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Molecular mimicry and clonal deletion: A fresh look

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ABSTRACT

In this article, I trace the historic background of clonal deletion and molecular mimicry, two major pillars underlying our present understanding of autoimmunity and autoimmune disease. Clonal deletion originated as a critical element of the clonal selection theory of antibody formation in order to explain tolerance of self. If we did have complete clonal deletion, there would be major voids, the infamous "black holes", in our immune repertoire. For comprehensive, protective adaptive immunity, full deletion is necessarily a rare event. Molecular mimicry, the sharing of epitopes among self and non-self antigens, is extraordinary common and provides the evidence that complete deletion of self-reactive clones is rare. If molecular mimicry were not common, protective adaptive immunity could not be all-encompassing. By taking a fresh look at these two processes together we can envision their evolutionary basis and understand the need for regulatory devices to prevent molecular mimicry from progressing to autoimmune disease.

1. Strategies of immunity

The immune system can be viewed as the evolutionary solution to the ever present risk of microbial infection (Rose and Mackay, 2014). Humans share with other vertebrates a combination of two distinct, but interactive, immune systems. The older, constitutive innate immune system, inherited from our invertebrate predecessors, provides broad, immediate protection against the vast array of potential infections. It includes protective mechanisms including barrier protection afforded by skin and mucous membranes, and specialized cells and cell products that can contend rapidly with any microbial invaders that penetrate the barriers.

The second kind of immune response, fashioned in part from preexisting elements of innate immunity, is the adaptive immune system found in vertebrates. Rather than the broad, immediate, but sometimes temporary protection against infection afforded by innate immunity, the more potent adaptive immunity focuses on key antigens of a particular pathogen. Adaptive immunity provides the additional attribute of memory so that immunity once learned is hastened and amplified following a second exposure to the same microorganism. Adaptive immunity depends upon populations of specialized lymphocytes, T cells and B cells, each of which expresses a distinct specific recognition structure or receptor (Delves, 2014). Unlike the genetically determined innate immune system, the receptors of the lymphocytes are somatically `generated by hypermutation and random recombination (Jerne, 1971). This stochastic process provides a sufficiently wide repertoire of receptors to enable the population of lymphocytes to recognize and respond to virtually any possible intruder entering the body, living or not. Although it takes days or even weeks for an adaptive immune response to reach protective levels, its focus on the particular pathogen enables it to bind with much higher affinity than the broad receptors on cells of the innate immune system.

To produce their beneficial biologic effects, the lymphocytes must recognize particular antigenic epitopes on the invader. The lymphocytes must also receive a non-antigen-specific stimulatory signals, signals that are often derived from the earlier, innate immune response. Because of its potency it is of the greatest importance that the adaptive immune response be prevented from attacking antigens of the body of the host where it may do harm in the form of autoimmune disease.

1.1. Clonal deletion

The success of adaptive immunity rests on the assumption that the total range of receptors on the lymphocyte population, both T cells and B cells, is large enough to recognize any potential pathogen. The antigen selects, binds to and activates the appropriate lymphocyte causing it to replicate serially and produce a clone of lymphocytes bearing the same antigen-specific receptor. The clonal selection theory of Burnet predicted that premature exposure to its cognate antigen would lead to death of the lymphocyte rather than proliferation (Burnet, 1959). For example, if an encounter with the cognate antigen occurs during the generation of the lymphocyte at an early

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time when antigen specificity is first conferred, cell death and subsequent clonal deletion will result. This process of negative selection was proposed by Burnet as the mechanism for the elimination of self-directed lymphocyte clones during development of the adaptive immune response.

Clonal deletion can occur centrally during the initial differentiation of antigen-specific T cells or B cells or even later in peripheral sites. In the case of T cells, the site of T cell differentiation is the thymus (Sprent and Webb, 1995). During the process of "thymic education", T cells with their antigen-specific receptors encounter corresponding antigen-presenting cells in the thymic medulla. When the thymic medullary cell presents a particular epitope of the antigen, responding T cells undergo apoptotic cell death. In principle, the progency of these cells will, therefore, be completely absent. The host, unable to respond, will be considered tolerant of the particular antigen (Hamilton and Crome (Ohashi)).

