Hans-Werner Vohr
Editor

Encyclopedia of Immunotoxicology

Second Edition

Springer Reference

Encyclopedia of Immunotoxicology

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With 148 Figures and 108 Tables

Editor
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Bayer HealthCare
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To Heide, Florian, Hannah and Lucas

Preface to the Second Edition

Nearly 10 years ago, Springer published the first edition of the *Encyclopedic Reference of Immunotoxicology*. The first edition's success is attributed to a great number of good friends and colleagues all over the world, who wrote the entries and supported the work, the Editorial Board and last but certainly not least, the dedicated people at Springer. Numerous problems, questions and misunderstandings were solved with patience and competence.

Immunotoxicology is a relatively young field of toxicology and is therefore relatively dynamic. Although the immunological basis for immunotoxicology has remained largely unchanged, several major new developments in methodology and guidelines prompted Springer to request an update of the first edition. Due to the high number of changes introduced in the second edition and the high workload experienced by the various contributors we faced difficulty at times with respect to updating each and every entry. However, with the dedication and passion of the Editorial Board, we managed to release this version. In all, 20 new entries were introduced and over 75 % of entries were updated. A special thanks to all the individuals that took a large amount of their time to support these changes: Leigh Ann, Bob, Henk, Jacques, Jörg, and Peter.

With great regret I had to take note of the death of dear friends and distinguished colleagues who provided very valuable and much-noted contributions to the first edition. In memory of these colleagues we decided to leave their entries as they are for this second edition with only minor editorial changes.

Finally, I want to give sincere thanks to all the authors for their new contributions and updates to existing entries. In addition to all the folks from Springer who were involved in preparing the second edition, I would like to thank Mauricio Quinones and Andrew Spencer, who played a major role in the success of the first edition, and were very supportive in preparation of the current edition.

Without the support, enthusiasm and patience of all the people mentioned here, completion of the second edition would not have been possible. This

edition includes a very impressive amount of updates and new entries. Perhaps most exciting is the availability of the References online. This allows readers to utilize only those parts of the book that are of interest for their research. The online availability will further allow continuous updates by the authors, resulting in a dynamic and evolving Reference that will match the evolution of the field of immunotoxicology.

April 2015 Hans-Werner Vohr

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A

ABO Blood Group System

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Synonyms

ABO histo-blood group system; Major human blood group system

Definition

The most important histocompatibility and blood group antigen system, consisting of two main antigens and four main phenotypes inherited in a Mendelian fashion.

Characteristics

The ABO blood group system was discovered by Karl Landsteiner in 1901. By mixing the separated sera with suspensions of red cells obtained from the blood of different individuals, four patterns of agglutination were obtained. These patterns subdivide the population into four main blood groups (with approximate European Caucasian frequencies in parentheses): O (46.5 %); A (42 %); B (8.5 %); and AB (3 %). The frequency of the four ABO groups varies in different populations: native Americans are almost exclusively group O, while Asians have a proportionately higher incidence of group B. There are two antigens, A and B, though A is subdivided into A_1 and A_2. The O phenotype is the absence of A and B (Table 1).

Almost without exception, every person has antibodies in their serum to those A or B antigens they lack from their red cells and tissues. In addition to anti-A and anti-B, group O individuals have a cross-reacting antibody called anti-A,B. Testing of red cells with selected potent anti-A, anti-B and anti-A,B reagents, while simultaneously testing the sera of the same subjects with reagent red cells (group A_1, A_2, B and O), provides the basis for ABO grouping.

The major subgroups of A are A_1 and A_2. A_2 is a weaker A antigen than A_1, but the difference between them is also qualitative. These subgroups can be distinguished with specific anti-A_1 reagents and are only significant clinically if the serum of an A_2 or A_2B individual reacts with A_1 cells at 37 °C and so may cause destruction of transfused group A_1 red cells. Anti-A_1 reagents can be a lectin prepared from Dolichos biflorus seeds, sera of group B subjects absorbed with group A_2 red cells, or mouse monoclonal antibodies. Naturally occurring anti-A_1 is present in the serum of 1–8 % group A_2 and 22–35 % group A_2B individuals, but is too weak to be used as a grouping reagent. Other variants of A(A_{int}, A_x, A_{end}, A_3, A_m, A_y, A_{el}) and B(B_3, B_x, B_m, B_{el})

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ABO Blood Group System, Table 1 The ABO blood group system

Phenotype	Antigens	Genotypes	Antibodies in serum
A_1	A_1, A	A^1/A^1, A^1/A^2, A^1/O	Anti-B
A_2	A	A^2/A^2, A^2/O	Anti-B, (anti-A_1)[a]
B	B	B/B, B/O	Anti-A
O	None	O/O	Anti-A, -B, -A, B
A_1B	A_1, A, B	A^1/B	
A_2B	A, B	A^2/B	(Anti-A_1)[a]

[a]Present in the plasma of some A_2 and A_2B individuals

are characterized by varying degrees of weakness of A or B antigens and by the absence of the appropriate ABO antibodies from their plasma. For example, the red cells of A_x individuals fail to react with anti-A from group B individuals, although they react with strong anti-A in group O people and with some monoclonal anti-A reagents; A_x individuals do not have anti-A in their serum. A and B variants are rare and usually of little clinical significance in blood transfusion.

