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Auto-immunity as Evolutionary by Product of Adoptive Immunity and Source of Anti-tumor Immunity Failure

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Abstract

One of the biggest threats to survival is infection, so that the immune system is under permanent and strong evolutionary pressure to be highly responsive. By tracing the evolution of the invertebrate immune system, it can be seen that it largely followed the "classical" model based on bi-directional "predator-prey" relationships. Similarly, the evolutionary emergence of MHC system and the mechanisms of immune recognition in vertebrates came as a direct result of a microbe-exerted selection pressure. The new possibilities gave rise to new conveniences and brought about certain risks in the new forms, like auto-immunity, alloimmunity and reproductive efficacy. To that effect, the evolutionary emergence of the MHC has enabled a more effective defence from intracellular parasites, such as viruses. However, the whole complex of processing/presenting/recognizing of antigens could be closely related to the auto-immunity as a by-product of the evolution of MHC system and adoptive immunity. On the other hand, tumor development is frequently accompanied by the immune response against "self" and altered antigens expressed by tumor cells, because these antigens are the most prevalent molecules recognized by the immune system. The activation of the auto-immune process in parallel with an effective anti-tumor response could mean the failure of protective control mechanisms of the immune reaction that may be responsible for the prevention of auto-immune diseases. At the same time, the activation of suppressor/modulatory mechanisms possibly accompanied by the activation of anti-tumor auto-immune-like immune response could be a factor of anti-tumor immunity failure in all vertebrates.

Keywords: Auto-immunity, vertebrate, mammals, tumor, evolution

Evolution of the Vertebrate Immune System

Some evolutionary processes can be studied directly, while the evolution of the immune system and immunity cannot. The evolution of immunity is a macro-evolutionary process, which can be studied by examining the patterns in biological populations or species of related organisms and inferring process from pattern. One of the possible ways to carry out a detailed investigation into the issue of the evolution of the immune system is virtually by comparing the characteristics of the immune system across species and classes. In addition, the determination of the genes and molecules conserved throughout evolution is helpful in identifying the mechanisms of the immune system evolution, while variable genes as well as the emergence of new genes along evolution enable the identification of various evolutionary pressures, their duration and strength. This provides a better understanding of how the immune system works under physiological and pathological conditions. This approach, however, is not an easy one since only few percent of the total number of species that have inhabited the planet to date are available for research. Notwithstanding this limiting factor, previous studies have produced sufficient findings for the construction of a hypothetical model of the evolution of the immune system in vertebrates, and also cleared the pathway towards reaching further relevant presumptions and conclusions.

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The evolution of the immune system is a direct consequence of microbes-exerted selection pressure on multicellular organisms. The vertebrate immune system was to some extent inherited from invertebrates, whereas a part of it has advanced considerably in the course of its own evolution. Although certain vertebrate-specific properties such as immune recognition and immune memory have also been identified in invertebrates in rudimentary forms, it is particularly those qualities like progressive development of humoral and cellular adoptive immunity, Major Histocompatibility Complex (MHC), variable class I and class II genes, precise mechanisms of immune recognition and long-term immune memory that reflect the fundamental evolutionary advancement of the vertebrate immune system.

The presumption that auto-immunity could have represented evolutionary new forms of strong selection pressure closely associated with the evolution of the mammalian immune system correlates with the unique control mechanisms of immune response verified in this vertebrate. In short, the evolution of the mammalian immune system has possibly undergone the pressures of at least four quite diverse factors: microbes, auto-immunity, alloimmunity/reproductive efficacy and tumors. However, there is opinion that auto-immunity and tumors cannot be sources of strong selection pressures, as most of these generally occur after leaving offspring. On the contrary, alloimmunity/reproductive efficacy might have been the source of a very strong selection pressure that greatly influenced the evolution of the mammalian immune system.

The possible effects of such heterogeneous and complex evolutionary pressures are the evolutionary development of the mammalian immune system into one of the most complex, most organized and multilevel controlled system in the world of living beings.