If one scrutinizes the literature that has accumulated on naturally occurring T cell tolerance in some sixty years since formulation of the clonal selection theory, one can see that central clonal deletion represents a spectrum in its effectiveness (Kappler et al., 1998; MacDonald et al., 1988; Streilein et al., 1982; Wirnsberger et al., 2011). In a few instances, the elimination process appears to be complete (Dighiero and Rose, 1999). Examples are best seen in major cell and tissue antigens, often complexed carbohydrates and expressed on the cell surface. The major blood group antigens, ABO, and the Forssman antigen, are prime examples of antigens capable of inducing complete, specific clonal deletion. Thus, a blood group A individual is completely unable to produce anti-A, although a blood group B individual produces a vigorous response to this closely related antigen. In examples of complete clonal deletion, it is usually predictable that the tolerant individual will produce the antibodies specific for the absent alloantigen. Thus blood group A individuals spontaneously produce an anti-B. Similarly, Forssman negative animals elaborate natural Forssman antibodies.

Prenatal or neonatal exposure to a non-self-antigen can induce a form of acquired tolerance that can be life-long. In a brief report, Owen (1945) showed that genetically dissimilar bovine twins sharing fetal vascular anastomoses will harbor the alloantigenic red blood cells of the opposite twins. Indeed, Traub's (1936) studies of lymphocytic choriomeningitis virus infections of mice demonstated persistance of virus introduced during embryonic or neonatal life. Such "tolerant" mice may become life-long carriers of the virus even though they can produce high titers of antiviral antibody and develop immune complex-mediated glomerenephritis (Oldstone and Dixon, 1967). In experiments by Jamieson and Ahmed (1987) , carrier mice cured of viral infection by adaptive transfer of immune donor T cells were capable of producing their own population of cytotoxic T cells. These findings suggest that acquired immune tolerance is related mainly to the purging of antigen-specific T cells in the thymus and can be reversed by reconstitution with freshly minted bone marrow-derived T cells. Elimination of virus enabled the carrier mouse to produce cytotoxic T cells.

At the other end of the clonal deletion spectrum are antigens that are not well expressed in the thymus. In these instances, autoimmunity can be induced relatively easily by presenting the cognate antigen in the proper context. Classical instances are the tissue antigens from "immunologically privileged" sites such as in the anterior chamber of the eye, sperm in the testes and, to some extent, brain (Medawar, 1948). In these organs, allogeneic and even xenogeneic tissues are able to survive, suggesting some combination of barriers and local tolerance. When they are presented in other sites, these "sequestered" antigens readily induce autoimmune responses (Streilein et al., 1997). Simply tying the vas deferens introduces sperm into the body and stimulates sperm-specific autoantibodies (Samuel and Rose, 1980). Immune privilege in the eye can be overcome by increasing the proportion of T cells bearing a receptor specific for a retina-specific antigen (Horai et al., 2013). A spontaneous form of autoimmune disease may develop in neonatally thymectomized mice, a process dependent upon the genetic constitution of the host and the contribution of the host microbiome (Pillai, 2013). Presumably the production of inflammatory immune responses within the lens or other privileged sites would itself be detrimental to their key functions (Stein-Streilein and Caspi, 2014) and evolution has provided them with special mechanisms of tolerance.

The notion that antigen expression in the thymus is key in central clonal deletion is reinforced by recent studies on immune regulatory (AIRE) genes (Venanzi et al., 2004; Laan and Peterson, 2013). Mutations or inherited allotypic differences in this gene family determines the ability of the medullary thymic epithelial cells to acquire and present a tissue-limited or organ-specific antigen. The main antigens that have been associated with AIRE gene mutations are represented in the endocrine system. Thus, humans with certain alleles in AIRE gene often suffer from multiple endocrinopathies, a predilection perhaps related to the pronounced organ-specific antigens in these highly specialized organs. Although the presence or dysfunction of AIRE-like genes in other examples of autoimmune disease is still unknown, induction of autoimmune disease is t common with tissue-limited, organ-specific antigens (Witebsky et al., 1957).

Excluding the polar examples, most antigens entering the body are likely to be met with some measure of partial clonal deletion (Gallegos and Bevan, 2006). This gradient may be based primarily on the affinity between the peptide epitope of the antigen and the T cells receptor, or on the affinity of the peptide with the major histocompatibility complex (MHC) element of the presenting cell. Even subtle alterations of naturally occurring epitopes by chemical manipulation will sometimes prevent and raise the probability of an autoimmune disease. Altered cardiac myosin can be used as a vaccine to prevent or even treat experimental autoimmune myocarditis (Cihakova et al., 2008). A halogen-derived product raises the antigenicity of the liver enzyme CYP2E1 and enhances production of autoimmune hepatitis in mice (Njoku et al., 2005). Another example is seen in thyroglobulin where the thyronine epitope with an iodine substituent is a more active autoantigen than the same peptide lacking iodine (Barin et al., 2005). There are many other examples where even minor changes in antigen induced by infection, or by exposure to drugs or environmental chemicals, may raise the affinity of antigenic peptides and facilitate an autoimmune disease process (Nyland et al., 2010).

