Evolution of the Human Immune System

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Human immune system is an orchestra of various defence mechanisms functioning at different levels, from individual cells to the whole body. They evolve interactively in concordance with human environment and history.

Introduction

Human immune system includes innate and adaptive defence mechanisms connected into a complex multilayered network by cytokines and hormones (**Figure 1**). While some mechanisms are universal, others are restricted to specialized immune cells. The division of defence mechanisms into innate and adaptive is based on the nature of their immune receptors. Innate receptors are encoded in genome as separate genes. Adaptive receptors are encoded as arrays of gene segments that are randomly recombined into diverse receptors during development of T and B cells. In general, immune response includes two phases: recognition of a pathogen and an effector phase such as phagocytosis or secretion of protective molecules, e.g. antibodies. Pathogens are recognized by the dual strategy of detecting the presence of foreign markers and the absence of markers characteristic of 'self' (Janeway and Medzhitov, 2002). The innate immune system employs detection by a pattern recognition receptor (PRR) of a group of related molecules characteristic of microbes or nonfunctional 'self'. Examples of microorganisms-specific patterns include an elevated level of mannose, components of bacterial cellular walls, certain deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) modifications, and viral double-stranded RNA (dsRNA). Endogenous molecules recognized by PRR are those that are not exposed on healthy cells, for instance phosphatidylserine is translocated to the cell surface only in apoptotic cells. Often, several PRRs cooperate to increase the specificity of recognition. In contrast, the unique repertoire of adaptive receptors is generated *de novo* in each individual and is further selected for specificity to antigens encountered during the individual's lifetime. A second encounter with the antigen leads to faster expansion of cells expressing antigen-specific receptors and, therefore, to a stronger immune response, which constitutes immunological memory. The strategy of recognizing pathogen-specific antigens is complemented by that of recognizing markers characteristic of normal 'self' and eliminating everything without such markers. Immune response also needs a 'danger' signal for initiation (Matzinger, 2002). An example of such a signal is uric acid released from injured cells. **See also**: Immunity: Humoral and Cellular; Immunological Danger Signals; Infection: Immunological Barriers; Innate Immune Mechanisms: Nonself Recognition; Pattern Recognition Receptor

Some researchers restrict the term 'immune system' to the adaptive immunity and refer to other mechanisms as 'nonspecific innate immunity'. The distinction between the innate and adaptive systems is however increasingly blurring. In some instances, innate immunity has memory and can be as specific as adaptive; certain innate receptors can be diversified by recombination and other mechanisms. B and T cells, however, are unable to perform their functions without the help of innate immune cells and, strictly speaking, cannot be considered as a separate system.

Many human immune mechanisms functioning at the cellular level can be traced back to unicellular organisms, others such as phagocytosis were acquired after the emergence of multicellular organisms, whereas adaptive immune mechanisms developed in vertebrates, and some specific adjustments emerged in mammals. New layers of immune defence evolved in interaction with the pre-existed mechanisms. Depending on the species, some mechanisms acquired a more important role in immune protection, while others regressed in accord with the environmental demands, the organism's lifestyle and the selection pressure from particular pathogens. Human immune system continues to evolve. There is probably no immune mechanism characteristic exclusively of humans but human-specific traits can be discerned in evolution of mechanisms inherited by humans from their animal ancestors.

