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Natural Autoantibodies and Their Implications

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Introduction

It is considered that the principal function of the immune system is the protection of individuals and animals against environmental pathogenic agents. Furthermore, it is accepted that antibodies induced after immunization with environmental pathogenic agents and antigens are highly specific. Therefore it is generally believed that under normal physiological conditions antibodies directed against internal or self antigens are not synthesized. Thus the immune system is organized to recognize, in an extremely selective and specific manner, antigens of the external environment while it tolerates antigens of the organisms; when this tolerance to self antigens is broken, autoantibodies are produced and a pathological state is induced. On this basis autoimmunity is always related with a pathological state. However, these concepts are correct for the acquired, but not for the natural or physiological immunity.

Indeed as early as 1900, Landsteiner and his group demonstrated that antibodies reacting with a variety of antigens are present in the sera of normal humans and animals that have never undergone experimental immunisation (Landsteiner 1945). These antibodies, later called natural antibodies, often expressed poor specificities and were able to react with various antigens of the organism. Studies performed by several groups over the past 15 years confirmed these early results and have clearly established that the normal serum contains large amounts of natural autoantibodies (NAb) capable of recognizing various autoantigens. Thus, these studies have introduced the new concept that in fact two forms of autoimmunity can co-exist. The first is physiological and is manifested by the presence of numerous autoantibodies which, not only are not harmful but, to the contrary, may play important physiologic roles. The second form of autoimmunity is associated with pathological manifestations. Such a distinction is convenient but the boundaries between these two forms of autoimmunity are not always easy to define.

It should be added in this brief introduction that the physiological autoimmunity described below concerns only the humoral response as manifested by the NAb. In normal individuals and animals there exist also numerous autoreactive T cells but this aspect of the physiological autoimmunity is at present poorly studied.

Properties and Characteristics of Natural Autoantibodies

NAb have been found in the sera of normal humans, mice, rats and phylogenetically distant fish (Schwartz & Datta 1989, Avrameas 1991, Shoenfeld et al. 1993). They are present in germ-free and also antigen-free mice, i.e. in animals that have never been in contact with external antigens even with those usually found in the food

(Underwood et al. 1985, Pereira et al. 1986). A series of studies have established that human and mouse NAb belong to the IgM, IgG or IgA isotype. The majority of human and murine IgM and IgG NAb isolated from normal sera using specific immunoadsorbents, when tested on a large panel of antigens were found to be polyreactive and able to recognize both self internal and non-self external antigens (Guilbert et al. 1982, Adib et al. 1990, Berneman et al. 1992, Berneman et al. 1993). Immunoadsorption experiments with normal human sera have shown that, depending upon the individual's sample, 40 to 95% of all immunoglobulins correspond to polyreactive NAb. However, these are minimal estimated values, and it is likely that even higher quantities of NAb are present in normal human sera (Berneman et al. 1993).

Analysis of human B-cell clones derived from peripheral blood lymphocytes, obtained after human-mouse heterohybridization or by Epstein-Barr virus infection, has shown that up to 35% of the monoclonal immunoglobulins secreted can react, like the human polyclonal NAb, with more than two self and non-self antigens (Seigneurin et al. 1988). Similarly 2-50% of the hybridoma clones, derived from different lymphoid organs of mice during the course of development were found to synthesize polyreactive NAb capable of recognizing several self and non-self antigens (Dighiero et al. 1983, Prabhakar et al. 1984, Dighiero et al. 1985, Souroujon et al. 1988). NAb are preferentially, but not exclusively, produced by $CD5^+$ B lymphocytes (Casali et al. 1989).

Polyreactive NAb bear common idiotypes and establish among themselves a dense idiotypic network (Lymberi et al. 1985, Holmberg et al. 1986, Vakil & Kearney 1986).

Most polyreactive NAb are directly encoded by the germline and are subjected to practically no mutations (Baccala et al. 1989, Chen et al. 1991, Martin et al. 1992). Furthermore, it has been shown that polyreactive NAb use the same genetic elements as the antibodies directed against foreign non-self antigens while, in general, there is no pronounced predominance among subgroups in the VH and VK gene families (Casali & NotKins 1989, Schwartz et al. 1989, Shoenfeld et al. 1993).

