

# The Evolutionary Origin of the Immune System, Neonatal Tolerance, Mhc Restriction

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## Abstract

Immunology has made tremendous progress during more than half century after Burnet's clonal selection theory was published, but there are still more questions than answers. What is the function of the immune system, given that invertebrates have lived without one for millions of years, although they are also susceptible to infections and tumors? On the other hand, the emergence of the immune system in evolution did not deliver higher animals from either infections or cancer. The concept of linked functions is an attempt at answering these and other related questions. The concept assumes that the evolutionary origin of the immune system is related to a primary nonimmune function rather than to self/nonself recognition. However, the mechanisms used to fulfill this function proved to be a suitable basis for immune recognition, which, according to the concept, occurs at the level of receptor-bearing immune cells rather than receptors themselves. Since cross-reactivity is a common phenomenon, it is assumed that specific combinations of antigenic determinants, rather than determinants per se, serve as recognition criteria, antigen processing and MCH-II restriction being necessary steps of the immune recognition of these combinations. The new views on adaptive immunity suggest new approaches to preventing graft rejection and treating chronic infections and malignant tumors.

**Keywords:** immune system; evolution; recognition; primary function; secondary function

## Introduction

In October 2012, there was the 55th anniversary of the publication in the Australian Journal of Science where F.M. Burnet put forward the clonal selection theory. Its importance for immunology and general biology is hard to overestimate. The most attractive and well-proven postulate of the theory is that each particular clone of lymphocytes bears a single type of receptors with a unique specificity. This laid the basis for predicting neonatal immunological tolerance, which was excellently demonstrated by P.B. Medawar and won both scientists the Nobel Prize.

To date, however, much more questions than answers have accumulated in immunology.

### Questions

The basic question to be answered concerns the biological function of the immune system. It is generally believed to have originally evolved as a system for recognizing nonself antigens and eliminating their carriers, i.e., microorganisms and atypical cells. This, however, seems to be an oversimplification. There is no doubt that the immune system is involved in the elimination of nonself antigens; but was its evolutionary origin related to this very function? Normal and opportunistic microfloras are genetically foreign to the host, and so the embryo in the womb is to its mother, yet they are biologically necessary, and they are not attacked by the immune system. Many dangerous microorganisms may be useful under the conditions of healthy or asymptomatic carriage [1-2]; in this case, the immune system remains tolerant to them, too. In other words, the body not always reacts to nonself antigens as to a danger. Therefore, it is hardly correct to relate the evolutionary origin of the immune system to the

nonself. This is more likely to be its additional, parallel function. Since genetically foreign objects that are necessary for the body are not attacked by its immune system, it should be assumed that this system is capable of "smart recognition," which requires more than just lymphocytes bearing receptors for nonself antigenic determinants. This makes discerning the mechanisms of "smart recognition" an important task.

There are other unsolved questions. If our current views on the biological role of the immune system are correct, then lymphocytes with specific receptors for all possible nonself antigens should provide enough immune protection. On the other hand, why is such a specific response necessary at all? Macrophages and some other much less specific protection factors can successfully eliminate microorganisms all by themselves. What is the need for different populations of T and B cells interacting (via their receptors) with different determinants of the same antigen? Why do major histocompatibility complex class II (MHC-II) molecules form complexes with nonself antigens (MHC restriction), when it is MHC-I molecules that serve as targets in rejecting xeno- or allografts? What is nonself-antigen processing for? It is intuitively understandable that both antigen processing and MHC restriction are involved in recognition of the nonself; but why are they needed, if there already are receptors for nonself antigens? Could it be that the specificity of immune receptors is not always a specificity for nonself antigens, and, hence, additional determinants of the nonself have to be revealed in the course of processing and MHC restriction? What purpose does immunological memory serve? The probability of a second infection with the plague, cholera, or tick-borne encephalitis pathogen is