Components of the Human Immune System

Defence mechanisms on the cellular level

Somatic cells in a human body are not passive victims of infection relaying for rescue exclusively on the immune cells. They respond actively to pathogens by changing expression
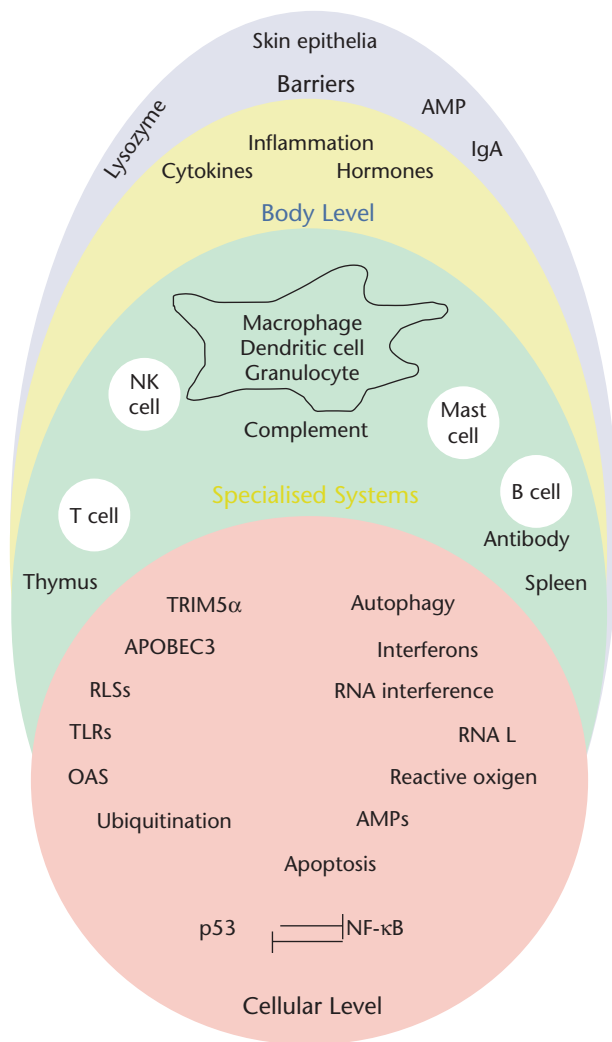
Figure 1 Human immune system is a multilayered network of various defence mechanisms. Each cell in a human body has various means to fight pathogens. Basic cellular mechanisms such as ubiquitination, RNAi and apoptosis contribute to immune defence. Specialized immune cells such as B cells and macrophages and humoral systems such as complement work autonomously but in communication with other mechanisms. All responses are coordinated at the body level by various mediators. Skin and epithelial barriers of the body are protected by secretion of antimicrobial substances.

of hundreds of genes. The nuclear factor (NF)-κB network mediates many immune mechanisms. NF-κB can also respond to general stress resulting, for instance from ultraviolet (UV) light or DNA damage, and it interacts with another stress response system, the p53 network. Activation of p53 leads to cell cycle arrest and apoptosis while NF-κB mediates cell survival and proliferation. NF-κB regulates the levels of p53 and antagonizes its effects by upregulation of antiapoptotic genes. NF-κB and p53 require the same coactivators p300 and CREB binding protein (CBP) and regulate each other by competing for these coactivators.

Cells use many tactics to fight pathogens. Tripartite motif-containing 5α (TRIM5α) protein prevents uncoating of viral capsid so that the virus cannot perform reverse

transcription and eventually being degraded. APOBEC3 (apolipoprotein B messenger RNA (mRNA)-editing enzyme catalytic polypeptide-like 3) proteins incorporate themselves into the virions and in the course of reverse transcription edit deoxyCytidine (dC) residues into deoxyUridine (dU) on the nascent DNA strand. Resulting hypermutation renders the provirus defective. RIG-I (retinoic acid-inducible gene I)-like helicases (RLRs) are expressed in cytoplasm of all cells and recognize various features of viral RNA, e.g. dsRNA leading to activation of NF-κB and other pathways and expression of interferons (IFNs). dsRNA can also be recognized by toll-like receptors (TLRs) and 2′,5′-oligoadenylate synthetase (OAS). The adenosine derivate produced by OAS activates RNAse L that degrades viral and cellular RNA blocking the infections. Interferons released by infected cells create an antiviral state in neighbouring cells by inducing transcription of hundreds of genes including OAS, APOBEC3G and RLRs.