Clonal deletion of B cells is also incomplete. In addition to negative selection during their generation in the bone marrow, B cell can undergo a process of receptor editing whereby lymphocytes with autoreactive receptors can avoid deletion by undergoing a secondary receptor re-arrangement (Prak et al., 2011).

Since clonal deletion is generally imperfect, lymphocytes capable of self-directed autoimmune responses are common (Ada and Rose, 1988; Enouz et al., 2012). All through the lifespan, diverse T and B cells are being generated in the bone marrow and developing in the thymus or some peripheral lymphoid organ. In the case of B cells, their products are commonly encountered in the form of natural autoantibodies; that is, autoantibodies induced without a deliberate or defined process of immunization (Rose and Brinckerhoff, 1969). Much of the total immunoglobulin content of human serum comprises naturally occurring autoantibodies (Avrameas et al., 1983). They are present in all normal subjects, although often somewhat difficult to demonstrate because of their low affinity and extensive cross-reactivity. Self-reactive T cells are also well described in the literature, but their low binding affinity presents special problems. T cell "degeneracy" raises the issue of defining and maintaining T cell specificity (Van den Berg et al., 2001).

Although some form of B cell and T cell natural autoimmunity is universal, autoimmune disease, relatively speaking, is not a

frequent event. (It must be pointed out, however, that between 5% and 8% of Americans have some type of autoimmune disease.) Because of the imperfect nature of clonal deletion, both passive and active methods of regulation are required (Rose et al., 1980). In the case of B cells, the encounter with an antigen in the absence of the required non-antigen-specific signals may lead to a state of suspended animation or anergy (Nossal, 1994). This process can be reversed if the secondary stimulatory signals are later provided from some source such as an infection. T cell unresponsiveness has also been well described and related not only to the absence of the non-antigenic signals, but to the mode of antigen presentation itself. Thus, administration of antigen by certain routes such as oral or nasal, or presentation by particular populations of dendritic cells, can result in negative rather than positive responses (Guerder et al., 2013).

In addition to passive regulation, active regulation is an important mechanism for presenting the everyday autoimmune responses from reaching a clinically significant level (Wirnsberger et al., 2011). Specialized populations of T lymphocytes, naturally occurring or induced, and acting by an antigen-specific or non-specific manner are described frequently in the current literature. A host of other cells including B cells, NK cells and myelocytes, as well as cell products, contribute actively to maintaining the homeostatic control of self-reactive lymphocytes (Shen et al., 2014; Lindau et al., 2012).

As implied above, T cells and B cells are tailored to recognize and respond to particular short amino acid sequences. The sequences may be continuous or discontinuous. Neighboring sequences may exert effects during the immunization process. Yet, the reactive sequences do not always have to be perfect duplicates of the peptide used for immunization. A few key anchoring amino acids at certain sites within the immunogenic peptide sequence are mainly responsible for establishing T cell receptor affinity for the peptide. An antigen-specific T cell is able to recognize a somewhat broader array of peptides than the one that induced it.

Incomplete clonal deletion has a sound evolutionary basis. It is important that a host recognize the pathogenetic epitopes of a near-universe of potential pathogens. There is even chance that an individual may have long standing memory of some novel pathogen due to a prior adaptive immune response if some measure of cross reaction among epitopes occurs. Protection of the host would be quicker and more effective, and more readily spread to additional epitopes, due to molecular mimicry.

2. Molecular (epitope) mimicry

The concept of molecular mimicry was first proposed in a seminal paper by Damian (1964). He suggested that microorganisms may develop antigen determinants that resemble antigens of the host as a mean of avoiding recognition and elimination by the host. There are, in fact, several examples where molecular mimicry appears to be in effect. The beta hemolytic streptococcus will sometimes have a hyaluronic acid covering. Since hyaluronic acid is present in human joint fluid, the host may be partially tolerant of the bacterium.

The concept of molecular mimicry was soon expanded by Fujinami et al. (1983) and Oldstone (1998) to explain autoimmune disease. They suggested that because of the common cross reactions between epitopes of invading microorganisms and antigens present in the body, the miocroorganism may stimulate an injurious autoimmune response. Molecular mimicry, or more narrowly defined, epitope mimicry, may be a common cause of human autoimmune diseases (Fujinami and Oldstone, 1985; Cusick et al., 2012).