extremely low. On the other hand, many people have had influenza and other common infections many times in their lives. What is the function of lymphocyte cooperation? The function of MHC-II molecules is clear in terms of current knowledge—they are involved in the presentation of nonself antigens to immunocompetent cells. However, what is the function of MHC-I molecules? Is it to ensure that a graft from another individual be rejected? This is doubtful. Why is the immune system necessary at all, given that invertebrates have managed to live without it for millions of years? If the spine cord or at least a nerve trunk is injured, the consequences for the body will be serious, whereas removal of the spleen, appendix, or thymus from the body of an adult will little affect its viability. However, early postnatal thymectomy results in wasting syndrome. In other words, many of the components of the immune system and processes occurring in it seem superfluous in the context of our views on its functions (elimination of the nonself by means of preexisting receptors for nonself antigens). For obvious reasons, this cannot be the case. Could all these "superfluous" components and processes be related to another function of the immune system?

It seems inexplicable that healthy animals and humans have natural autoantibodies and autolymphocytes. According to Burnet's theory and generally accepted views, the appearance of autoantibodies should result in autoimmune diseases. However, the presence of autoantibodies is not necessarily accompanied by these pathologies [4,5], although autoreactive lymphocyte clones are often found in patients with autoimmune diseases.

The origin of repertoire-specific receptors of immune cells is also mysterious. Specific T- and B-cell receptors for all possible nonself antigens preexist in the body, even if neither the given individual nor its evolutionary ancestors have ever encountered some of them (eg., synthetic antigens). Since there is plethora of both natural and artificial antigens, the origin of the repertoire of immune receptors remains an open question.

In order to explain the origin of the diversity of immune receptors, the hypothesis on the generator of diversity has been put forward. The generator of diversity is a mechanism for random variation of the amino acid sequences of the V regions of immunoglobulins resulting in random extension of the repertoire of immune receptors. Rearrangement of immune receptor genes and somatic mutagenesis do occur. However, are they random, and are they related to the extension of the repertoire? Regarding the origin of receptors for nonself antigens, it would be pertinent to recall some facts.

### Forgotten Facts

The problem of the origin of the immune receptor repertoire seems factitious if we consider some long-known facts that appear to have been forgotten. It would be unreasonable to deny that the number of potential antigens, including the existing antigens, the antigens that will appear when new individuals are born, and artificial antigens, approaches infinity. However, it is as well to remember that immune receptors interact with antigenic determinants or epitopes rather than antigens per se. Well-known factual data suggest that the determinants do not contain any genetic information, which should make them unsuited to serve as determinants for self/nonself recognition.

### This is evidenced by the following facts:

1. It is possible to raise antibodies against haptens (sugars, including glucose, and lipids, which occupy the entire antigen-binding region of such antibodies), although, in contrast to proteins, they have nothing to do with genetic information.
2. Sugars constitute the immunodominant regions of many natural antigens that contain a protein component as well (glycoproteins).
3. Many strong natural antigens have no protein components; their specificity is determined by diandtrisaccharides (streptococcal and pneumococcal polysaccharides, ABO antigens, etc.).

4. The antigen determinants of protein antigens consist of only a few (no more than ten) amino acid residues, which cannot reflect the genetically specific complex structure of the entire molecule and, hence, should not be recognizable as nonself.

5. This is also true for T epitopes, which, in contrast to B epitopes, have a linear structure and are included in peptides consisting of several (usually from 7 to 20) amino acid residues, their specificity and immunogenicity being determined by only one to three residues [6-9]. Considering that an average protein molecule consists of 200-300 amino acid residues, it is unlikely that two or three consecutive, linearly arranged residues constitute the key determinant for specific recognition of the entire molecule.

These data allow us to assume that the specificity of immune receptors is not directly related to nonself antigen recognition, even though this specificity is involved in the elimination of the nonself. It is conceivable that antigen determinants and epitopes are markers playing a role in another function, unrelated to self/nonself recognition, and that their evolutionary origin was related to this unknown function. This also means that cross-reactivity should be quite a common phenomenon.