Several other mechanisms are activated in infected cells. Autophagy removes old organelles and proteins by isolation and digestion of a part of the cell. It also controls bacterial, parasitic and viral infections. Autophagy is triggered by aggregates of PRRs with pathogens. Reactive oxygen species are used to kill pathogens in some cells. Ubiquitination is a routine cellular process controlling protein levels by proteasome-mediated destruction of ubiquitinated proteins. *Pseudomonas aeruginosa* produces cytotoxins disrupting cell signalling and immunity. Ubiquitination of those cytotoxins limits infection. Another antiviral mechanism is RNA interference (RNAi) also functioning as gene regulator. Response of the last resort for an infected cell is apoptosis. Apoptosis can be triggered from within the cell, or specialized immune cells can induce it in the infected cell. A cascade of the enzymes caspases mediates apoptosis. Caspase precursors are activated by cell stress or by damage to cell components; activated caspases cleave proteins essential for cell survival.

Many cells produce antimicrobial peptides (AMPs), one of the evolutionary oldest immune weapons. AMPs are amphipathic proteins that can associate with the microbial membrane causing its permealization and other damage. A single cell in the human gut can produce more than 20 AMP with different activities. This mechanism is of importance in newborns, whose adaptive immunity is immature and whose skin cells produce various AMPs. **See also**: Antimicrobial, Host Defence Peptides and Proteins

Specialized immune cells and systems

Specialized immune cells and systems such as phagocytes and complement evolved early in animal lineage. Besides their immune function they clean the organism of apoptotic, old, infected and transformed cells and damaged, misfolded and aggregated proteins. Humans have a diversified network of phagocytes such as macrophages involved in immune response, tissue remodelling and homoeostasis, granulocytes specialized in defence against various

pathogens and dendritic cells regulating the adaptive immunity. The first function of phagocytes in human ontogeny is not defence but removal of apoptotic cells during organogenesis. This process differs from phagocytosis of pathogens by the nature of cytokines released. Phagocytes engulfing apoptotic cells secrete anti-inflammatory factors such as interleukin 10 (IL-10), whereas those engulfing pathogens secrete pro-inflammatory mediators, e.g. IL-6 that attract and activate other immune cells. **See also**: Immune Response: Evolution; Phagocytosis

Complement is a humoral cascade of enzymes involving approximately 30 proteins. It starts by either lectin recognition of microbial and self-antigens (lectin pathway) or complement component 1q (C1q) recognition of antigen-bound antibodies (classical pathway) and leads to complement component 3 (C3) cleavage. It results in exposure and cleavage of the internal thioether bond. The cleaved thioether forms a new bond with any neighbouring biological substrate attaching C3 to it. It starts a cascade of enzymatic cleavages of other complement proteins and their deposition in complex with C3. It may result in the formation of the membrane attack complex and membrane lysis. Accumulation of complement on a particle facilitates its phagocytosis. Cleaved complement proteins regulate immune cells and promote inflammation. Since binding of cleaved C3 is not specific, human cells produce factors preventing deposition of complement on their surface. **See also**: Complement System: Evolution

Mast cells are evolutionary conserved cells carrying proteases important in immune defence and compounds regulating inflammation. The innate immune mechanisms are still the major line of defence in human body. Humans cannot survive without macrophages, complement or mast cells. **See also**: Mast Cells

T and B cells represent the adaptive branch of immune system. B-cell antigen-binding receptors (BCR) are dimers of immunoglobulin heavy and light chains. T-cell receptors (TCRs) are dimers of α and β or δ and γ chains. Secreted BCR are known as antibodies. Receptors are selected during ontogeny of T or B cells for absence of reactivity with self-molecules. BCRs recognize antigens directly while $TCR\alpha\beta$ recognize peptides associated with highly polymorphic major histocompatibility complex (MHC) molecules. Cytotoxic T cells recognize MHC class I associated with peptides derived from self-proteins, which are expressed on all cells. T-helper (T_H) cells assisting B cells recognize MHC class II associated with peptides from foreign proteins, which are expressed only on immune cells. T helpers can be further subdivided into T_H1 and T_H2 subsets with pro- and anti-inflammatory properties. After an encounter with a particular antigen T and B cells bearing antigen-specific receptors proliferate and B cells increase specificity of their receptors to the antigen in consecutive rounds of mutation and selection. Cells that lack normal MHCI, which is often down-regulated in transformed or infected cells, are recognized by natural killer (NK) cells. There are two types of killer-cell immunoglobulin-like receptors (KIRs) recognizing MHCI, inhibitory and activating encoded by polymorphic gene

