EPITHEORESE KLINIKES FARMAKOLOGIAS. KAI FARMAKOKINETIKES, INTERNATIONAL EDITION 6: 105-111 (1992)

Greek Edition Volume 10, 1992 Issues No 1 and 2

Specific Defense Mechanisms by

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S U M M A R Y : Immunology is a relatively young branch of medical science; it influences our understanding, as we|l as diagnosis and therapy of many different illnesses. Immunology deals with the specific immune responses, that is with the defense mechanisms which operate only when a person has been previously exposed to a particular substance. Substances capable of stimulating immune responses are known as *antigens,* which can stimulate the production of *antibodies.* There are two kinds of specific immune mechanisms: *humoral immunity,* which involves the production of antibodies by B-cells, and *cell-mediated immunity,* in which special T-lymphocytes react directly with foreign material.

Lymphocytes have the pivotal role in the immune system. They bear the major responsibility for the actions of the immune system. They cannot phagocytize, but instead demonstrate other special properties.

- Lymphocytes carry specific surface receptors which allow each cell to react with one individual antigen. This is the basis of immunologi

cal specificity, (a) Lymphocytes divide after stimulation by antigen {and the presence of growth factors) to form cell clones of identical specificity. They are long-lived (months or years) and can retain information about antigens for a long time. This is the basis of immunological memory, (b) Lymphocytes can circulate between the bloodstream, the lymphatic system and tissues. This ensures that specific memory, acquired as a consequence of a local immune reaction, is distributed throughout the whole body.

When lymphocytes leave the bone marrow, they consist of two large groups. One group moves to the thymus and is there processed (acquisition of new surface antigens) and maturated (under the influence of the hormone *thymosin)* to become effective or *immunologically competent.* These cells later leave the thymus as T-lymphocytes. The other group of cells travels directly to the lymphoid tissues where they become *B-lymphocytes.*

B-lymphocytes, when exposed to foreign antigens, they synthesize RNA and differentiate to *plasma cells,* which produce .and secrete immunoglobulines (antibodies) into the body fluids ("Humor"). They thus contribute to what is called humoral immunity. The antibodies react with circulating antigens, but are unable to enter living cells.

T-lymphocytes, in contrast, react directly with their targets, i.e. with body cells infected

by viruses, or transformed into tumor cells. T- cells therefore contribute to what is called cellular immunity.

Functionally distinct lymphocytes all look the same under the light microscope. However, they carry different markers (glycoproteins) on their surfaces, which can be identified with the help of monoclonal antibodies. In this way it is possible, not only to distinguish B- and T- cells, but also to discriminate further subpopulations of these. Lymphocyte-1 ike cells which possess neither T- nor B-cell markers are referred to as Null cells. Null cells comprise the Natural Killer (NK) cells and the Natural Cytotoxic (NC) cells.

Each B-cell is programmed to produce a specific antibody. When a B-cell receives an antigenic stimulus, it divides to give rise to several large plasma cells which produce and secrete immunoglobulins (antibodies). The surface of the B-cell is also enveloped in the antibodies, which allow the B-cells to recognize the specific antigens. Most B-cells are under the regulatory control of the T-lymphocy- tes (T-H cells stimulate; T-S cells suppress).

T-cells have two important functions: they orchestrate the interplay of the different immune cells, and are also able to directly attack body cells which have been infected by viruses or are transformed into tumour cells. Functionally, T-cells can be divided into the following groups: (a) T-H^lper cells: activate B-cells, stimulate other T-cells, NK cells and macro-phages. (b) T-Suppressor cells: inhibit completely or in part B- and other T-cells. (c) Cytotoxic T-cells {killer T-cells): locate and destroy virus-infected body cells, (d) Delayed hypersensitivity T-cells: attract and activate other cells, e.g. macrophages. ,

All T-cells which participate in cell-mediated immunity can become involved in the formation of memory cells, and hence can lead to a secondary, later immune response of increased effectiveness. The effects of T.-cells can be attributed largely to the secretion of *lymphoki-nes,* which include factors responsible for the attraction (chemotaxis) of macrophage cells and also *lymphotoxin* (which kills foreign cells) and *interferon*, which inactivates viruses.

Cellular immunity plays an important role in the body's defence against viral, bacterial and fungal infections, in transplant rejection and in the defence against neoplastic growths. The presence of T-cell immunity to tuberculosis can be demonstrated with the Mantoux *reaction* (tuberculin reaction).