Structure of the ABO Antigens

A and B antigens are carbohydrate structures, synthesized by glycosylation of oligosaccharide precursors with H antigen activity. The H antigen is synthesized from its precursor by a glycosyltransferase, a fucosyltransferase that is encoded by a gene that is genetically independent of *ABO*. Carbohydrate chains carrying the A, B, and H antigens are present on (i) the highly branched *N*-linked polysaccharides of integral membrane proteins, (ii) the heavily branched polysaccharides that form the polyglycosyl moieties of either soluble glycoproteins present in secretions or of polyglycosylceramides in the red cell membrane, and (iii) the short chain oligosaccharides of simple glycolipids in plasma. The immunodominant sugars of the A and B antigens are at the non-reducing ends of the various polysaccharide chains expressing A or B, and are attached by an α1-3 linkage to a fucosylated galactose residue with H antigen activity, such that the simplest A and B epitopes are trisaccharides with the structures given in Formula 1 (where R represents the remainder of the polysaccharide chain).

N-acetylgalactosamine (GalNAc) and galactose (Gal) are the immunodominant monosaccharides of the A and B epitopes, respectively. The presence of the fucose residue, the immunodominant sugar of the H antigen, is essential for A and B expression.

The β-Gal residue of the terminal trisaccharides can be attached to R in at least six different ways:

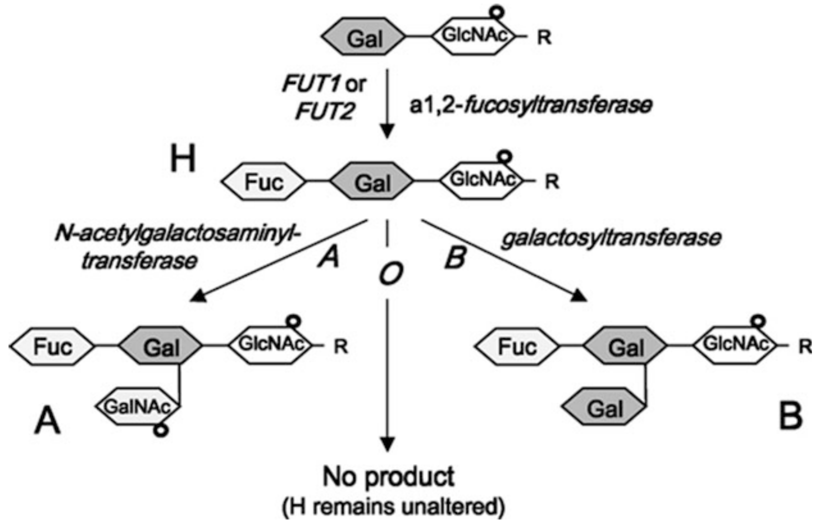
- Type 1 Galβ1→3GlcNAcβ1→R
- Type 2 Galβ1→4GlcNAcβ1→R
- Type 3 Galβ1→3GalNAcα1→R
- Type 4 Galβ1→3GalNAcβ1→R
- Type 5 Galβ1→3Galβ1→R
- Type 6 Galβ1→4Glcβ1→R

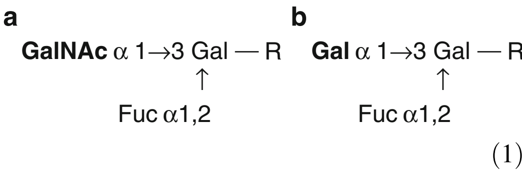
Of these peripheral core structures, type 2 is the most abundant on red cells; integral red cell membrane glycoproteins and glycolipids have almost exclusively type 2 sugars, though some glycolipids also have type 3 or type 4 structures. Red cells may also contain glycolipids, passively adsorbed from plasma, that have type 1 chains. The existence of these various epitopes on red cells probably explains the heterogeneity in reactivity of different A and B antibodies with group A and B variants. Types 1 and 2 are abundant in body secretions and endodermally derived tissues.

Biosynthesis and Molecular Genetics

The genes controlling the expression of A and B antigens are codominant alleles at the *ABO* locus on chromosome 9q34. The products of the *A* and *B* genes are glycosyltransferases, which catalyze the biosynthesis of the A and B antigens. They comprise a 353 amino acid polypeptide organised into three domains: a short N-terminal domain; a hydrophobic domain that spans the Golgi membrane; and a large C-terminal domain containing a catalytic site. The *A* gene product is an *N*-acetylgalactosaminyltransferase that transfers GalNAc from a UDP-GalNAc donor to the C3 position of the fucosylated Gal residue of the H antigen, to produce an A-active structure (Fig. 1).

ABO Blood Group System,
Fig. 1 Biosynthesis of H antigen from a common precursor and of A and B antigens from H





(1)

The *B* gene product is a galactosyltransferase that transfers Gal from UDP-Gal to the fucosylated Gal of H, to produce a B-active structure (Fig. 1). The *O* allele produces no active enzyme, hence the H structure remains unconverted.

The *ABO* gene consists of seven exons. The two largest exons, exons 6 and 7, contain 77 % of the coding sequence and are the most important in determining the substrate specificity of the gene products.