families. Cytotoxic lymphocytes use such effector molecules as granulysin, perforin and granzymes to kill infected cells as well as the pathogens inside. **See also**: Antibody Responses: Development; Antigen Recognition by T Lymphocytes; B Lymphocytes; Cells of the Immune System; Lymphocytes; NK Cell Receptors

The adaptive immune system depends on support from innate immune cells. T cells recognize antigens presented by the phagocytes. Cytokines released by activated macrophages skew the T_H development to either T_H1 or T_H2 subsets. B cells need costimulation by innate immune cells to be activated. T and B cells can also be regulated by direct binding of certain ligands to PRRs expressed on their surfaces. Adaptive immune response can be very efficient but it takes one to two weeks to develop. Immediate response is based on the innate immunity. Various defence mechanisms communicate using chemokines, cytokines, AMPs, hormones, reactive oxygen species and other means. Immune cells can also be influenced by factors produced by nonimmune cells. **See also**: Interleukins

Whole-body level

Inflammation is a whole-body response to infection, which includes among other changes, fever and increased secretion by the liver of defence-related proteins such as the components of complement and soluble PRRs. Inflammation can be triggered by cytokines secreted by activated phagocytes, as well as by complement and other factors. Immune response can be modulated by hormones and by psychological stress. Stress results in the release of corticosteroids inhibiting the production of pro-inflammatory cytokines. Short-term stress mobilizes the organism's resources and stimulates the immune system, while prolonged stress suppresses it. **See also**: Inflammation: Acute

How Immune System Evolves

Coevolution with pathogens

There is a constant pressure from pathogens on human immune system. Many pathogens develop sophisticated tools to block or subvert immune response. They diversify their surface molecules, mask the most recognizable antigens, disguise themselves as host cells, produce molecules specifically disabling host defence mechanisms, manipulate host cellular machinery, etc. Major modifications of pathogens may arise by acquiring genomic material from another human and nonhuman pathogen. A completely new pathogen may evolve from a harmless commensal species or arise by crossing species barriers. Effectiveness of a particular immune mechanism varies depending on a pathogen. Pathogens coevolve with human immune system. For example, natural selection has favoured human immunodeficiency virus (HIV) mutants able to escape cytotoxic T cells. As soon as a pathogen develops tools to escape a particular immune mechanism, this mechanism becomes