Notwithstanding the possibility that auto-immunity might be the by-product of the evolution of adoptive immunity, this phenomenon could have been one of the factors significantly influencing the course of the evolution of vertebrate immune system and development of the mechanisms for the control of immune reaction. The evolutionary modelling of the vertebrate immune system under the influence of microbes and auto-immunity, did not probably result in the weakening of the killer mechanisms efficacy and MHC genes variability, but could have been followed by the introduction and co-evolution of evolutionary new mechanisms for the control of immune reaction, that could have restrained the potentially “self”-destructive power of the adoptive immunity.

1. The evolution of the vertebrate immune system from cartilagofish to mammals is characterized by several processes featuring clearly perceivable evolutionary trends (1):
2. The grouping and clustering of MHC genes;
3. Associating of TAP/LMP genes with a less variable class of MHC genes (class I in fishes and class II in mammals);
4. The emergence of auto-immunity like a form of selection pressure;
5. The sophisticated mechanisms of “self”-tolerance mechanisms;
6. The sophisticated mechanisms of immune reaction control mediated by cells of innate immune system;
7. The increasing of the number of the immune cell subtypes involved in the control of immune reaction (Th1, Th2, APCs, DCs);
8. The regulation of immunoreactivity mediated by sex hormones;
9. The increasing of the number of cytokines;
10. The regulation of immunoreactivity mediated by a complex cytokine network;

These phenomena could be associated with a better and more precise control of the immune reaction. However, it is very difficult to answer the question how big the contribution of the selection pressure of auto-immunity on the evolutionary development of the vertebrate immune system is. Judging from the pathogenesis of auto-immune diseases which are clearly associated with the basic features of the adoptive immunity like MHC, and also from the high incidence of auto-immune diseases in mammals, this phenomenon could be a significant factor of the selection pressure and evolutionary modelling, and permanent re-modelling, of the vertebrate immune system and their control mechanisms.

Auto-immunity in Vertebrates

There is a large body of data that many auto-immune diseases are a characteristic of vertebrates and that they are associated with MHC molecules. In fact, there is no firm evidence that would suggest the existence of auto-immune phenomena in invertebrates (2,3). The presumably MHC molecules of aberrant

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target cells, TCR and APCs need to interact abnormally before auto-immune disease can fully develop. In this abnormal interaction, additional aberrancies in other regulatory systems may play a role in a further exacerbation of the "self"-directed immune response, such as defects in the hormone and cytokine synthesis and secretion. The various aberrancies are partly genetically determined by a variety of separate genes, particularly MHC and related genes like TAP/LMP, but they may also be environmentally induced by viruses, chemicals, drugs or injuries (4).

In evolutionary new condition of strong (adoptive) immunity, the survival advantage imposed by an extremely reactive immune system is jeopardized if that system turns against the host and causes "self" destruction. Thus, evolutionary pressures selecting for a hyperactive immune system must be combined with similar pressures optimizing "self"-tolerance. Accordingly, the mechanisms which evolved in response to the auto-immunity-imposed evolutionary pressure or, more precisely, co-evolved with the phenomenon of auto-immunity, are related to various forms of immune tolerance, strong and multileveled control immunomodulatory and suppressive mediated by sex hormones, IL-10, TGF-β, Th2 cells, apoptosis and/or anergy of "self"-reactive clones, blood-barrier sequestration of "self" molecules, cells, tissues and organs (5,6).