The *A* (or more specifically A^{1}) and *B* alleles differ at seven nucleotide positions, four of which (in exon 7) generate four amino acid differences. Two of these, at positions 266 (Leu from *A*, Met from *B*) and 268 (Gly from *A*, Ala from *B*), are responsible for determining whether the enzyme has predominantly GalNAc-transferase (A) or Gal-transferase (Gal) activity.

The most common *O* allele (O^{1}) has a nucleotide sequence almost identical to that of the A^{1} allele, but with a single base deletion in exon 6, which generates a change in reading frame at amino acid position 87 and a new in-frame stop codon. Consequently, O^{1} encodes a truncated polypeptide, which is only 116 amino acids long, lacks the catalytic domain and is enzymatically inactive. Another common *O* allele, (O^{1var}) has at least nine nucleotide differences from O^{1}, but still has the single base deletion and so is functionally identical to O^{1}. A third type of *O* (O^{2}) encodes a charged arginine, instead of neutral glycine (A) or alanine (B) at the vital 268 position, abolishing the enzymatic activity of the resultant protein.

The A^{2} gene product is a GalNAc-transferase with different kinetics to those of the A^{1}-transferase, making it apparently less efficient. The A^{2} allele closely resembles A^{1}, but has a single base deletion at the 3′ end of the gene, in the codon before the usual translation stop codon. The resultant reading-frame shift abolishes the stop codon, so the gene encodes an enzyme with an extraneous 21 amino acids at its C-terminus.

A variety of different mutations account for the rare ABO subgroups and demonstrate that the molecular background to most of these variants is heterogeneous. These mutations include missense mutations, splice site mutations, nonsense mutations, and nucleotide insertions. In addition, there are many different hybrid genes in which exons 1–6 derive from one allele and exon 7 derives from another. For example, $A^{1} - O^{1v}$, $B - O^{1v}$ and $O^{2} - O^{1v}$ all give rise to an A_x phenotype, because exon 6 does not contain the single

nucleotide deletion characteristic of O^{1} and so produces an active enzyme and exon 7 has the O^{1v} sequence, which is similar to *A*, but encodes an important Phe216Ile substitution, accounting for the weak A activity. The rare Asian phenotype, B_m, in which red cells express a very weak B antigen but levels of secreted B are normal, results from a deletion in *ABO* intron 1 encompassing an erythroid-specific promoter site.

Knowledge of the nucleotide sequences that distinguish the *ABO* alleles has made it possible to devise molecular genetic tests for predicting ABO phenotype, though they are not considered accurate enough for transfusion purposes.

H antigen, the acceptor substrate for the A and B transferases, is synthesized by addition of fucose (Fuc) to the C2 position of the terminal Gal of a peripheral core structure (see above and Fig. 1). This fucosylation is catalyzed by an α1,2-fucosyltransferase. Two genes on chromosome 19 encode α1,2-fucosyltransferases: *FUT1* is active in mesodermally derived tissues and is responsible for H expression on red cells; *FUT2* is active in endodermally derived tissues and is responsible for H expression in secretions, plasma and respiratory and digestive epithelia. Homozygosity for inactivating mutations in either of these genes results in absence of H in the appropriate tissues, and therefore absence of A or B antigens from those tissues, regardless of *ABO* genotype. *FUT2* is polymorphic and inactive *FUT2* alleles are common. About 20 % of Caucasians lack H, A, and B from their secretions and other endodermally derived tissues and are referred to as ABH non-secretors. They have normal ABH antigens on their red cells. Inactive *FUT1* alleles are rare and homozygosity results in very rare phenotypes in which the red cells lack H, A and B (regardless of *ABO* genotype). Individuals who are homozygous for inactive alleles of both *FUT1* and *FUT2* have the extremely rare blood group known as the Bombay phenotype (red cell H-deficient non-secretors). They almost invariably make a potent anti-H, making it very difficult to provide compatible blood for transfusion.

Tissue Distribution and Ontogeny

The A and B transferases are abundant in intestinal and gastric mucosa, respiratory mucosa, salivary glands and epithelia of the urinary tract. H, A and B antigen expression in these tissues is under the control of the *FUT2* locus, so the antigens are only expressed in those tissues in ABH secretors. The transferases are in free solution in plasma and secretions: mucin droplets, ovarian cyst fluid, milk and saliva. Molecules glycosylated by the transferases include membrane enzymes, membrane structural proteins and receptors, as well as secreted proteins, such as immunoglobulin A and coagulation factors.

During ontogeny ABH activity is at its highest in the early embryo from the fifth week post-fertilisation; ABH antigens are found in large amounts on endothelial cells and most epithelial primordia, and in practically all early organs, including blood islands of the yolk sac, erythropoietic foci of the liver, digestive tube epithelia, pharyngeal pouches, the thymus, the pituitary, thyroid glands, trachea and bronchi, hepatic and pancreatic diverticula, the cloaca, urachos and allantois, mesonephros and the ducts of the metanephros. The central nervous system, liver, adrenal glands and secretory tubules show no ABH activity at this stage.

The number of A and B sites on the red cell is increased approximately fourfold in adults compared with neonates. There are $25–37 \times 10^4$ A sites per red cell in the newborn and $81–120 \times 10^4$ in the A_2 adult, and $20–32 \times 10^4$ B sites per red cell in the newborn and approx. 75×10^4 in adults.