useless in protection against the infection. Next, this immune mechanism can evolve to circumvent the pathogen's invention. Alternatively, it may regress; other immune mechanisms may take over the protection against this pathogen. An example of host–pathogen coevolution is myeloid Fc-alpha receptor 1 (FcaR1), a receptor for IgA-Fc, mediating phagocytosis of IgA-coated pathogens and the bacterial decoy staphylococcal superantigen-like 7 (SSL7) of *Staphylococcus aureus* inhibiting it (**Figure 2**). The SSL7- and FcaR1-binding sites on IgA-Fc overlap. The IgA-binding domain of FcaR1 was subject to positive selection in hominids at the time corresponding to duplication of IgA (Abi-Rached *et al.*, 2007). IgA-Fc also was a subject of selection at positions corresponding to SSL7 binding. Therefore FcaR1-IgA interface evolves under two types of selection. Pressure from pathogens selects for variants of IgA with reduced affinity for decoy proteins like SSL7. If IgA changes, new FcaR1 variants binding the novel IgA need to be selected. In rodents and rabbit IgA acquired resistance to SSL7. In rats, FcaR1 kept up and evolved to bind the new IgA but it failed in mouse and rabbit and was lost from their genomes. Thus, immune system evolution may take different directions even in close-related specie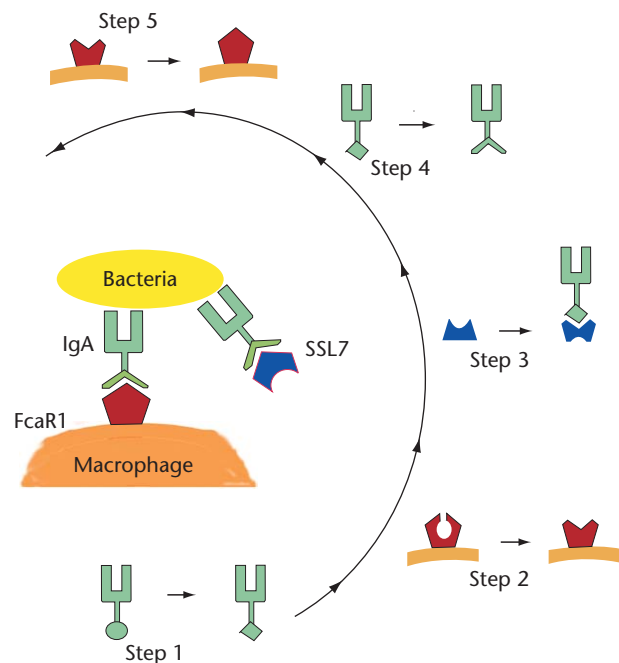s. **See also**: Immune Response: Evasion and Subversion by Pathogens; Immune System: Evolutionary Pressure of Infectious Agents; Virus Evolution

Mechanisms of immune genes changes

Most immune mechanisms originated a long time ago. The last major innovation, the adaptive immune system, happened approximately 450 million years ago. The speed of its emergence suggests it brought enormous advantage to its carriers. Introduction of such a complex system changed the balance between defence mechanisms. For example, versatile antibodies likely replaced many PRRs previously functioned in the complement cascade; IgA diminished AMPs' role in protection of mucosal surfaces etc. Consequently, vertebrates may have fewer PRRs. Sea urchin has 222 TLRs versus approximately 10 in mammals. Adaptive immune system is conserved in its major features from sharks to humans but many adjustments took place with vertebrate expansion to the land and the advent of mammals. Immune proteins have on average a higher rate of amino acid change between different species of mammals than do most other proteins. Major changes are, however, mediated not by changes in protein-coding sequences but by gene duplication, diversification and turnover in gene families involved in positive selection. Of 9990 gene families of a common ancestor of primates, rodents and canines more than half either expanded or shrank. For example, AMP genes became expanded and diversified in marsupials more than in placental animals, may be because marsupial younglings are less protected. The chymase locus encoding proteases was duplicated before the radiation of placental mammals with subsequent gene loss in some lineages. Now the rat chymase locus is approximately 15 and 9 times larger than the corresponding dog and human loci. Diversification of duplicated genes occurs in different ways. The repertoire of Fc receptor (FcR) proteins was created by recombination involving domains shuffling and species-specific gain or loss of individual exons or entire genes. *IFN-α* genes evolved by duplication and subsequent gene conversion. *KIR* gene was duplicated in early mammals. The *KIR3DX1* stays as a single gene in primates but has expanded in cattle. The other *KIR* acquired a transposon insertion in intron 3 and evolved in primates into a large family of genes by duplication, recombination and sequence diversification. As a result, immune system of every mammalian species is unique in many respects. **See also**: Immunology: Comparative Immunology of Mammals; Vertebrate Immune System: Evolution

Another way of diversification is through modification of regulatory sequences. About 20% of conserved non-coding elements in the genes of placental animals developed after separation of this lineage. Immune system genes have higher gene diversity in their 5′ noncoding regions than do the genes of other proteins.

