growth of the cellular elements of the system. It also involves diseases of other systems, where immune reactions play a part in the pathology and clinical features. The diseases caused by disorders of the immune system fall into two broad categories: Other immune system disorders include various hypersensitivities such as in asthma and other allergies that respond inappropriately to otherwise harmless compounds. In fact, many of the infections acquired by neonates are caused by low virulence organisms like Staphylococcus and Pseudomonas. In neonates, opsonic activity and the ability to activate the complement cascade is very limited. Phagocytic activity is also greatly impaired in newborns. This is due to lower opsonic activity, as well as diminished up-regulation of integrin and selectin receptors, which limit the ability of neutrophils to interact with adhesion molecules in the endothelium. Although, the number of total lymphocytes is significantly higher than in adults, the cellular and humoral immunity is also impaired. At birth, most of the immunoglobulin present is maternal IgG. Some IgA is provided by breast milk. These passively-acquired antibodies can protect the newborn for up to 18 months, but their response is usually short-lived and of low affinity. If a child is exposed to the antibody for a particular antigen before being exposed to the antigen itself then the child will produce a dampened response. Passively acquired maternal antibodies can suppress the antibody response to active immunization. Similarly the response of T-cells to vaccination differs in children compared to adults, and vaccines that induce Th1 responses in adults do not readily elicit these same responses in neonates. This can be the reason for distinct time frames found in vaccination schedules. Oestradiol usually begins to act around the age of 10 and testosterone some months later. Other androgens, however, such as DHEA , increase immune response. Physical changes during puberty such as thymic involution also affect immunological response. Ecoimmunology and Behavioral immune system Ecoimmunology, or ecological immunology, explores the relationship between the immune system of an organism and its social, biotic and abiotic environment. More recent ecoimmunological research has focused on host pathogen defences traditionally considered "non-immunological", such as pathogen avoidance, self-medication, symbiont -mediated defenses, and fecundity trade-offs. For example, the Monarch

butterfly often lays its eggs on certain toxic milkweed species when infected with parasites. These toxins reduce parasite growth in the offspring of the infected Monarch. However, when uninfected Monarch butterflies are forced to feed only on these toxic plants, they suffer a fitness cost as reduced lifespan relative to other uninfected Monarch butterflies. Aphids , for example, rely on several different symbionts for defense from key parasites, and can vertically transmit their symbionts from parent to offspring. Immunotherapy The use of immune system components to treat a disease or disorder is known as immunotherapy. Immunotherapy is most commonly used in the context of the treatment of cancers together with chemotherapy drugs and radiotherapy radiation. However, immunotherapy is also often used in the immunosuppressed such as HIV patients and people suffering from other immune deficiencies or autoimmune diseases. Immunodiagnostics The specificity of the bond between antibody and antigen has made the antibody an excellent tool for the detection of substances by a variety of diagnostic techniques. Antibodies specific for a desired antigen can be conjugated with an isotopic radio or fluorescent label or with a color-forming enzyme in order to detect it. Cancer immunology The study of the interaction of the immune system with cancer cells can lead to diagnostic tests and therapies with which to find and fight cancer. Reproductive immunology This area of the immunology is devoted to the study of immunological aspects of the reproductive process including fetus acceptance. The term has also been used by fertility clinics to address fertility problems, recurrent miscarriages, premature deliveries and dangerous complications such as pre-eclampsia. Theoretical immunology[edit] Immunology is strongly experimental in everyday practice but is also characterized by an ongoing theoretical attitude. Many theories have been suggested in immunology from the end of the nineteenth century up to the present time. The end of the 19th century and the beginning of the 20th century saw a battle between "cellular" and "humoral" theories of immunity.

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3: The molecular biology of autoimmune disease.

The occurence of autoimmune disease has been a challenging paradox ever since Ehrlich first elaborated the concept of 'horror autotoxicus'. Over the past 35 years the list of known or suspected autoimmune diseases has expanded to include Graves' disease, myasthenia gravis, multiple sclerosis and insulin-dependent diabetes mellitus (IDDM).