Intense research in this field was performed in the 1970s and 1980s. The results showed that at least two antigens in a random set of about 140 antigens interacted with the same antibody with a high binding constant. A weaker crossreactivity was more frequent; it was usually detected in a set of about 20 antigens [10]. Obviously, excessive occurrence of cross-reactions with high binding constants would be impossible. As noted in an excellent monograph on the subject [11], had it been so, antibody populations would have cemented all biological structures, without displaying any population specificity.

As to antigens with hapten determinants, it is certain that their specificity is determined by moieties that are identical in all individuals, irrespective of the genotype. As mentioned above, these are lipid or sugar moieties, although the antigens contain protein components, which are directly related to genetic information. Thus, the moieties that are widely spread in the living nature and are likely to be present in the host body (eg., glucose) have been "selected" to be immunodominant regions of antigens instead of the regions whose structure is genetically determined, individual-specific, and, hence, recognizable as self/nonself. This eliminates the question of the availability of immune receptors against any nonself antigen but raises another important question: If immune receptors are targeted at the determinants of nonself antigens that are similar to those of the host's own antigens, then how does the immune system differentiate between self and nonself? A possible answer is that nonself recognition occurs at the level of whole cells rather than surface immune receptors, which, however, are also involved in the process.

### Nonimmune recognition

The immune system has certainly not appeared out of nothing. It must have had an evolutionary predecessor that was optimal for self/nonself recognition on a nonimmune basis. In other words, self/nonself recognition is likely to be a secondary function of the immune system.

Toll-like receptors (TLRs), which were first discovered in drosophila and then in many other animals and plants, are of special interest in this context. TLRs are involved in the formation of the dorsoventral pattern at the embryonic stage of development and in antifungal protection in adult flies [12-17]. In this case, the primary nonimmune function serves as the basis for the secondary function related to the response to nonself agents. The primary function, however, entails interaction with the host's own structures (self antigens). Since the same receptors interact with both self and nonself antigens, it is presumable that the structures that are similar to the host's own ones are "selected" on nonself antigens to serve as binding sites.

This relationship between TLRs and the immune system allows us to assume that other structures of the immune system also fulfill a primary function entailing interaction with self antigens at the embryonic stage. This hypothetical function is not related to self/nonself recognition, which is the more probable as the structure of epitopes can hardly be related to self/nonself differentiation.

The so-called primitive or quasi-immune response is strong evidence that nonself recognition is possible without involvement of the immune system.

Nuclear–cytoplasmic incompatibility is clearly illustrated by experiments with nucleus transplantation in protozoans. It is easy to remove the nucleus from an amoeba and put it into another, preliminarily enucleated amoeba. Transplantations of nuclei between representatives of different species or strains of amoebas or infusorians (xenotransplantations) usually lead to death. If, eg., the nucleus of *Amoeba discoides* is transplanted into the enucleated cytoplasm of *A. proteus*, the cytoplasm will participate in cell divisions, but viable clones will rarely be formed. However, about 90% of transplantations within a protozoan strain (allotransplantations) are successful and do not affect the cell viability.

Graft incompatibility based on genetic differences between donor and recipient is observed in the hydra. For example, *Hydractiniaechinata* has one locus with six alleles that controls histocompatibility.

It has been demonstrated that unicellular eukaryotes can differentiate between self and nonself even at the level of different individuals of the same species. If a pseudopodium of the testate amoeba *Arcellapolyopa* is cut off, it rapidly coalesces with the cell after their contact is restored. If the excised pseudopodium is put into contact with another individual of the same species, coalescence may or may not occur.

In annelids (segmented worms), phagocytic cells cannot take up live spermatozoa of the same species but actively eliminate those of other species, as well as dead cells [18].

Radioresistant graft rejection in higher animals occurs after their immune system has been destroyed with irradiation. In some cases, F1 hybrids reject grafts from their parental line, which violates the laws of transplantation.