Clinical Relevance

The ABO system is polymorphic (see Polymorphism) and the antigens are strongly immunogenic (see Antigen), capable of eliciting 'naturally occurring' and immune antibodies. These antibodies can give rise to acute intravascular hemolytic transfusion reactions and rejection of transplanted organs (see below).

Relevance to Humans

Disease Associations

Many pathogenic microorganisms are capable of attachment to cell surface carbohydrate structures, so ABH antigens can be exploited as receptors for invasion of these cells. Secretor status may play an important role as it controls ABH expression in many tissues that are vulnerable to infection. Consequently, the degree of susceptibility to a variety of bacterial, viral, fungal and protozoan infections is associated with specific ABO and secretor phenotypes.

Microorganisms that are reported to bind to ABH antigens include *Helicobacter pylori*, *Propionbacterium granulosum*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Candida albicans*, *Streptomyces*, several strains of *Escherichia coli*, noroviruses and rotaviruses. Heat-labile enterotoxin produced by *E. coli* isolated from humans preferentially binds to glycolipids isolated from A, B, and AB human red cells, compared with O cells. Noroviruses responsible for acute epidemic gastroenteritis bind to glycoconjugates containing ABH structures and ABH non-secretors are resistant to symptomatic infection with most norovirus strains.

Statistical associations between a multitude of diseases and ABO and secretor phenotypes have been claimed. Though many may result from flawed statistics, the fact that these polymorphisms represent glycosylation changes on cell membranes and soluble glycoproteins makes almost any disease association feasible. For example, thrombosis is more prevalent in groups A and B, whereas hemorrhage is associated more with group O. This may be explained, at least in part, by the higher levels of the clotting agent von Willebrand factor (VWF) in the plasma of A or B individuals, resulting from the additional GalNAc or Gal residues present on A or B glycans on VWF restricting access of the VWF-cleaving enzyme, ADAMTS13. ABO is statistically associated with pancreatic cancer, with the highest risk for group B, intermediate risks or A and AB, and the lowest risk for O.

ABH activity is often absent from malignant tumours, despite being present on the surrounding epithelium. The prognostic value of this loss of ABH antigens is controversial. Another phenomenon associated with malignancy is the illegitimate A antigen, occasionally expressed on tumours of group O or B people. About 10 % of colonic tumors from group O patients homozygous for the O^{1} allele express A antigen and contain active A-transferase activity. This might result from loss of the product of exon 6 of *ABO* and the consequent absence of the nucleotide deletion characteristic of O^{1}, creating an A-active enzyme.

There is increasing evidence that group O individuals are less susceptible to severe *Plasmodium falciparum* malaria than group A. Malaria may have been a major factor in the global distribution of the ABO groups.

ABO Antibodies

The clinical importance of the ABO blood group system in blood transfusion derives from the high prevalence of its antibodies and their in vivo potency. The “naturally occurring” antibodies of the majority of group A or B individuals are mainly IgM and probably produced in response to environmental ABO antigens, especially those of microbes in the gut and respiratory tract. Such IgM antibodies, although displaying optimal activity in the cold, are reactive at 37 °C and can activate the complement cascade up to the C9 stage, leading to the immediate intravascular lysis of transfused incompatible red cells in vivo. Approximately one in every three random, ungrouped blood donations would be incompatible with a given recipient. Such incompatible transfusions can lead, in about 10 % of cases, to renal failure, disseminated intravascular coagulation, and death. Severe haemolytic transfusion reactions occur mainly in group O people, who have stronger ABO antibodies. The majority of the signs and symptoms of severe ABO intravascular hemolytic transfusion reactions can be attributed to the generation of C3a and C5a fragments as a result of full complement activation, with the consequent release of vasoactive amines

from mast cells and of cytokines such as interleukins IL-1, IL-6, IL-8 and tumor necrosis factor (TNF) from mononuclear cells. The release of thromboplastic substances from lysed red cells activates coagulation.

Successful ABO incompatible solid organ and haemopoietic progenitor cell transplants are performed regularly. ABO incompatibility, however, will cause hyperacute rejection of transplanted solid organs unless appropriate precautions are taken and may lead to pure red cell aplasia and extended transfusion dependency following of haemopoietic progenitor cell transplantation. Minor ABO incompatibility (e.g., O graft to A or B recipient) may lead to hemolysis of the recipients own red cells several days after transplantation, caused by antibodies produced by engrafted donor ‘passenger’ lymphocytes.

Group O adults and a small proportion of group A and B individuals have “naturally occurring” (usually weak) IgG in addition to stronger IgM ABO antibodies. The IgG component can cross the placenta and bind to fetal red cells. Lysis of fetal red cells, however, is generally minimal and hemolytic disease of the fetus and newborn (HDFN) caused by ABO antibodies is usually mild or inapparent in Western Europe and North America. HDFN due to ABO antibodies only affects the offspring of group O mothers. In some parts of the world, ABO HDFN is more prevalent, though seldom severe, and this is attributed to environmental factors such as the greater stimulation of ABO antibodies by microbes and parasites.

Some individuals possess plasma IgA ABO antibodies, irrespective of immunization. ABO antibodies of colostrum are often wholly IgA, although sometimes IgM antibodies can also be found.