Overactivity of T-cell immunity causes one form of hypersensitivity reaction. T-lymphocyte function may be suppressed by steroid hormones or by the drug azathioprine. Such drugs are used to prevent rejections of a grafted tissue or organ.

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The Use of Antiarrhythmic Drugs in Patients with Renal Failure

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S U M M A R Y : Renal failure is commonly thought to have its role effect on the renal elimination of drugs. As will become apparent, renal failure has a variety of influences on drug kinetics, such as reducing nonrenal (presumably hepatic) drug elimination, protein binding, and the volume distribution of some drugs. The reasons for such changes are not always readity discernible, but nonetheless such changes must be taken into account if the antiarrhythmic drugs are to be used safety in patients with renal failure. In order to provide practical qutdelines for prescribing antiarrhythmic drug regimens in patients with renal failure, the literature has been reviewed and summarized!

The Potential Role of DNA Méthylation in Gene Expression and Development of New Therapeutics

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S U M M A R Y : This paper represents a comprehensive review on the potential biological role of DNA méthylation in gene expression during growth and differentiation of eukaryotic cells. It describes how méthylation of DNA or RNA occurs *via* the active méthylation cycle and how chemical or pharmaceutical agents pertúrbate these processes in a way that affect expression of various genes including those coding for 'hemoglobin chains. Agents like 5- azacytidine that inhibit DNA méthylation and activate expression of genes can be useful in treating diseases characterized by gene inactivation. Finally, the potential role of RNA méthylation in both growth and differentiation of neoplastic cells is also discussed.

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DNA Repair Mechanisms in Mammalian Cells: Hierarchies in the Repair

by S.M. Piperakis

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S U M M A R Y : When mammalian cells are exposed to various agents which cause damage to DNA, the repair which takes place in the different parts of the genome is heteroge neous. It is believed that pyrimidine dimers are repaired in at least three levels: (a) an accelerated repair of the transcribed strand of transcriptionally active genes, (b) fast repair of active housekeeping genes and (c) slow repair of inactive genes.

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Interaction Between Cephalosporins and Alcohol

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S U M M A R Y : Disulfiram-type reactions after ingestion of alcohol have been reported in patients treated with a number of cephalosporin antibiotics; predomintanly with agents containing the methythiotetrazole side chain, although other similar configurations have also been reported. Patients should be instructed to avoid ethanol during and after antibiotic administration. The reactions in most cases have been miid but hypotension and ventricular arrhythmias have occured. Patients experiencing the cephalosporin-ethanol reaction usually require no treatment; however, supportive measures may sometimes be necessary.

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The Role of the Myocardial Depressant Factor in Shock

by D.I. Chaniotis, M. Lymberi, P.A. Molyvdas, J.C. Stavridis

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S U M M A R Y : A variety of endogenously formed vasoactive substances (mediators) are

liberated in ischemia and shock states. This review is concerning a very potent substance, termed Myocardial Depressant Factor (MDF), which is determined into the plasma during all types of circulatory shock, having a broad profile of pathophysiological actions. Some of the effects of MDF include myocardial contractility depression (negative inotropic effect), constriction of splachnic vessels and impairment of phagocytosis. The pancreas (ischemic or hypoxic) has been found to be the major site of production of the MDF in shock. This substance appears to be a peptide which has a molecular wight of 500-800 daltons and as a toxic factor contributes to the lethality of circulatory shock (irreversible shock).

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Defense Mechanisms C. Antigens and Antibodies

by
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S U M M A R Y : Antigen is any substance that induces the formation of antibodies and/ or cells of immunity that interact specifically with it. In general, antigens are substances that the body recognizes as foreign. Antigens may be introduced into the body and such antigens are often large particles, e.g. bacteria, cells, large proteins, sugars or lipids; in certain circumstances small molecules and even material from one's own body (auto-antigens) can acquire antigenic characteristics. Immunogen is any substance that stimulates the formation of antibodies and/or cells of immunity. Allergen is the antigen that causes manifestations of allergy (acquired hypersensitivity to the antigen);, allergens bind to immunoglobulins of type E.