Monoclonal human and mouse NAb although they exhibit extensive polyreactivities possess their own fine specificities and therefore each one can be considered as unique and corresponding to the product of a single clone (Ternynck et al. 1986). Thus, it seems probable that, despite its polyreactivity, each NAb, is prone to react preferentially with one structure rather than another. In general NAb possess low affinities but, in contrast, high avidities (Ternynck et al. 1986). Affinity or intrinsic affinity expresses, in physico-chemical terms, the monovalent binding of an antibody to a small molecule (epitope), whereas avidity, or functional affinity, represents the multivalent binding of an antibody to a macromolecule carrying identical or similar epitopes. It has been clearly shown that for an IgG antibody there is a 10^3 and for an IgM at 10^6-fold increase between functional affinity and intrinsic affinity (Hornick & Karusk 1972). Thus depending upon the local conditions, for example antigen and antibody concentrations and accessibility, a NAb may or may not bind to a macromolecule and, therefore, will or not be able to exert a possible biological function.

Biological Roles of Natural Autoantibodies

NAb, the main manifestation of physiological or natural autoimmunity, might possess potential biological activities. In fact, various functions have been attributed to NAb which are not mutually incompatible, but, to the contrary, they are even complementary to each other.

Immune Functions of NAb

That the idiotypic network, established early in ontogeny among NAb plays important roles in the regulation of immune responses to external antigens seems to be widely accepted. Thus it has been found that treatment of mice with idiotypically interconnected monoclonal natural autoantibodies reduced the expression of the corresponding idiotypes and resulted in either enhancement or suppression of the immune responses related to these idiotypes (Holmberg et al. 1986, Vakil et al. 1986, Sundblad et al. 1989). Similarly, mice injected with monoclonal IgM NAb, or anti-idiotypic antibodies to NAb were found, compared to control mice, to possess either heightened or lowered immune responses depending upon the antigen (Mahana et al. 1987, Mahana et al. 1988). Such treatment established an immunological memory, since the differences observed persisted after antigenic challenges and were related only to the IgG isotype (Mahana et al. 1988).

It has recently been found that IgM NAb present in normal mouse and human sera play important roles in such idiotypic regulations. It was shown that in mouse sera the IgG activity was weak or even absent. When IgG were separated however from the other serum proteins by affinity chromatography on immobilized protein A, they expressed extensive autoreactivities (Adib et al. 1990, Berneman et al. 1992). Immunoadsorption experiments have demonstrated that these isolated IgG were essentially polyreactive and their low activities noted in whole serum were mainly due to the presence of an IgM NAb population that, by binding to the F(ab')2 portion of the IgG, inhibited the binding of the IgG to autoantigens. It was found that in some pathologic situations, IgM failed to inhibit IgG autoantibody activities (Adib et al. 1990). Thus the IgG anti-DNA activity from (NZB × NZW)F1 mice was not affected by autologous IgM. Also the IgG anti-tubulin from mice infected with *Trypanosoma cruzi* were less inhibited by IgM from autologous serum than IgG anti-tubulin from normal mice. These results are compatible with the existence in normal mice of an idiotypic-like network regulating via an IgM NAb population the binding of IgG autoantibodies to self antigens. Modifications of this NAb idiotype-anti-idiotype system might lead to the expression and/or expansion of autoreactive IgG-producing clones. If so, one would expect that modifications occurring on the NAb network could interfere with the development of the lupus syndrome. In fact, it was found that injection to (NZB × NZW) of murine IgM and IgG preparations, enriched in NAb, resulted in a significant survival of the (NZB × NZW) mice and a dramatic decrease of their proteinuria (Hentati et al. 1994).