Cord blood usually does not contain ABO antibodies although maternally derived IgG anti-A or anti-B can sometimes be detected. Newborn infants do not produce ABO antibodies until 3–6 months of age, reaching a maximal level at 5–10 years of age. The vast majority of healthy adults have easily detectable ABO antibodies, except from those of AB phenotype. Weakening of ABO antibodies can occur naturally in individuals aged over 50; a third of patients over 65 have low ABO antibody levels. Very occasionally individuals lack the appropriate ABO agglutinins, especially if hypogammaglobulinemic, or if their plasma IgM levels are low. Antibody levels can be substantially reduced by exhaustive plasma exchange (used therapeutically in ABO incompatible bone marrow and organ transplantation) or by immunosuppression caused by therapy or by disease.

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ABO Histo-Blood Group System

► ABO Blood Group System

Abscess

Accumulation of pus in a cavity originating after tissue colliquation.

Cross-References

▶ Dermatological Infections

Acquired Immunity

Requires stimulation of effector mechanisms following exposure to foreign materials (e.g., xenobiotics). Also known as adaptive immunity and exhibits antigen specificity, diversity, memory, and self/nonself recognition that is mediated by activated B and T cells. Therefore, acquired immunity can be subdivided into antibody-mediated immunity (AMI) and cell-mediated immunity (CMI).

Cross-References

▶ Humoral Immunity
▶ Immunotoxicology

Acrocyanosis

Arterial vasoconstriction with persistent cyanosis of hands and feet.

Cross-References

▶ Septic Shock

Activated Macrophages

Inflammatory macrophages exposed to both interferon-γ and lipopolysaccharide (LPS), or primed macrophages exposed to LPS, or macrophages elicited with infectious agents such as mycobacteria that are the highest activated state for killing.

Cross-References

▶ Macrophage Activation

Activation-Induced Cell Death (AICD)

In the course of a proliferative T-cell response, death-inducing molecules are being upregulated ultimately inducing cell death in the activated cells, thereby limiting the immune response.

Cross-References

▶ Tolerance

Activator Surface

A surface that allows massive activation of C3 and covalent binding of C3b. A nonactivator surface such as a host cell limits this activation using the normal control mechanisms of the complement system (e.g., factor H, CR1, presence of sialic acid).

Cross-References

▶ Complement System

Active Immunotherapy

Immunotherapy based on the stimulation of the immune system of the host. Therapeutic vaccination is a typical example of active immunotherapy. *See also* ▶ Passive immunotherapy.

Cross-References

▶ Tumor, Immune Response to

Active Lymph Pump

Also known′ as the "intrinsic lymph pump." Contractile activity of smooth muscle cells located in walls of lymphatic vessels. Lymphatic contractions cause a decrease in lymphatic diameter and generate an increase in intralymphatic pressure needed for lymph propulsion in the downstream direction.

Cross-References

▶ Lymph Transport and Lymphatic System

Acute Graft-Versus-Host Disease

▶ Graft-Versus-Host Reaction

Acute Inflammation

On contact with pathogens specialized sentinel cells of the immune system release cytokines and other proinflammatory mediators in order to initiate a local and acute response by activating surrounding tissue cells and recruiting leukocytes to the site of infection.

Cross-References

▶ Immune Response

Acute Lymphocytic Leukemia

▶ Leukemia

Acute Myelogenous Leukemia

▶ Leukemia

Adaptive Immune Response

The acquired arm of the immune system that produces a specific immune response to each infectious agent encountered and is capable of remembering the agent, thus protecting the host from future infection by the same pathogen. It is synonymous with acquired immune response.

As a first step of an adaptive immune response an antigen-presenting cell, such as a dendritic cell, traps an antigen in the periphery and migrates to the lymphoid tissues. Here it presents the antigen to T cells, evoking either a humoral response with the help of B cells, or a direct cytotoxic T cell response. Whereas the humoral responses are mainly directed against extracellular pathogens such as most bacteria, the cytotoxic T cell responses are in the case of infection with intracellular antigens such as by viruses.

Cross-References

▶ Aging and the Immune System
▶ Assays for Antibody Production
▶ Lymphocytes

Adaptive Immunity

The adaptive or specific arm of immunity comprises T and B lymphocytes that both express a discrete and individual antigen receptor which is created by genetic rearrangement of specific gene segments. This creates millions of individual lymphocytes each with discrete antigen specificity. T effector cells either help the innate and adaptive immune responses or they delete virus-infected cells. B cells produce antibodies as important reagents to provide immunological memory.

Cross-References

▶ Graft-Versus-Host Reaction
▶ Immune Response

Adaptors

Adaptors are molecular scaffolds that recruit other proteins. These proteins contain two or more domains (i.e., SH2 and SH3 domains) which bind other proteins. They mediate protein-protein interactions but usually have no intrinsic kinase activity. In lymphocytes, adaptors recruit other proteins to the activated receptor where these proteins can be phosphorylated and activated.

Cross-References

▶ Signal Transduction During Lymphocyte Activation

ADCC

Antibody-dependent cellular cytotoxicity is a cytotoxic mechanism through which antibody-coated target cells are killed by different effector cells, such as polymorphonuclear leukocytes, mononuclear phagocytes, natural killer (NK) cells, dendritic cells, and platelets, which bear receptors for the Fc portion of antibodies.