The most important property of an antigen is a surface feature (determinant or epitope) that is recognized as foreign by the body and to which the antibodies attach. The term hapten is used for a substance that is so small and unable by itself to elicit an immune response. An hapten can only be recognized by an antibody when it is coupled to a large protein, which is referred to as a carrier protein. Inorganic substances, lipids and nucleic acids are among the common haptens, whereas carrier protein may be, for example, serum proteins or proteins on the surface of red blood cells. The hapten (the portion of an antigen) determines the specificity of the antigen. There is a group of thymus-dependent antigens (generally proteins) which can stabilize and activate T-lymphocytes, and there is a group of thymus-independent antigens (generally polysaccharides) which activate B-lymphocytes. Cross-reacting antigens characterize a reaction between an antibody and an antigen that is not specific for the antibody, but it is closely allied to the one that is. An example of such a cross-react ion is vaccination using killed or weakened bacteria, or their toxin. The antibodies induced are able to neutralize both the living pathogen as well as the toxin it secretes (e.g. Tetanus).

Antibody is a protein substance developed in response to, and interacting specifically with, an antigen (antigen-antibody reaction). All antibodies belong to a special group of serum proteins, the immunoglobulin (Ig). The terms immunoglobulin and antibody are used interchangeably; however, whereas all antibodies are immunoglobulins, not all immunoglobulins act as antibodies. Immunoglobulins comprise two identical pairs of light (κ and A) and heavy (y, M, a, 6 and e) chains assembled in the form of a Y. The chains are linked by disulphide bridges. The antigen-binding portion varies in its structure (variable part); the remaining part of the molecule is relatively constant from one immunoglobulin to another. Within the variable region the highest degree of variability is

found in the amino acid sequence which serves as the antigen binding site (hypervariable region), so that an antibody can specifically react with any antigen; each binding site is made up of the amino-terminal segment of one heavy and one light chain. Treatment with papain allows the antigen-binding fragment (Fab) to be separated from the crystallizable (Fc) fragment in the region where the two join; this is where the complement component C1q binds. The Fc portion serves to link the antibody to Fc-receptors on different cells, especially macrophages (IgG) and Mast cells (IgE). The immunoglobulins are secreted by B-lymphocy- tes that have been stimulated either by an antigen directly or by an antigen that has been processed by macrophages. The active B-lymphocyte appears as a plasma cell. IgM, IgA and IgE are produced by B-lymphocytes that have the corresponding immunoglobulin determinants on their surfaces. Most IgG is produced by co-operation between B-lymphocytes and T-tymphocytes in the presence of macrophages.

Five major groups of Igs are normally present in the human adult; they approximately comprise 100 million antibody molecules in the serum of a healthy adult.

- IgG (or yG) represents the principal immunoglobulin in human serum; IgG antibodies are found throughout the tissue spaces and directed against a wide variety of antigens. Because it moves across the placental barrier, it is important in producing immunity in the infant prior to birth; newborn infants are already provided with maternal IgG antibodies. Via their Fc-region, these antibodies are able to bind to C1q and to Fc-receptor on macrophages and thus stimulate the phagocytosis of bacterial pathogens or other antigens. They can also neutralise toxins. In human there are four subclasses of IgG, of which only IgG4 is unable to bind complement.
- IgA (or yA) is the principal immunoglobulin in exocrine secretions such as milk, respiratory and intestinal mucin, saliva and tears. This is probably important in protecting mucosal surfaces from invasion by pathogenic bacteria. In serum (as a monomer like IgG) IgA is formed in the lymph nodes and in the spleen. It is unable to bind complement; antigens in the bloodstream, after having penetrated, for example, the gut lumen, are picked up by serum IgA and eliminated via the liver. The secretory IgA (s-IgA) is produced (the largest part) by the plasma cells in the lamina propria of the gut, of the bronchial tract or associated secretory glands. s-IgA is made up of two IgA molecules joined together via a J-chain (glycoproteine- serving as a protection against digestive enzymes) and a secretory segment {polypeptide-facilitating the transport of the IgA through the epithelium and its secretion into tears, saliva, or milk). Also s-IgA is unable to bind complement and hence cannot opsonize. It can however fix bacteria and viruses with its Fab segment, giving rise to immune complexes, thereby preventing them from adhering to the epithelial cells. This "neutralization" of germs is the most important function of IgA in the mucosal membranes. Immunization against certain diseases such as poliomyelitis, which gains access to the body via the gut, can be achieved with an oral vaccine that stimulates the production of IgA in the gut. Similarly, in the respiratory tract the major humoral defense is IgA, which is particularly important in combating viral infections of the respiratory tract such as influenza. When an IgA deficiency occurs (without been balanced by an increased IgM activity or if there is additionally a lack of IgG antibodies) people are prone to infections of the respiratory system or intestinal track.
- IgM (yM) is a globulin formed in almost every immune response during the early period of the reaction (primary reaction); IgM is the first antibody class to appear. IgM has a pentameric structure (five IgM monomers); thus unable to penetrate the placenta and can reach mucosal surfaces only in the case of inflammation with vascular permeability. Because of the pentamer