Similar results were obtained with normal human sera (Berneman et al. 1993). Thus, IgG autoreactivity was weak in the entire normal sera of individuals; however, when IgG was separated from the other serum proteins by affinity chromatography on immobilized protein-G, these antibodies exhibited strong autoreactivities. Depending upon the individual's IgG preparation examined and the autoantigen tested, the autoreactivities of isolated IgG, compared to those of the whole serum, increased up to 94 fold. These IgG autoreactivities diminished considerably when IgG-depleted serum was added to the autologous isolated IgG. Similarly isolated autologous IgM anti-F(ab')2, that differed in their autoreactivity patterns from one individual to another, partially inhibited the binding of IgG to the autoantigens. Furthermore, it was found that the individual's IgG samples examined separately exhibited higher autoreactivities

with all autoantigens tested than with the same-but-pooled samples. Moreover isolated IgG NAb on immunoadsorbents showed much higher reactivities with the various autoantigens tested than the corresponding initial IgG preparations (Berneman et al. 1993). These results support the notion that in addition to IgM-IgG, IgG-IgG idiotypic interactions are also responsible for the diminished IgG autoreactivities observed in normal human sera. Compared to normal sera these interactions are significantly altered in sera from lupus patients. In general, IgG autoreactivities increase only slightly after isolation on immobilized protein G; such an alteration is particularly evident for IgG anti-DNA antibodies. In other autoimmune diseases, however, like in pemphigus vulgaris or allergic situations, these alterations seem to be limited to only one or two autoantigens (Avrameas, unpublished observations). It is possible that clinical improvements that have been noted to occur in patients suffering from various autoimmune diseases after injection of normal human IgG preparations (Dietrich et al. 1992) is due to the re-establishment of this deficient NAb network.

The immunoregulatory roles of NAb can be exerted not only through idiotypic interactions but also through their interactions with the various molecules involved in the functioning and regulation of the immune system. Thus recently, it was shown that IgG, but not IgM, from autologous and homologous normal human sera inhibited autologous mixed lymphocyte reaction (MLR) that is mediated by autoreactive T cells (Wolf-Levin et al. 1993). IgG was also found to suppress allogenic MLR stimulated by phytohemagglutinin (PHA)-activated T-cells but not allogenic MLR stimulated by non-activated peripheral blood mononuclear cells. This observation, in conjunction with the fact that treatment of PHA-activated T cells with IgG, but not of peripheral blood mononuclear cells, resulted in a significant inhibition of autologous MLR and suggested that the mechanism of inhibition is related to the surface molecules expressed on PHA activated stimulator cells. In accordance with this conclusion it was noted that autologous IgG specifically binds to PHA-activated T cells and that adsorption of IgG with such activated lymphocytes substantially decreased the inhibitory capacity of IgG. It was concluded that the inhibitory activity is specific, does not exist in all IgG molecules, and that such IgG NAb may play an important role in regulating the amplification of immune responses mediated by autoreactive T-cells. Similarly, affinity purified human NAb to interferon γ (IFNγ), although they were not found to impair antiviral activity of IFNγ, they were shown to interfere with *in vitro* immunomodulating activities of this cytokine (Turano et al. 1992). Thus, NAb to IFNγ were able to suppress the increase of the expression of Fc receptors and HLA-DR antigens induced on cells by IFNγ. Furthermore, these antibodies interfered in mixed lymphocyte cultures with the proliferation and cytotoxic generation of lymphocytes, probably by inhibiting the endogenously produced IFNγ.

It has been proposed that B-cells carrying polyreactive NAb as receptors, after stimulation by an interacting external antigen, similar but not identical to an internal self antigen, are induced to undergo a series of divisions and mutations which under the selective pressure of the antigen, might lead to the production of antibodies highly specific to a given epitope of that antigen (Dighiero et al. 1983). Several results obtained at the humoral, cellular and molecular level seem to strongly support this hypothesis (Guilbert et al. 1985, Gilbert et al. 1992, Van Es et al. 1992).