Cross-References

▶ Antibody-Dependent Cellular Cytotoxicity
▶ Cell-Mediated Lysis

Adherens Junctions

An intercellular junctional structure, most prominent in epithelial cells. In the adherens junction, the cell-cell adhesion is mediated by Ca^{2+}-dependent adhesion molecules, the cadherins. The cytoplasmic tail of these cadherins is indirectly linked to the actin cytoskeleton.

Cross-References

▶ Cell Adhesion Molecules

Adhesion Molecules

Proteins expressed on the surface of cells that mediate binding of immune system cells to other cells. The system of adhesion molecules facilitates movement of immune system cells from the circulation to lymphoid tissues or to sites of immune system activity, e.g., infection or inflammation.

There are three major families of proteins including integrins, the immunoglobulin superfamily, and selectins.

Cross-References

▶ Cell Adhesion Molecules
▶ Glucocorticoids
▶ Leukocyte Culture: Considerations for In Vitro Culture of T Cells in Immunotoxicological Studies

Adoptive Transfer PLNA

▶ Popliteal Lymph Node Assay, Secondary Reaction

Adrenocortical Hormones

▶ Glucocorticoids

Adrenocortical Steroids

▶ Glucocorticoids

Adrenocorticotropic Hormone (ACTH)

ACTH is secreted from the anterior pituitary gland in response to corticotropin-releasing hormone, enters the blood stream and is transported to the adrenal glands, stimulating the synthesis and release of glucocorticoids. Its production is increased in times of stress.

Cross-References

▶ Glucocorticoids
▶ Stress and the Immune System

Adult Respiratory Distress Syndrome (ARDS)

A descriptive term for diffuse infiltrative lung lesions of diverse etiologies which are accompanied by severe arterial hypoxemia.

Cross-References

▶ Septic Shock

Advanced or Extended Histopathology

▶ Histopathology of the Immune System, Enhanced

AFC

▶ Plaque-Forming Cell Assays

Afferent Lymphatics

Lymphatics are small vessels that contain clear fluid (lymph) that is collected from the tissues. The vessels that drain the tissues and transport fluid to lymph nodes are described as afferent lymphatics.

Cross-References

▶ Local Lymph Node Assay

Affinity Maturation of the Immune Response

▶ B-Cell Maturation and Immunological Memory

Aflatoxins

Naturally occurring toxin metabolites produced from some strains of fungi. They act by combining with DNA, suppressing DNA and RNA synthesis and play a role in the etiology of cancer of the liver.

Cross-References

▶ Respiratory Infections

Agglutination

In principle agglutination is the clumping of particles. In the context of this encyclopedia these particles can be cells or erythrocytes agglutinated by antigen specific antibodies. The agglutination of red blood cells is called hemagglutination.

This phenomenon is used as a diagnostic tool, e.g., for blood typing for transfusion, or for the Coombs Assay. Aggregation of erythrocytes in grapelike clusters are also seen on Romanofski stained peripheral blood smears of patients with IMHA.

Cross-References

▶ Antiglobulin (Coombs) Test

Aging and the Immune System

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Synonyms

Immunosenescence

Definition

Aging is the process of growing older starting from birth, whereas senescence is referred to as the process of somatic deterioration at older age. Our body is constructed to function optimally until the age of reproduction. After this time point, increasing age-related alterations and changes affecting the organism as a whole as well as the immune system can be observed. The deterioration of immune function in old age is termed "immunosenescence." The characteristics described here of the aging immune system are related to the post-reproduction period.

Characteristics

The thymus is the central lymphoid organ where bone-marrow-derived T cells learn to distinguish between self and nonself. This organ is almost fully developed at birth, but its involution starts soon after puberty. At the age of 60 years, thymic tissue is almost completely replaced by fat, resulting in a decreased thymic output of naive T cells in elderly persons. Aging is therefore accompanied by decreasing numbers of naive T cells. The loss of naive T cells is associated with a reduced IL-2 production, as observed in old age. Interestingly, the total count of T cells does not decrease with age, which is a consequence of proliferation of antigen-experienced memory cells which substitute for the decline of naive T cells. The increased number of memory/effector cells leads to altered cytokine production with a shift toward pro-inflammatory cytokines such as the interferon IFN-γ. The increased whole-body load of IFN-γ observed in the elderly may accelerate immune responses that lead to tissue injury. Elevated levels of pro-inflammatory cytokines are also associated with a number of age-related diseases (see Relevance to Humans).

A decreased T cell reactivity toward mitogens and antigens – which is probably due to increased membrane rigidity and decreased expression of costimulatory molecules such as $CD28^{-}$ – has been reported. Another characteristic of the immune system in the elderly is a restriction in the T cell repertoire. While newborns show a diverse spectrum of antigen recognition, elderly persons are often affected by the dominance of huge expanded clones specific for only few antigens as a result of chronic infections with, for example, persistent viruses. The appearance of multiple $CD8^{+}$ T cell clonal expansions is one of the most dramatic qualitative changes in the memory cell population during aging. These clones often lack the costimulatory molecule CD28 and their telomeres are short, suggesting that they are end-stage cells. Concerning the humoral immunity, both the B cell mitogen response and absolute B cell number remain unaltered in old age. However the antibody response toward primary and secondary immunizations is lower compared with young subjects,

probably due to a poorer cooperation between T and B cells.