structure, IgM has up to ten antigen binding sites and is therefore particularly effective in binding microorganisms, causing them to clump and through complement binding to be opsonized. The isoagglutinins of blood groups A and B belong to this class, as do antibodies against the bacterial body of typhoid and paratyphoid bacilli.

- IgE (yE) is a gamma globulin produced by cells of the lining of the respiratory and intestinal tract. IgE is cytophile and binds via IgE- receptors to the surface of Mast cells and basophilic leukocytes and to a small extend also to other cell types. Degranulation of these cells is thereby induced in the context of a Type I allergic reaction (asthma and hay fever); about 50% of patients with allergic diseases (atopic patients) have increased IgE levels {in trace amounts in normal persons). IgE may have a role in the defence against intestinal parasites as roundworms and tapeworms. IgE does not bind complement.
- IgD (yD) is a protein that is present in normal human serum in very small amount. It is unable to fi* complement and its function is not known. It may have a regulatory role on the surface of B-cells as an antigen-trapping determinant.

Each immunoglobulin light chain is the product of at least 3 separate structural genes: a variable region VL gene, a joining region JI gene and a constant region CI gene. Each heavy chain is the product of at least 4 different genes: a variable region Vh gene, a diversity region D gene, a joining region JH gene and a constant Ch region gene. The molecular mechanisms responsible for the generation of the single immunoglobulin chains from multiple structural genes include gene rearrangement and class switching.

Immunoglobulins belong to a superfamily which includes receptors, such as interleukin-1 receptor, interleukin-6 receptor, the IgE receptors (FceRI) and the IgG receptors (FcyR). The IgE receptors FccRII belong to the lectin superfamily.

Histocompatibility or tissue antigens are those present on all cell types except erythrocytes and trophoblasts; they stimulate an immune response (both antibody production and lymphocyte sensitisation) whenever a person receives nucleated cells with antigens different from those of his own cells (except of identical twins). These antigens are controlled by genes; the group of these genes on chromosome 6 and their encoded proteins is the Major Histocompatibility Complex (MHC) (Major, because it controls for strong transplantation antigens). The *HLA system* (human leucocyte-A system) is the most important system of tissue antigens. The HLA antigens are glycoprotein components on cell membranes, whose structure is very similar to that of immunoglobulins, with a heavy and a light polypeptide chain. There are two classes of HLA antigens subserving different functions, the class I and class II. The formation of class I antigens is genetically regulated-controlled by genes at three loci on chromosome 6 designated HLA-A, HLA-B and HLA-C. These antigens are identifiable of the membranes of all nucleated cells of the body, excepting erythrocytes. They appear to be especially produced together with proteins which are newly synthesized by cells. This is the case for cells infected by viruses, since these cells must produce viral antigens. The antigens of class II HLA are also referred to as Ia-antigens from "Immune response associated". Their formation is controlled from the gene region D of the HLAi complex on chromosome 6. These antigens are only present in the membrane of B-lymphocytes and antigen-presenting cells (i.e. macrophages, monocytes and dentritic cells); where there is in- flamation, T-lymphocytes also exhibit class II antigens (not normally).

T-cells must possess receptors to react specifically to antigens. They therefore recognize

antigens, such as virus antigens, only when attached to a cell membrane, and only in association with one of endogenous Class I or Class II molecules. Therefore, the T-cell receptor must comprise an antigen-specific part and a part recognizing an HLA molecule. The cytotoxic T-cells recognize antigens on the membrane of cells which have Class I molecules. They thus form the principal components in the defence against virus infected cells. T-helper cells recognize antigens on those cells which possess Class II molecules.

These are largely macrophages and B-lymphocytes. The macrophages present individual antigens on their membranes to the helper cells. T-cells have simultaneously to recognize both foreign antigen as well as the self antigen (HLA Class I or Class II). This mechanism is known as HLA restriction.

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