Related terms[edit] Viral apoptotic mimicry, defined by the exposure of phosphatidylserine â€" a marker for apoptosis â€" on the pathogen surface, in the case of apoptosis, the dead cell surface that is used to gain viral access to the interior of immune cells. Immunological tolerance[edit] Tolerance is a fundamental property of the immune system. Tolerance involves non-self discrimination which is the ability of the normal immune system to recognize and respond to foreign antigens, but not self antigens. Autoimmunity is evoked when this tolerance to self antigen is broken. This is known as maternal-fetal tolerance where B cells expressing receptors specific for a particular antigen enter the circulation of the developing fetus via the placenta. It is here where the first wave of B cell tolerance arises. Within the bone marrow, pre-B cells will encounter various self and foreign antigens present in the thymus that enter the thymus from peripheral sites via the circulatory system. Within the thymus, pre-T cells undergo a selection process where they must be positively selected and should avoid negative selection. B cells that bind with low avidity to self-MHC receptors are positively selected for maturation, those that do not die by apoptosis. Cells that survive positive selection, but bind strongly to self-antigens are negatively selected also by active induction of apoptosis. This negative selection is known as clonal deletion , one of the mechanisms for B cell tolerance. Approximately 99 percent of pre-B cells within the thymus are negatively selected. Only approximately 1 percent are positively selected for maturity. B cell tolerance then must occur within the periphery after the induction of B cell tolerance within the thymus as a more diverse group of antigens can be encountered in peripheral tissues. This same positive and negative selection mechanism, but in peripheral tissues, is known as clonal anergy. The mechanism of clonal anergy is important to maintain tolerance to many autologous antigens. Active suppression is the other known mechanism of T cell tolerance. Active suppression involves the injection of large amounts of foreign antigen in the absence of an adjuvant which leads to a state of unresponsiveness. There are also various processes which lead to B cell tolerance. Just as in T cells, clonal deletion and clonal anergy can physically eliminate autoreactive B cell clones. Receptor editing is another mechanism for B cell tolerance. This involves the reactivation or maintenance of V D J recombination in the cell which leads to the expression of novel receptor specificity through V region gene rearrangements which will create variation in the heavy and light immunoglobulin Ig chains. These mechanisms are known by many to be intrinsic. However, there are pathogenic mechanisms for the generation of autoimmune disease. Pathogens can induce autoimmunity by polyclonal activation of B or T cells, or increased expression of major histocompatibility complex MHC class I or II molecules. There are several ways in which a pathogen can cause an autoimmune response. A pathogen may contain a protein that acts as a mitogen to encourage cell division, thus causing more B or T cell clones to be produced. Similarly, a pathogenic protein may act as a superantigen which causes rapid polyclonal activation of B or T cells. Pathogens can also cause the release of cytokines resulting in the activation of B or T cells, or they can alter macrophage function. Finally, pathogens may also expose B or T cells to cryptic determinants, which are self antigen determinants that have not been processed and presented sufficiently to tolerize the developing T cells in the thymus and are presented at the periphery where the infection occurs. Molecular mimicry is defined as similar structures shared by molecules from dissimilar genes or by their protein products. Either the linear amino acid sequence or the conformational fit of the immunodominant epitope may be shared between the pathogen and host. This is also known as " cross-reactivity " between self antigen of the host and immunodominant epitopes of the pathogen. An autoimmune response is then generated against the epitope. Due to similar sequence homology in the epitope between the pathogen and the host, cells and tissues of the host associated with the protein are destroyed as a result of the autoimmune response. However, due to the amino acid variation between different proteins, molecular mimicry should not happen from a probability standpoint. Assuming five to six amino acid residues