These phenomena have been termed primitive or quasi-immune responses. Quasi-immune recognition is not confined to graft rejection and elimination of non-conspecific spermatozoa; eg., it is involved in the response to viruses [19]. The hazard of infectious diseases and tumors is apparently as real for invertebrates as it is for vertebrates [20-22], but nevertheless invertebrates survive without the immune system. On the other hand, higher animals, having developed the immune system, have not been relieved from either infections or tumors.

Quasi-immune response is a good example showing that self/nonself recognition does not require highly specialized immunoglobulins, T-cell receptors, or MHC molecules. Together with the above data suggesting that immune receptors are essentially unsuitable for nonself recognition, this supports the assumption that immune receptors and the entire immune system originally fulfilled a primary nonimmune function. Apparently, they were adapted for the immune function in the course of further evolution. It is logically conceivable that the receptors serving this nonimmune function were the first to appear. The next stage was the development of interactions between receptor-bearing cells in the form of cell cooperation (see below), which includes antigen recognition but seems redundant in terms of the functioning of the immune system as it is viewed now. In this case, recognition, either quasi-immune or immune, is not a goal in itself; it is rather a by-product of another, nonimmune function, which could be the evolutionary basis of the immune system. Hence, the traditionally known function of the immune system may be only "the tip of the iceberg."

The pattern of expression of MHC molecules, which are integral elements of the system of self/nonself recognition, is evidence in favor of a nonimmune function of the immune system. First, MHC-I genes are expressed in mouse embryos in the middle of gestation (days 10-13), when the immune system cannot respond to nonself antigens yet [23]. Second,

MHC molecules are found even on nerve cells, which are inaccessible for immune cells [24]. MHC-I molecules have been shown to take part in the formation of interneuronal synapses [25]. In all these cases, MHC molecules obviously fulfill a nonimmune function.

Since neonatal tolerance, TLRs, rearrangement of immune receptor genes, preferential replacement of embryonic  $\gamma/\delta$  T-cell receptors with  $\alpha/\beta$  ones [26], early postnatal involution of the thymus, and wasting syndrome are directly or indirectly related to the embryonic stage of ontogeny, it seems likely that the primary function of the immune system is related to embryonic development.

Mold et al. [27,28] have demonstrated that, contrary to the neonatal tolerance concept, the fetal immune system is not immature. It is quite active—even more active than the adult immune system, in some respects. The difference is in the cell lineages from which the fetal and adult immune systems originate and in their functions. This should convince us that the immune system fulfills a different function at the embryonic stage of development. Since the same receptors (and cells) of the immune system interact with both self and nonself antigens, then, once this system is engaged in the embryonic function, it cannot respond to a nonself antigen; hence neonatal tolerance.

Thus, the lack of relationship of the immunodominant regions of antigens with genetic information, quasi-immune recognition, and the data on a different function of the immune system at the embryonic stage indicate that the immune system originally evolved to fulfill a primary nonimmune function rather than to recognize and eliminate the nonself. However, this primary function was best suited for self/nonself recognition, and it was adapted for recognizing nonself objects in further evolution. Therefore, the mysterious properties of the immune system noted above should be accounted for by the mechanisms of the hypothetical primary function.

The primary function of the immune system seems to be the necessary basis for recognition of nonself by comparing with self. The idea about this comparison is not new; it emerged once it became known that immune response develops to complexes formed by nonself antigens and MHC molecules, rather than to the antigens themselves. This was unexpected, considering that the body has preexisting immune receptors to any given antigen. It was assumed that a nonself antigen specifically modifies the MHC molecule so that it becomes "nonself" and is recognized as such by the immune system. However, this explanation of the MHC restriction phenomenon leaves the question open, because it tells us nothing about the mechanism of self–nonself comparison. In addition, this returns us to the problem of an infinite number of types of immune receptors: that cannot be the case; even the number of electrons in the universe is presumed to be finite. The important thing is that, although there undoubtedly should be a huge amount of existing and potential antigens, the required number of immune receptors for them is much less. Indeed, receptors do not interact with the whole antigen molecule, which certainly bears features of genetic individuality; instead, they interact with its small regions that are not unique and may be present in the host's body. Considering the aforementioned data on the frequency of cross-reactivity to different antigens [10], about 150 clones of cells and antibodies with different specificities should be more than enough for any nonself antigen to have the corresponding receptor in the immune system. Yet how does the recognition occur?