Some immune system loci are subjects to balancing selection that acts to maintain polymorphism in either coding or regulatory regions. *MHC* genes and variable (V) regions of immunoglobulin and *TCR* genes evolve by birth and

Figure 2 Coevolution of humans and *Staphylococcus aureus*. FcaR1, a receptor for IgA-Fc, expressed on myeloid cells mediates phagocytosis of IgA-coated pathogens. *S. aureus* produces a bacterial decoy SSL7 that binds IgA-Fc region preventing FcaR1 binding and phagocytosis. Immunoglobulin duplication and diversification took place in primates (step 1). FcaR1 was positively selected for binding with the new IgA (step 2). Bacterial decoy proteins developed high affinity to this IgA (step 3). Next, IgA forms with low binding to the bacterial decoy were selected (step 4). Now, FcaR1 needs to change again to bind the new IgA (step 5) and so on. If FcaR1 fails to keep up, it may be lost from the genome.

death process (Nei and Rooney, 2005). There could be several mechanisms for maintenance of high-level polymorphism in these families. An individual with a rare allele may be able to fight newly emerged or mutated pathogens that could not be recognized by other individuals. Such advantage would lead to increase of the frequency of the rare allele in the population, until the pathogen develops adaptations to it, then new mutant alleles will emerge. Individuals heterozygous for *MHC* alleles may survive better since they can respond to a wider array of pathogens than individuals with less diversity. Possibility of autoimmune reactions may be a constraining factor in the evolutionary drive for polymorphism of immune receptors. **See also**: Major Histocompatibility Complex (MHC) Genes: Polymorphism

Human versus Other Primates Traits in Evolution of Immune System

Much attention has been recently devoted to differences between human and other hominids. Hominid lineage is considered to have diverged from Old World monkeys about 30 million years ago. The lineage leading to humans split from orangutan about 14 million years, from gorilla about 6.2–8.4 million years and from chimpanzee 4.2–6.2 million years ago. Variability of human genes is less than in apes possibly because the human population experienced bottlenecks and expansion. Many features of immune system are shared among hominids. *HLA-C* genes are present only in humans, chimpanzee, gorilla and orangutan. Despite the fact that *HLA-C* are the most recently evolved MHC class I genes they are the dominant ligands for inhibitory *KIR*, which are also actively evolving in hominids.

Only few retroviral human pathogens are known, including HIV, which crossed into human population only recently. Yet the human genome contains over 230 000 copies of endogenous retroviruses suggesting that our primate ancestors encountered many exogenous retroviruses. It might have spurred the evolution of the primate genes participating in antiviral defence. Primates have five *APOBEC3*, while other mammals have only one. Retroviruses encode proteins neutralizing APOBEC3s. HIV viral infectivity factor (Vif) protein prevents APOBEC3G's insertion into HIV-1 virions. In contrast, Vif cannot bind APOBEC3G of African green monkey, which differs from the human protein by a single amino acid. Therefore, it appears that a single residue difference in APOBEC3G may determine if a particular animal retrovirus can infect humans.

Human TRIM5α does not block HIV-1 but inhibits other retroviruses such as murine leukaemia virus. TRIM5α protects rhesus macaque from infection by HIV-1 but not by simian immunodeficiency virus (SIV). A single amino acid substitution in human TRIM5α leads to HIV-1 restriction. Inability of TRIM5α to protect humans from HIV may be a result of adaptation to another retrovirus, *Pan troglodytes* endogenous retrovirus 1 (PtERV1), extant about 4 millions years ago. Traces of PtERV1 have been found in the genome of chimpanzees but not humans. Human TRIM5α prevents entrance of a resurrected PtERV1 into human cells (Kaiser *et al.*, 2007). Therefore it is likely that resistance to this virus acquired by human lineage long time ago left us vulnerable to HIV infections.