Dendritic cells are the most professional antigen-presenting cells (APC) showing a unique ability to induce adaptive immune responses via the presentation of antigenic peptides to T cells. Dendritic cells generated in vitro from peripheral blood monocytes of elderly people are not impaired in their capacity to induce T cell responses and seem to persist unaltered in number, function, and surface marker expression during the aging process. In contrast, dendritic cells isolated directly ex vivo from old people are reduced in their functional capacity to stimulate immune responses. This may indicate a negative impact of an aged environment on the functional state of the dendritic cells, rather than an impaired cell function per se.

The innate immune system is not as dramatically affected as the specific immune system described above. Although natural killer (NK) cell lytic activity seems to be diminished in old age at the single-cell level, the overall cytotoxic activity remains intact as the numbers of NK cells have been reported to be higher in old than in young persons.

Investigations of the effect of aging on neutrophil bactericidal responses showed that neutrophils from elderly donors were able to generate superoxide and to opsonize *Escherichia coli* efficiently. In contrast, the phagocytic index was significantly decreased in neutrophils from the elderly, compared with young donors, proposing a contribution of aged neutrophils to immunosenescence. In summary, alterations of both specific and innate immunity result in an enhanced pro-inflammatory status which is characteristic of old age.

Preclinical Relevance

It is useful to distinguish between primary and secondary age-dependent alterations of immune reactivity. Primary age-related immune deficiencies occur also in healthy elderly persons due to an age-dependent intrinsic decline of immune function. Secondary age-related alterations result as a consequence of other environmental conditions such as malnutrition, insufficient blood supply, metabolic changes, and drugs.

Relevance to Humans

Infectious Diseases

It is well known that the frequency and severity of infections increases with advancing age. This can be attributed to a clear-cut decline of the immune function in the elderly. As explained, T cells in particular are affected by the aging process. Due to their declining helper function, the whole complex process of acquiring immunity following bacterial or viral infection or vaccination is disordered. Cohort studies showed declining antibody titers with ongoing age. This seems to be a problem, particularly when elderly persons are immunized with new antigens, such as tuberculin bacillin emulsion (TBE) or rabies.

Alzheimer’s Disease

Alzheimer’s disease is the most common form of dementia in the elderly. The critical step in the development of the disease is probably the deposition of amyloid leading to the formation of neuritic plaques and subsequently to cognitive impairment. As small amyloid deposits can also be found in the brain of healthy elderly persons and the aggregation and deposition of amyloid starts very early, probably 10–20 years before the onset of clinical symptoms, it is likely that further factors bias the outcome of the disease. Recently it has become evident that pro-inflammatory cytokines play a pivotal role in the pathogenesis of Alzheimer’s. Large studies demonstrated that the disease was less frequent in patients treated regularly with anti-inflammatory drugs compared to untreated control groups. Further, combinations of the pro-inflammatory cytokines tumor necrosis factor α (TNF-α), or the interleukin-1α (IL-1α), and IFN-γ have been shown to trigger the production of amyloid. Amyloid aggregation per se also seems to induce a chronic inflammatory reaction in the brain. The increased production of pro-inflammatory cytokines in old age may therefore facilitate the development of dementia.

Atherosclerosis

For long it has been presumed that an autoimmune-inflammatory process forms the basis of the disease. According to a recent concept, heat-shock protein HSP 60 is a relevant antigen for this immune response. HSPs are highly conserved components of pro- and eukaryotic cells which are expressed upon exposure to stress. Antibodies and T cells reactive against HSP 60 seem to cause damage of arterial endothelial cells, especially in the areas of major hemodynamic stress. Moreover a cholesterol-rich diet showed additive effects in rabbits which were immunized with recombinant mycobacterial HSP 60, leading to more severe atherosclerosis than in normally fed animals. Hence, atherosclerosis may have its seeds in an immunologically mediated disease, starting early in life and becoming increasingly evident with ongoing age and under the influence of additional risk factors such as smoking and high cholesterol intake.

Osteoporosis

The term osteoporosis describes a condition characterized by rarefaction of the bone mass that may be localized or involve the whole skeleton. Primary and secondary osteoporosis can be distinguished. Secondary osteoporosis may be the result of various underlying diseases such as rheumatoid disorders, malnutrition, malignancies, or side effects of drugs. Primary osteoporosis often occurs in terms of senile or postmenopausal osteoporosis after the age of 50 years and is associated with a loss of bone mass exceeding 1.5–2 % per year. Senile osteoporosis and postmenopausal osteoporosis are the most common primary forms of this condition. Low calcium intake, lack of physical activity, and low hormonal status are regarded as the main causes of age-dependent osteoporosis. Further the relative increase of pro-inflammatory cytokines in the elderly may disturb the balance between bone formation and resorption by activating and recruiting osteoclasts and has therefore important effects in the development of osteoporosis.

Cancer

Malignant transformation is the end point of multiple consecutive oncogenic damages leading to the final loss of cell-cycle control. In humans, the majority of cancer occurs in the final decades of life, culminating in a lifetime risk of one in two for men and one in three for women. The dramatic increase of malignant tumors in the elderly is probably due to a combination of several physiological changes throughout life, including telomere dysfunction, age-dependent deterioration in genome maintenance and stability, epigenetic mechanisms promoting carcinogenesis, altered stromal milieu, and decreased control function of the immune system. As tumorigenesis – at least of certain malignancies – may be under the control of the innate and the adaptive immunity, a functional impairment of these defense mechanisms by immunosenescence may result in increased susceptibility to tumors.