are used to induce a monoclonal antibody response, the probability of 20 amino acids occurring in six identical residues between two proteins is 1 in or 1 in 64,, However, there has been evidence shown and documented of many molecular mimicry events. The largest protein database in the world, known as the UniProt database formerly SwissProt , has shown reports of molecular mimicry becoming more common with expansion of the database. The database currently contains 1. The probability of finding a perfect match with a motif of 5 amino acids in length is 1 in 3. Therefore, within the SwissProt database, one would expect to find 1. However, there are sequence motifs within the database that are overrepresented and are found more than 5 times. This motif is also expressed on numerous other proteins, such as on gp of the Epstein-Barr virus and in E. This motif occurs 37 times in the database. The possibility exists, then, for variability within amino acid sequence, but similarity in three-dimensional structure between two peptides can be recognized by T cell clones. This, therefore, uncovers a flaw of such large databases. They may be able to give a hint to relationships between epitopes, but the important three-dimensional structure cannot yet be searched for in such a database. In some cases, pathogenic mimics can possess a structural architecture that differs markedly from that of the functional homologues. Therefore, proteins of dissimilar sequence may have a common structure which elicits an autoimmune response. It has been hypothesized that these virulent proteins display their mimicry through molecular surfaces that mimic host protein surfaces protein fold or three-dimensional conformation , which have been obtained by convergent evolution. It has also been theorized that these similar protein folds have been obtained by horizontal gene transfer , most likely from a eukaryotic host. This further supports the theory that microbial organisms have evolved a mechanism of concealment similar to that of higher organisms such as the African praying mantis or chameleon who camouflage themselves so that they can mimic their background as not to be recognized by others. For example, charged residues can explain the enhanced on-rate and reduced off-rate of a particular antigen or can contribute to a higher affinity and activity for a particular antigen that can perhaps mimic that of the host. Similarly, prominent ridges on the floor of peptide-binding grooves can do such things as create C-terminal bulges in particular peptides that can greatly increase the interaction between foreign and self peptide on the MHC. It is now apparent that sequence similarity considerations are not sufficient when evaluating potential mimic epitopes and the underlying mechanisms of molecular mimicry. Molecular mimicry, from these examples, has therefore been shown to occur in the absence of any true sequence homology. Molecular mimicry is thus occurring between two recognized peptides that have similar antigenic surfaces in the absence of primary sequence homology. For example, specific single amino acid residues such as cysteine creates di-sulfide bonds , arginine or lysine form multiple hydrogen bonds , could be essential for T cell cross-reactivity. These single residues may be the only residues conserved between self and foreign antigen that allow the structurally similar but sequence non-specific peptides to bind to the MHC. Autoreactive T cells are activated de novo by self epitopes released secondary to pathogen-specific T cell-mediated bystander damage. Thus, inflammatory responses induced by specific pathogens that trigger pro-inflammatory Th1 responses have the ability to persist in genetically susceptible hosts. This may lead to organ-specific autoimmune disease. The result of this is an autoimmune response that is triggered by exogenous antigen that progresses to a truly autoimmune response against mimicked self antigen and other antigens. HIV-1 gp41 is used to bind chemokines on the cell surface of the host so that the virion may gain entrance into the host. Antibodies are produced for the HIV-1 gp41 protein. These antibodies can cross-react with astrocytes within human CNS tissue and act as autoantibodies. This virus has been shown to cause CNS disease in mice that resembles multiple sclerosis, an autoimmune disease in humans that results in the gradual destruction of the myelin sheath coating axons of the CNS. Bystander myelin damage is caused by virus specific Th1 cells that cross react with this self epitope. To test the efficacy in which TMEV uses molecular mimicry to its advantage, a sequence of the human myelin-specific epitope was inserted into a non-pathogenic TMEV variant. These involve the hepatitis B virus mimicking the human proteolipid protein myelin protein and the Epstein-Barr virus mimicking anti- myelin oligodendrocyte glycoprotein contributes to a ring of myelin around blood vessels. This disease causes fluctuating muscle weakness and fatigue. The disease occurs due to detectable antibodies produced against the human acetylcholine receptor. Similar to HIV-1, gpD also aids in binding to chemokines on the cell surface of the

host to gain entry into the host. Despite this, an autoimmune response still occurs. This further shows an immunologically significant sequence homology to the biologically active site of the human acetylcholine receptor. Control of the initiating factor pathogen via vaccination seems to be the most common method to avoid autoimmunity. Inducing tolerance to the host autoantigen in this way may also be the most stable factor. The development of a downregulating immune response to the shared epitope between pathogen and host may be the best way of treating an autoimmune disease caused by molecular mimicry. However, in many cases this has been shown to be ineffective because cells and tissues have already been destroyed at the onset of the infection. Molecular mimicry is, however, only one mechanism by which an autoimmune disease can occur in association with a pathogen. Understanding the mechanisms of molecular mimicry may allow future research to be directed toward uncovering the initiating infectious agent as well as recognizing the self determinant. This way, future research may be able to design strategies for treatment and prevention of autoimmune disorders. The use of transgenic models such as those used for discovery of the mimicry events leading to diseases of the CNS and muscle disorders has helped evaluate the sequence of events leading to molecular mimicry.

4: Molecular Mimicryâ€"Understanding the Link between Vaccines and Autoimmune Disease | The Crazz F

Autoimmune diseases are common and often associated with considerable morbidity or - in diseases such as IDDM, myasthenia gravis and multiple sclerosis - mortality. In this volume, experts of international stature in basic science and clinical medicine with a common interest in understanding the.

5: Immunology - Wikipedia

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6: Molecular analysis of the cause and expression of autoimmune diseases

1. Immunol Today. Nov;10(11) The molecular biology of autoimmune disease. Demaine AG. PMID: [PubMed - indexed for MEDLINE].

7: Molecular mimicry - Wikipedia

The Molecular Biology of Autoimmune Disease by Alan M. McGregor, , available at Book Depository with free delivery worldwide.

8: Immunology, Pathology & Infectious Disease | IGPBS | University of Nebraska Medical Center

The Molecular Biology of Autoimmune Disease Edited by Andrew G. Demaine J-Paul Banga Alan M. McGregor Department of Medicine King's College School of Medicine.

9: Laboratory of Immune System Biology | NIH: National Institute of Allergy and Infectious Diseases

The application of molecular biology to elucidate the genes coding for the molecules paramount in eliciting the immune (or autoimmune) response and recently the cloning of the genes coding for the.

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