Great apes seem not to have human T cell-mediated diseases such as T cell-mediated cirrhosis, bronchial asthma, rheumatoid arthritis and type 1 diabetes, and they do not show increased levels of autoantibodies. Chimpanzees can be infected by HIV but do not develop acquired immunodeficiency syndrome (AIDS). These differences may depend on the differential expression of Siglecs, sialic acids binding Ig-superfamily lectins. Siglecs 3, 5–11 are inhibitory signalling molecules downregulating immune activation via cytosolic tyrosine-based inhibitory motifs. Siglec-5 and several other Siglecs are expressed in great apes but not human lymphocytes (Nguyen *et al.*, 2006). Therefore in humans, T cells may be hyperactive. Forced expression of Siglec-5 in human T cells inhibits their activation. The change in Siglecs regulation may be related to the inactivation of the gene encoding the enzyme cytidine monophosphate (CMP)-*N*-acetylneuraminic acid hydroxylase due to the insertion of Alu element about 2.7 million years ago resulting in less sialic acid on human cells.

Despite the high homology between chimpanzee and human genes at the level of amino acid sequences, human genome contains 1418 genes that do not have direct orthologues in chimpanzee, many of which are related to immune defence. For example, duplication of parts of the κ locus is found only in humans. Gene loss also involves many immune genes such as MBL1 (mannose binding lectin 1) influencing susceptibility to sepsis. Primate MBL1 was duplicated in the common ancestor of humans and rhesus monkeys. After the duplication, both genes remained functional in rhesus monkeys and chimpanzees, but became pseudogenes in humans.

Many differences between human and chimpanzee come from changes in gene regulation. At least 0.3% of the human genome comprises conserved noncoding sequences (CNC). Human-specific CNC of 1356 have been found by comparison of human and chimpanzee genomes (Bird *et al.*, 2007). An example of differential regulation of immune gene is an IL-4. Binding site for the transcription factor, nuclear factor of activated T cells (NFAT), in the promoter of IL-4 in human includes a substitution at position −524. The human T-containing site drives more than three-fold greater expression of IL-4 than C-containing site of the great apes. This variation affects the balance between T_H1 and T_H2 cells predisposing the carriers of T-site to allergies and certain infections, but probably protecting them from some retroviral infections.

Evolution of Immune Genes in Modern Human Population

Evolution of immune system continues in modern humans. Many studies report geographically restricted patterns of

selection in humans, although overlapping tendencies are also observed. Signatures of positive selection were found in population exposed to malaria. Several *MHC* alleles common in West Africans but rare in other ethnic groups are associated with protection from severe malaria (Hill *et al.*, 1991). CC chemokine receptor 5 (*CCR5*)-Delta 32-deletion allele has been selected in Europe. It confers resistance against HIV-1 but was selected not against HIV, which has arisen as a human pathogen only recently, but against some other infections such as bubonic plague or smallpox. Positively selected genes were identified among all types of immune genes including *RNAse L*, cell receptors for pathogens entry, components of NF-κB pathway, mitogen-activated protein kinase *MAPK14* and others. **See also**: Human Leukocyte Antigen (HLA) System and Human Disorders; Major Histocompatibility Complex: Human

A single nucleotide polymorphism in human caspase-12 results in the synthesis of either a truncated protein or a full-length caspase proenzyme. The full-length allele is absent in most populations except African and is of low frequency in the Middle East and South Asia. Full-length caspase-12 decreases lipopolysaccharide-stimulated cytokine production and in so doing increases the risk of developing sepsis. It is interesting that several other genes related to susceptibility to sepsis were pseudogenized in humans.