Regulatory Environment

In the research on human immunosenescence, only a limited number of animal models are available: mice live up to 2 years under germ-free laboratory conditions compared to humans with a life span of about 80 years in an unprotected environment; the nematode *Caenorhabditis elegans*, which is frequently used to study aging processes, lacks an immune system. So, further attempts have been made to standardize research guidelines in the human system. To exclude changes based on extrinsic factors such as illnesses, chronic diseases, or the use of medication, the SENIEUR protocol (from SENIor EURopean) was designed, defining “healthy elderly people.” In this protocol, strict admission criteria for further immunogerontologic studies were specified. The SENIEUR protocol therefore helps to distinguish between any alterations caused by aging per se and those caused by diseases. However, the strict selection of admission criteria may limit the significance of the studies. Therefore, careful selection of a suitable model system is obligatory and different approaches may be used to compliment one another.

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Ah Receptor (AhR)

The endogenous receptor in mammalian cells for PAHs such as BaP and dioxin-like compounds that mediates signaling and gene transcription via the DRE.

Cross-References

▶ Polycyclic Aromatic Hydrocarbons and the Immune System

Air Pollution

▶ Respiratory Infections

Airborne Contagion

▶ Respiratory Infections

Alexin

▶ Complement System

Allelic Discrimination

A method to detect different forms of the same gene that differ by nucleotide substitution, insertion, or deletion. In a bi-allelic system, two different fluorochrome-labeled probes are designed to hybridize each to a specific allele and are included in a PCR amplification of sample material. An increase in fluorescence of both dyes indicates allelic heterozygosity while an increase in only one signal reflects allelic homozygosity.

Cross-References

▶ Polymerase Chain Reaction

Allergen

Non-infectious antigens that induce hypersensitivity reactions, most commonly IgE-mediated type I reactions or cell-mediated type IV reactions.

Cross-References

▶ Flow Cytometry
▶ Food Allergy

Allergen Hypothesis

A relationship exists between the allergen concentrations experienced in infancy and the subsequent development of sensitization and asthma.

Cross-References

▶ Asthma

Allergic Contact Dermatitis

A delayed inflammatory reaction on the skin seen in type IV hypersensitivity, resulting from allergic sensitization.

Cross-References

▶ Contact Hypersensitivity
▶ Local Lymph Node Assay (IMDS), Modifications
▶ Skin, Contribution to Immunity

Allergic Reactions

▶ Hypersensitivity Reactions

Allergic Reactions to Drugs

▶ Drugs, Allergy to

Allergic Rhinitis (Hay Fever)

A typical immediate-type allergic reaction in the nasal mucosa. It is also known as hay fever, and causes runny nose, sneezing, tears.

Cross-References

▶ Hypersensitivity Reactions

Allergy

An immunological response to an allergen which may involve various organ systems.

Cross-References

▶ Food Allergy
▶ Hypersensitivity Reactions

Alloantigens

Alloantigens are surface molecules for example on erythrocytes (ABO system) or lymphocytes (MHC molecules) which are expressed by an individual but not by others of the same species.

Cross-References

▶ Rodents, Inbred Strains

Allogeneic

This term describes the genetic relationship between individuals of the same species in an outbred population, i.e., it refers to the intraspecies genetic variations.

Cross-References

▶ Graft-Versus-Host Reaction
▶ Idiotype Network

Allogeneic Determinants

The part of the antigen molecule that binds to a receptor on T cells which have a genetic dissimilarity between the same species.

Cross-References

▶ Mixed Lymphocyte Reaction

Alloreaction

This describes the stimulation of T cells by non-self antigens and determines the recognition.

Cross-References

▶ Cyclosporin A

Alloreactive

Stimulation of T cells by MHC molecules other than those expressed on self.

Cross-References

▶ Mixed Lymphocyte Reaction

Allotransplantation

Transplantation of an allograft, that is a graft of tissue from an allogeneic or non-self donor of the same species.

Cross-References

▶ Mixed Lymphocyte Reaction

Allotype

Products of allelic genes encoding immunoglobulin heavy or light chains originally detected in rabbits by immunization of one rabbit with immunoglobulin from another (alloimmunization). Complex allotypes are due to multiple amino acid differences between alleles and lead to several allotypic determinants detectable with alloantisera. Simple allotypes result from single base changes in alleles that replace one amino acid with another.

The MHC locus is highly polymorphic, giving rise to a range of different allotypic MHC molecules.

Cross-References

▶ Antigen-Specific Cell Enrichment
▶ Rabbit Immune System

Allotypic Epitopes

Immunoglobulins isolated from one strain of a species and injected into another strain will induce a response of allotypic epitopes.

Cross-References

▶ Humanized Monoclonal Antibodies

Alternative Activation

▶ Macrophage Activation

Alternative Pathway

A pathway of the complement system that is activated by pattern recognition of foreign surfaces independent of antibody, and is initiated by the spontaneous hydrolysis of C3. This pathway includes the complement components C3, factor B and factor D, resulting in the formation of a C3 convertase to cleave C3.

Cross-References

▶ Complement and Allergy