Surprisingly, auto-immunity is not a feature of a young immune system, when the immune network functions at its prime. Instead, the risk of developing auto-immune disease increases with age. In general, auto-immunity manifests in hosts who have passed the apex of their reproductive years and in whom evolutionary pressures towards prompt immune responsiveness are declining. The ageing of the immune system should be associated with the loss of function, and the likelihood of developing auto-immunity should progressively decrease. The traditional paradigm interprets auto-immunity as an aberrant response of the adaptive immune system to "self" molecule(s), consistent with the view that auto-immunity is a result of overreacting. It has been proposed that T lymphocytes specific for such "self" molecule(s) induce a memory response, which is relatively resistant to natural immuno-suppressive mechanisms. Tissue destruction has been understood as the after-effects of persistent immunocompetent cells. This model ignores that the risk for auto-immunity is inversely related to the functionality of the adaptive immune system throughout a lifetime. The new evolutionary concept of auto-immunity proposes that the accelerated immunity and failure of control mechanisms after reproductive time might be the primary risk factor for auto-immunity.

From the evolutionary point of view, the immune system based on adoptive immunity has been made into a more complex and advanced defence system, developed under a strong selection pressure of microbes during the vertebrate evolution. Such model of vigorous immunity in vertebrates produced a new form of selection pressure, known nowadays as auto-immunity. Because the positive selection pressure of the adoptive immunity was probably stronger than the negative pressure of auto-immunity, the selection pressure of auto-immunity gave rise to the emergence of the control immunomodulatory and immunosuppressive mechanisms and to the "deferring" of the emergence of auto-immune diseases until post-reproductive age. Recent data have provided evidence of a feed-back loop between reproductive hormones, mainly estrogens, and the expression, distribution and activity of cytokines. For instance, *in vitro* studies using mice cell cultures showed that while androgens decreased the production of IFN-γ, IL-4 and IL-5, estrogens enhanced IFN-γ production by murine lymphoid cells. Moreover, estrogens treatment of macrophages from male mice increased IL-1 secretion. In $CD4^+$ cell clones from auto-immune patients, both IL-10 and IFN-γ production were increased in the presence of estradiol (5,6,7).

In general, females have a more responsive immune system than males. Females have a greater humoral response, as evidenced by higher serum Ig concentrations than males (8) and a greater antibody response to various antigens after immunization (9). In addition, females reject skin allograft faster and have a reduced incidence of tumors, indicating that they also have a greater cellular immune response (10,11). This difference in immune response is thought to be responsible for the greater susceptibility of females to the auto-immune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. This gender difference has also been observed in animal models of auto-immune disease in NZBxNZW mice (5).

A protective effect of testosterone is thought to underlie why males are less susceptible to auto-immune disease than females. This is based on studies that include removing testosterone from male mice via castration as well as by treatment of female mice with testosterone. For example, the castration of male non-obese diabetic mice resulted in an increased prevalence of diabetes (12), and the castration of male

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mice increased the incidence of auto-immunity (7). Conversely, female non-obese diabetic mice implanted with testosterone pellets had a lower incidence of diabetes and less incidence of auto-immune disease, respectively, compared with those implanted with placebo pellets (6). The same studies have indicated that gender differences in susceptibility may be due to gender differences in cytokine production upon auto-antigen-specific stimulation. In males, compared with females, greater Th2 and less Th1 cytokine production has been observed. The balance between cytokines produced by Th1 and Th2 lymphocytes is considered central to the development of auto-immune disease. Th1 lymphocytes produce IFN-γ, IL-2, and TNF-α. Th2 lymphocytes secrete IL-4, IL-5, IL-6, IL-10, and IL-13. These two cell types are mutually inhibitory, and their development occurs under very specific conditions. If a naive T lymphocyte is initially stimulated with antigen in the presence of IL-12, the immune response is skewed toward Th1. However, if a naive T lymphocyte is initially stimulated with antigen in the presence of IL-4, the immune response is skewed toward Th2 (5,6). The same and other studies have collectively shown that immune cells under male sex hormones produce more IL-4 and IL-10, and less IFN-γ and IL-12, supporting the conclusion that the male immune system is shifted toward Th2 immunity (6,7). The mechanisms underlying why there is a sex hormones difference in cytokine production remain unknown. Many possibilities exist such as differences in the levels of male sex hormones, differences in female sex hormones, and differences in genes located on sex chromosomes.