There are now several examples of epitope mimicry in human disease. The best studied instance is the induction of rheumatic fever by *Streptococcus pyogenes*. The epidemiologic association of the beta hemolytic streptococcus with rheumatic fever arose as a by-product of the second World War. I have recently described it in another article (Rose, 2014). Briefly, a train of evidence developed showing that antibodies from rheumatic fever patients often reacted with the M antigen of the hemolytic streptococcus. Conversely, streptococcal pharyngitis often was associated with production in children of autoantibodies to structures in a heart. In a series of eligent investigations, Madeleine Cunningham was able to define the streptococcal antigens responsible for cellular and antibody responses in rheumatic heart disease (Cunningham, 2012). She has used these defined antigens to reproduce the cardinal pathologic signs of rheumatic heart disease rodents. There are a few other examples where the evidence that epitope mimicry is a cause of a particular disease has been well supported by reproducing the disease experimentally (Getts et al., 2013). One form of Guillain Barre syndrome is associated with *Campylobacter jejuni* (Sheikh et al., 2004). Another example may be Lyme disease where there is mimicry between the outer surface protein A of *Borrelia burgdorferi* and the human's leukocyte function-associated antigen-1 (Gross et al., 1998). There is a body of evidence suggesting that a childhood form of narcolepsy is associated with H1N1 influenza vaccine (Lind et al., 2014).

Given the amount of attention paid to molecular mimicry as a cause of autoimmune disease in recent years, it is surprising that there are not more well documented instances in the human (Rose and Mackay, 2000). In most cases investigators readily demonstrate autoantibodies induced by a pathogen that cross react with an antigen of the host. In some studies, it has been possible to show that antigen-specific self-reactive T cells are present in the blood. The problem is that when studied, these antibodies and T cells react with many other antigens that have no known relevance to the clinical disease (Bachmaier et al., 1999). Sometimes the antibodies actually react with plant proteins as well as with a long list of animal peptides (Wucherpfennig and Strominger, 1995; Massilamany et al., 2013). There are still only a few instances where the mimicking peptide has been found capable of inducing a replica of the disease in an experimental animal. Thus, current evidence establishes that molecular mimicry is a common event, following many infections, but not necessarily a common initiating cause of human autoimmune disease (Fujinami et al., 2006).

3. Evolutionary imperatives

Evolutionary selection requires that a human host be able to respond to the great majority of present and future pathogens as rapidly and effectively as possible. At the same time, autoimmune responses that lead to injury of the host must be avoided. Evolution dictates that these two imperatives be balanced. We know that many of the epitopes of the pathogen, including the critical ones that afford protection to the host, may be mimicked in the body of the host. If clonal deletion were thorough and complete, the host would be unable to respond to many critical antigens because they are represented in the host's body. The result would be a “black hole”, a void in the immunologic repertoire that compromises effective protection against the invading microorganisms. Clearly, it is imperative that clonal deletion be incomplete and autoimmunity is generated to a large array of self-antigens throughout the life span (Ada and Rose, 1988). This continuing risk must be carefully regulated on a daily basis. Should regulation fail either generally or in reference to a particular pathogeneic (protective) epitope, autoimmune disease may ensue.

The probability of autoimmune disease rises with the strength of the stimulus and the genetics of the host. While heredity in a heterogeneous population like humans is only a minor factor in

determining the risk of developing an autoimmune disorder (usually there is less than 50% concurrence even in identical twins), inbreeding of animals has made it a determining factor, not only in rats and mice, but sometimes in guinea pigs and beagle dogs. Our initial discovery that the major histocompatibility complex is the source of the main susceptibility genes in thyroiditis has been established in virtually all autoimmune diseases in animals and humans (Vladutiu and Rose, 1971; Bacon et al., 1974; Vladutiu and Rose, 1974). The remaining inherited susceptibility is apportioned among a large number of genes, most of which contribute a small measure of susceptibility (Beisel et al., 1982). Many of these genetic alleles are normally involved in regulation of the immune response, in lymphocyte migration, or in target antigen susceptibility. Defining the genetic predisposition to autoimmunity, both general and disease-specific, has been a major advance in both basic and applied immunology.

Another component of genetic susceptibility to autoimmune disease is sex since the great majority of autoimmune disease patients are female. It must be recognized, however, that the differences in sex preference among different diseases represents a spectrum of susceptibilities from diseases like Graves' disease and lupus, which are highly biased towards females to rheumatoid arthritis and multiple sclerosis that are more balanced in sex predilection to few diseases including myocarditis which occurs more in males. Such a spectrum underlines the complexity of sex and the endocrine network in influencing the autoimmune response.