A remarkable example of flexibility of evolutionary changes comes from the study of immunoglobulin loci. Human heavy chain constant region genes are encoded in order: *G3-G1-EP1-A1-G2-G4-E-A2*. Duplication of the *G-G-E-A* region happened in the common ancestor of hominoids with subsequent deletion of the *E* gene in each hominoid species. The distinctive feature of IgG4 antibodies is that they cannot activate complement and have anti-inflammatory activity. An explanation for these features has only recently been found. Classical antibody molecule is a tetramer of two identical dimers with the same specificities to antigens. Strikingly, IgG4 can exchange their dimer partners generating a hybrid antibody with Fab arms binding unrelated antigens (van der Neut Kolfschoten *et al.*, 2007). Moreover, IgG4 keeps swapping arms continuously interfering with immune complex formation by other antibody isotypes. It explains the anti-inflammatory effect of IgG4 and correlation of the IgG4 antibody levels with clinical response to treatment of IgE-mediated allergies. Allergy is a big problem in modern humans and one can expect that there would be some selection pressure to increase the level of IgG4. Indeed, tandem duplication of *G4* gene was found in 44% of heavy chain haplotypes in the Italian population. In another study, various types of duplicated and deleted haplotypes were found in Negroid (Gambian), Mongoloid (Japanese and Chinese) and Caucasoid (Iranian and Swedish) populations. The frequency of duplications is 22% in the Mongoloid population, 10% in the Caucasian and 5% in the Negroid, the corresponding frequency of deletions are 2, 1.5 and 3.5%, respectively. Duplication of the *A1-G2-G4-E* region is the most common polymorphism found in all populations investigated. Deletion of *G4* gene is the only deletion common to all racial groups and the only deletion type observed in Negroid populations. Duplication of a particular immunoglobulin gene may not lead to increase in its protein's level, but IgG4 levels are higher in individuals with *G4* duplication. From these data it can be hypothesized that *G4* experiences two types of selective pressure (**Figure 3**). In regions with high rate of infectious diseases like Africa people may benefit from deletion of *G4*. On the contrary, in regions like Italy with smaller burden of infectious diseases but high rate of autoimmune and inflammatory diseases, duplication of *G4* would be beneficial.

The fate of duplicated IgA is also interesting. IgAs are produced in quantities larger than all other antibodies and protect mucosal surfaces, approximately $400\,m^2$ in humans. IgA1 molecule is very efficient; it has a long hinge region; its Fab arms are almost orthogonal and can bind two distal antigens simultaneously. Unfortunately, many bacteria developed specific proteases cleaving IgA1 hinge. Moreover, the cleaved Fab fragments help bacteria infect epithelial cells. A duplicated gene, IgA2, evolved into a molecule with a very short hinge, not cleaved by these bacteria. IgA2 production specifically increases when IgA1 is cleaved.

With availability of genomic sequences from diverse populations researchers are switching from the analysis of candidate genes to the analysis of whole genomes. A number of genome-wide scans for positive selection have recently been performed (Wagner, 2007). They confirm that many immune genes and their regulatory sequences have been the subjects of positive selection in humans. Population genomics is still in its infancy and the specific predictions may vary among studies but this is where future discoveries are anticipated.
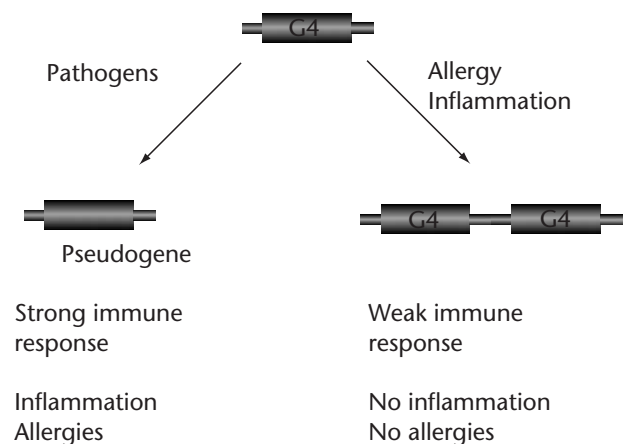

Figure 3 IgG4 is a regulatory antibody inhibiting the formation of immune complexes, inflammation and allergy. It is under the dual selection pressure. Pressure from pathogens requiring stronger immune response can lead to loss of G4, whereas pressure from inflammatory/allergic diseases can lead to its duplication.

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