Similar to previous studies, Stephanie *et al.* (13) found that levels of the Th2 cytokines IL-4 and IL-10 were higher and the IL-12 level was lower in splenocytes from males compared with females. Also, splenocytes from female mice implanted with testosterone pellets, like splenocytes from male mice, secreted more IL-10 and less IL-12. However, the treatment with testosterone did not cause increased IL-4 production. This clearly indicates that testosterone does not recapitulate all the cytokine differences seen in male versus female mice, and that the increase in IL-4 must be due to gender differences in other sex hormones and/or genes found on sex chromosomes (13). The finding of increased IL-10 production is equally as important as the finding of decreased IL-12 production upon testosterone treatment. Numerous studies have shown that IL-10 is essential in down regulation of cellular immune reaction. Specifically, the treatment of auto-immune patients with IL-10 has been shown to ameliorate disease (14,15), whereas the administration of anti-IL-10 antibodies has exacerbated disease (15). Although the treatment of auto-immune patients with IL-4 also ameliorated disease (16), studies of IL-4- and IL-10-deficient mice and IL-4 as well as IL-10 transgenic mice have shown that IL-10 may play a more critical role in the protection from auto-immunity. Indeed, IL-$10^{-/-}$ mice developed more severe auto-immune disease compared with wild-type mice, and overexpression of IL-10 rendered mice resistant to auto-immunity (17). Because IL-10 has been shown to play a protective role and IL-12 a disease-promoting role in auto-immunity, and because testosterone increases IL-10 and decreases IL-12, testosterone would appear to play an important role in susceptibility to auto-immunity and immune reaction control. Although many cells within spleen express the testosterone receptor (TR), testosterone probably can act directly upon $CD4^+$ T lymphocytes to increase IL-10 expression during stimulation with anti-CD3. The PCR analysis showed that $CD4^+$ lymphocytes express the TR, supporting the possibility of direct action of testosterone on these cells. However, the TR is also expressed by $CD8^+$ lymphocytes and macrophages. Thus, an indirect action of testosterone mediated through these cells was also possible. *In vitro* stimulation of $CD4^+$ T lymphocytes in the presence of testosterone and in the absence of other cells resulted in increased IL-10 production (13).

Estrogens modulate its effect by binding to estrogens receptors (EsR) present in the immune target cells. The EsR is a nuclear transcription factor that regulates gene expression. Some of the genes regulated by estrogens are progesterone receptor, *bcl-2* apoptosis inhibitor, *Fas*L and other growth-related genes responsible for estrogen's effects on cell death and proliferation. Different authors have shown EsR in human peripheral blood mononuclear cells, thymocytes, spleen cells and APCs. The recent discovery of a second estrogens receptor, EsRb, presents new possibilities for control of immune targets by different selective estrogens receptor modulators (5,6,7,13).

A shift toward Th2 cytokine production has been demonstrated during pregnancy and high dose estrogens therapy and is thought to be the primary mechanism by which estrogens suppress the cellular immune response. However, a low dose estrogens treatment is equally suppressive in the absence of a significant shift in cytokine production. Estrogens treatment in cytokine-deficient and wild type mice up-regulate Th2

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cytokine production. Also, estrogens effectively suppress the development of experimental auto-immunity in both, IL-4/IL-10 knockout mice and in auto-antigen-immunized wild type mice (5,6,7,13).