The intrinsic potency of an autoantigenic molecule is still unclear, but the importance of context in determining the strength of an autoimmune stimulus can be termed the “adjuvant” effect. We were first impressed by the importance of adjuvant in determining whether an autoimmune response resulted in benign autoantibody production or pathogenic autoimmunity in our first publications on experimental autoimmune thyroiditis (Rose and Witebsky, 1958). When the mouse model became available, we showed that the details of preparing and applying Freund adjuvant are critical in inducing autoimmune disease (Rose et al., 1971). Time has shown that the number of adjuvants affective in inducing autoimmune disease is rather limited, representing mainly the presence of mycobacterium in Freund adjuvant and bacterial lipopolysaccharide (Esquivel et al., 1977). Both of these microbial products act on the innate immune system, illustrating the pivotal role of the initial immune response in determining the signals that lead to adaptive immunity. Yet, it must be remembered that autoimmune disease can be induced even in the absence of an artificial adjuvant if a foreign antigen is used in immunization (Witebsky et al., 1957). Administering early inflammatory cytokines like IL1β and TNFα can induce autoimmune diseases even in mice that are genetically determined poor responders in experimental immunization (Lane et al., 1991, 1992).

The progression of adaptive immunity depends upon altering the delicate balance between vectors that promote disease and countervailing effectors that suppress the pathogenic process. This homeostatic balance is well illustrated through the classic investigations of Nishizuka et al. (1973) on neonatally thymectomized mice and Penhale et al. 1973) on thymectomized, irradiated rats. Our own studies of the OS chicken, which is genetically selected for spontaneous production of autoimmune thyroiditis, showed that thymectomy of the birds at an early post-hatching age significantly increased the severity of thyroid disease (Welch et al., 1973). Similar findings were obtained in the BUF rat which also developed spontaneous thyroidits (Silverman and Rose, 1974). The affect of thymectomy is closely age-related since thymectomy reduces autoimmune thyroid diseases only at early stages of development (Rose 1975, 2008). A distinict population of T cells capable of downregulating an autoimmune response is generated in the thymus and later migrates to peripheral sites (Rose and Talor, 1991). These studies foreshadowed the existence of a population of thymus-derived natural regulators and lead to the current delineation of CD4+/CD25/FoxP3 regulatory T cells (Sakaguchi and Rose, 1988). TP cell populations can serve as immune regulators. Under various conditions, the prior literature on CD8+ suppressor cells is still valid even if the population was never clearly separated from CD8+ effector T cells. The role of regulatory B cells are now well established (Mauri and Blair, 2014; Lin et al., 2014). Myeloid-derived suppressor cells, prominent in tumor immunology, are likely equally effective in some circumstances in autoimmune disease (Li et al., 2014).

As regulatory cell populations were being recognized, cell products with regulatory functions also become evident. Some clinical experiments arise because of the application of these regulators in cancer immunology. For example, patients given antibodies to CTLA4 are prone to a rare autoimmune endocrinopathy hypothysitis (Iwama et al., 2014). Current studies using anti-PD1 or anti-PDL1 already have suggested some risk of heightened autoimmunity (Kong & Flynn, 2014). This represents an area of research demanding greater attention for both the fundamental lessons it can teach us and the practical knowledge it can impart for clinical application.

Recent years has seen a recurrence of interest in the microbial population that inhabits the surfaces of the human body, including the intestines, mouth and skin (Belkaid and Hand, 2014). Now that the microbiome project has given science the tool of genetic identification of these commensal bacterial, associations with particular DNA patterns are even particular microorganisms with autoimmune disease has become evident. This finding would certainly be gratifying to Metchnkoff who first put us on the track of the innate immune system and predicted that the diet would be an important influence on the immune response.

Evolution demands that immunologic homeostasis be carried out on two levels. At the macro level the adaptive immune system is genetically constructed of counterveiling vectors such as regulatory cells and their cytokine products. They are constantly on guard to prevent the progression of benign naturally occurring autoimmunity as it arises daily to life-threatening autoimmune disease. On the micro level, homeostasis resets all through the life span because of the changing internal and external environment. External agents such as microorganisms or chemicals require shifts to the homeostatic balance as do the changes in hormones that require constant resetting. Being able to reset homeostasis continuously is the requisite of immunologic good health.

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