### The concept of linked functions

Thus, there is evidence that the immune system has a primary embryonic nonimmune function. On the other hand, the immune response of an adult animal or human is a response to nonself antigens. Therefore, it may be assumed that a specific combination of antigenic determinants, rather than the specificity of the determinants themselves, serves as the criterion of a nonself antigen. The widespread cross-reactivity suggests that identical or similar B-cell determinants, T-cell epitopes, and agretopes (MHC-II binding sites) may be found on different antigens; however, it is





unlikely that two genetically different antigens bear similarly arranged sets of similar determinants. In other words, we assume a combinational self/nonself recognition.

This model suggests recognition at the level of immune receptor-bearing cells rather than receptors. When interacting with self antigens in the framework of the primary (nonimmune) function, cells involved in it form primary linked groups corresponding to the combinations of determinants on self antigens. The cells belonging to the same primary linked group (T and B cells and antigen-presenting cells) should "recognize" one another by means of specific ligands and the corresponding receptors. Since the combinations of determinants on nonself antigens differ from those on self antigens, immune cells from different linked groups interact with each antigen. Cells from different linked groups cannot "recognize" each other because of the lack of complementary receptors, in which case immune response is triggered.

The combinational recognition model explains the immunological sense of antigen processing, cell cooperation, and MHC restriction as follows. Since immune receptors interact with nonself antigens via determinants that are similar to the determinants of embryonic self antigens, the specific features of the nonself should be revealed through special mechanisms, namely antigen processing and MHC restriction. As a result of processing, a peptide is excised from a definite region of the antigen molecule, the amino acid sequence of this peptide varying in genetically different antigens. Other specific features of the nonself are revealed at the level of MHC restriction. In this case, an MHC molecule, eg., Ia, serves as an anchor or frame molecule forming a comparison frame for a combination of antigen determinants. An MHC-II molecule interacts with the same complementary agretope on self and nonself antigens. The corresponding combinations of T- and B-cell specificities on self and nonself antigens differ from each other. The combinations of specificities on self antigens are "known" to the immune system from its primary function, where the cells involved formed specific linked groups. For example, let us assume that, in the framework of the primary function, an autoantigen A interacts with an a-T cell, a-B cell, and a-Ia molecule forming a specific linked group A. Cells from the primary linked group (T, B, and antigen-presenting cells) should recognize one another by means of the ligands that are specific for each group and the corresponding receptors. Possibly, the ICAM and LFA molecules involved in intercellular interaction play a role in this recognition. However, if the same a-Ia molecule interacts with a nonself antigen, other antigen epitopes are presented to T and B cells, so that cells and receptors from other linked groups (eg., a b-B cell and a c-T cell) interact with them. These cells do not recognize each other, which triggers an immune response to the antigen.

Intercellular recognition, including mutual recognition of immune cells, has long been known but still attracts researchers' attention [29]. However, experimental data on intercellular recognition within a linked group of immune cells, i.e., according to our hypothesis, cells interacting with the same autoantigen in the framework of the primary function of the immune system, would be of special interest. The model of recognition described above explains the necessity of a primary embryonic function of the immune system as a basis for combinational nonself recognition by comparing with self.

However, this hypothetical model of recognition raises another question. If the immune system interacts with nonself antigens via determinants similar to those of self antigens, why does the attack at nonself antigens not affect self ones; i.e., why does this not cause autoimmune diseases? According to Burnet's theory, this is because lymphocyte clones specific for autoantigens are eliminated early in ontogeny. It is already clear today that this is not the case, because natural autoantibodies are found in healthy animals and humans. These findings are explainable in terms of the hypothesis on the primary function entailing normal interaction of lymphocytes with self antigens. The point is that the autoantibodies involved in the primary nonimmune function should differ from "immune" autoantibodies. These differences are the most likely to be found in their nonspecific regions.