Anti-tumor Immunity as Auto-immunity

Tumor development is frequently accompanied by the immune response against "self" and altered antigens expressed by tumor cells, because these antigens on vertebrate tumors are the most prevalent molecules recognized by the immune system (18,19). This reflects the fact that tumor arise from the hosts' own tissues, and are not truly "foreign", except in the cases when tumor cells express the so-called fusion proteins and/or viral peptides. Thus, in some respects, the immune recognition of tumor appears to be different from the immune recognition of bacteria, and typically more akin to auto-immunity. In addition, the immune reaction to virally infected cells showing no malignant alterations, displays some characteristics of auto-immune reaction. This inevitably activates the regulatory mechanisms which prevent a complete destruction of tissues and organs. From these reasons, the recognition of "self" antigens on tumor cells in most circumstances presents problems for the host immune system. First, the immunity to tumor may not develop because all vertebrates pass across the embryonic phase of establishing of specific immune tolerance on "self" molecules. Second, even when the immune system can recognize and respond to tumor antigens, immunity may not be sufficient to reject cancers, due to the activation of the mechanisms which control auto-immunity. Finally, if immunity to "self"-tumor antigens develops, there are potential auto-immune sequelae, which may also result in the activation of the control suppressor/modulatory mechanisms of the immune reaction.

Auto-antibodies specific to different "self" molecules have been found in the sera of tumor bearers, which could be taken as an evidence for frequent joint activity of anti-tumor immunity and auto-immunity. This emphasizes the idea that tumor patients can mount tumor immunity which could be, in part, auto-immunity. In contrast to patients with auto-immune diseases, in the majority, if not all, tumor patients the immune system is unable to combat tumor growth.

Tumors seem to find ways to generate tolerance in the immune system by activating the control mechanisms of auto-immune reaction responsible for the tolerance against "self" molecules. These mechanisms include a down-regulation of MHC class I molecules and cellular constituents involved in the antigen processing and presentation pathways (20). Tumors can also induce several different biochemical defects in physiology of T lymphocytes. In addition, the immune response against tumors is hindered by the functional hierarchy in the immunogenicity of T and B cell determinants, abnormalities occurring in the communication between the cells of innate and adoptive immunity, as well as the inadequate cytokine network (21).

In line with Burnett's theory of clonal selection, T-cell clones specific to dominant determinants of tumor antigens are probably deleted during embryonic development in the process of negative selection. This could possibly continue into an adult stage as a central (thymic) deletion of tumor-specific clones, or even as a peripheral deletion in the course of extrathymic lymphocyte maturation (22). Thus, most of the tumor determinants are expected to be immunologically silent; hence effective tumor immunity cannot be induced via "self"-vaccination. Additionally, as tumor accumulates antigens during transformation they also gradually induce tolerance in T cells against these antigens.

Notwithstanding these and other escape mechanisms, in few cancer patients a spontaneous regression of malignant tumors was observed (23,24). Data about potential coupling of auto-antibodies and prolonged/sustained survival or even spontaneous tumor regression corroborate the previous observation. Breast cancer patients with a natural humoral response to MUC-1 and/or hsp90 exhibited a better outcome (25,26). Similar to immunological events in some auto-immune diseases, tumor in regression exhibited mainly a Th1 type response, as well as non-pathogenic auto-antibodies, but thus the form of auto-immunity did not always develop into the auto-immune disease. There is data that about the potential coupling of tumor immunity with auto-immunity has been suggested by the clinical observation that the patients with metastatic melanoma who develop vitiligo have a better prognosis (27). In addition, there are observations that support a possible protective role for the auto-immune diseases in cancer patients. In this respect, the mortality rate of cancer patients with multiple sclerosis was found to be significantly lower than that of cancer patients in general (23). This could be associated with the activation of control anti-auto-immune mechanisms which may also inhibit auto-immunity and anti-tumor activity of the immune system.

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In conclusion, the potential coupling of tumor immunity with auto-immunity has been suggested by the clinical observation that patients with metastatic tumor who develop auto-immune phenomena have a better prognosis and are more likely to respond to therapy (27,28). The differences in mechanisms underlying tumor immunity and auto-immunity could be a consequence of fundamental differences in effector mechanisms used to kill tumor cells versus normal cells. At the same time, the mechanisms controlling "self"-destructive immune reaction might be one of the important factors of anti-tumor immunity failure.

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