In contrast to Burnet's theory, the concept of linked functions assumes that elimination of embryo-specific antigens, rather than lymphocytes, is the key moment in the switching from the primary embryonic function to the immune one. The corresponding lymphocyte clones, relieved from their primary function, are involved in the response to nonself antigens. This guarantees against autoimmune damage. Embryo-specific antigens, eg.,  $\alpha$ -fetoprotein, have been known for a long time. The SSEA-1 antigen has been found on mouse embryo cells [30] and embryonic stem cells [31]. However, these are certainly not the antigens involved in the embryonic function of the immune system. In the given context, embryo-specific antigens similar to MHC molecules would be especially interesting; however, we have not found studies on this subject in available literature.

Neonatal tolerance is important though indirect evidence that elimination of autoantigens plays a role in the switching from the primary function to the immune one. If the immune system "selects," for its interaction with nonself antigens, the specificities that are similar to autoantigen determinants, then the appearance of a nonself antigen at the embryonic stage of ontogeny imitates non-elimination of an embryo-specific antigen. This prevents the corresponding lymphocyte clone from switching to the immune function, thereby leading to neonatal tolerance.

Thus, the hypothesis on the primary function of the immune system explains many phenomena listed above, including the specificity of interaction between immune receptors and antigens, preexistence of receptors for nonself antigens, neonatal tolerance, the necessity of antigen processing and MHC restriction, and lymphocyte cooperation. The above considerations suggest that the immune system is necessary not only for immune response to nonself antigens, but also for normal embryogenesis, where it fulfills a different (primary) function.

### What is this function?

According to Babaeva [32], the immune system is actively involved in regeneration. Probably, it also takes part in other functions. However, its main function is hardly related to regeneration, because regeneration also occurs in lower animals and plant, which have no immune system. Moreover, regeneration is much better developed in lower animals than in higher ones (a half of an earthworm regenerates into a whole animal, whereas a mammal cannot regenerate even a digit). Apparently, the evolution of the specialized immune system has been related to something in which higher animals fundamentally differ from lower ones. But what is this precisely? Unfortunately, there is no answer to this question yet.

### Conclusions

The concept of linked functions provides answers to many key questions of immunology concerning the evolutionary origin of the immune system, neonatal tolerance, MHC restriction, the origin of preexisting immune receptors for nonself antigens, cell cooperation, and the presence of natural autoantibodies in healthy animals and humans. This makes it possible to develop new approaches to preventing allograft rejection and treating chronic infections and cancer. I am far from considering this concept to be the ultimate truth. I rather regard it as a working hypothesis, which is, nevertheless, substantiated enough to justify its experimental testing and consider the possibility of its medical applications.

### Practical implications

The aforementioned assumption on "smart recognition" performed by the immune system pertains to privileged foreign substances that are present in the body without being rejected. What is the difference between these privileged foreign substances and, eg., a skin allograft? The difference is that the immune privilege for some foreign substances (such as a fetus in the mother's womb and normal and opportunistic floras) is determined at the genomic level. There are genes (let us call them immune-privilege genes) that contain information on privileged substances preventing their rejection. Allografts, necessary for the recipient as they may be, are



rejected precisely because their presence in the body is not genetically determined. In other words, the self/ nonself relationships between the antigen and the immune system are formed at the genomic level rather than only the receptor–cell level. Therefore, transplantology and immunology are facing the problem of how to make the presence of an allograft determined at the level of the recipient's genome. Most probably, the donor's MHC-I genes should be used for this purpose. Since modification of human germ cells is legally prohibited (which is certainly sensible), it is reasonable to use the recipient's lymphocyte stem cells, which will differentiate into lymphocytes whose genome will contain the donor's genes of immune privilege for the allograft.

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