Various other Functions of NAb

Since polyreactive NAb can react with internal self and external non-self constituents they may participate in various biological functions, not necessarily linked with the immune system and, depending upon the situation, may play either beneficial or harmful roles. IgG NAb reacting with a 1,3 terminal digalactose residues (anti-Gal) is a representative example of such opposite effects of NAb. Anti-Gal antibodies are present in all normal human sera and represent 1% of all IgG. Anti-Gal antibodies were found to possess a beneficial effect since they participate in the clearance of senescent or pathologically deformed erythrocytes (Galili et al. 1986). More recently it was observed that anti-Gal antibodies by binding onto the lipopolysaccharide of a blood isolate of *Serratia marcescens* blocked its alternative complement pathway lysis and made the organism serum resistant (Hamadeh et al. 1992). Thus anti-Gal have also a harmful effect by facilitating the survival of selected Enterobacteriacae in Gram-negative sepsis.

The existence of NAb possessing cytotoxic activities, various inhibitory actions, and capacities to enhance opsonisation of foreign and altered self constituents have been reported (Ivanyi et al. 1983, Matsiota et al. 1989, Sorace et al. 1990, Cunningham et al. 1992, De Maeyer-Guignard & deMaeyer 1986, Manciulea et al. 1989, Navin et al. 1989, Witz et al. 1984, Hinter et al. 1985, Lutz 1990). Thus, NAb can be considered as a first line of defense against external aggressions that have been phylogenetically conserved. Along these lines it has been shown that, in trout protected from bacterial infection by previous injection of bacterial extracts, the kinetics of serum anti-bacterial antibodies strictly followed those of NAb (Michel et al. 1990). In fish, where principally only one class of polymeric immunoglobulins exist, NAb probably constitute the unique antibody-mediated defense mechanism. Moreover, NAb isolated from the sera of normal rainbow trouts protected trout fibroblasts against viral infection *in vitro*. In order to be manifested the protective activity required structures of both the viruses and of the cell surface (Gonzalez et al. 1989). Similarly NAb act as first line defense mechanism against modified self constituents by participating in their clearance from the organism (Grabar 1975). Thus it has been shown that IgM and IgG NAb participate in the elimination of keratin after keratinocyte death, and in the elimination of senescent erythrocytes and cancer cells (Hinter 1985, Lutz 1990, Witz et al. 1984, Chow & Bennet 1989).

Natural Autoantibodies and Pathological States

Since NAb interact with the immense number of self constituents present in the organism they may participate not only in the homeostasis of the immune system but also in that of the whole organism. If so, one would expect that even in certain pathological situations bearing no relationship to the immune system, the pool of NAb might be modified, possibly followed by changes in their serum titers. Indeed, comparison of NAb present in normal human sera with those of patients suffering from various autoimmune diseases such as: lupus erythematosus, autoimmune hemolytic anemia, diabetes mellitus, Hashimoto's thyroiditis, either autoimmune-related (IgA) nephropathy, HIV infection, multiple sclerosis, Chagas' disease or non-autoimmune diseases such as: chronic hepatitis, hemophilia, schizophrenia, anorexia nevrosa, Alzheimer's disease, breast cancer has shown that, in almost all cases, significant modifications in the titers of NAb (Matsiota et al. 1987a, Matsiota et al. 1987b, Matsiota et al. 1988, Louzir et al. 1988, Matsiota et al. 1990, Ounanian et al. 1990).

Furthermore, polyreactive autoantibodies of the IgM, IgG and IgA isotypes were found to contribute to the formation of circulating immune complexes present in the sera of patients suffering from autoimmune and non-autoimmune diseases (Louzir et al. 1988). Thus, these results indicate that, at least when NAb are considered, various pathologies are associated with autoimmune reactions of varying intensities. However, it remains to be studied whether NAb are involved, directly or indirectly, in the establishment of the pathological processes.

Conclusions

Physiological or natural autoimmunity is characterised by the production by the B-cell compartment of the immune system of polyreactive NAb recognizing self and non-self constituents. NAb are synthetized, secreted into the blood, circulate, interact among themselves and also with the immense number of self constituents that compose the organism and establish a vast network in which external non-self constituents also participate. It appears that the main function of this network is the homeostasis of the immune system. In addition to this main function, NAb participate in "non-specific" immune defense mechanisms. Also, it is possible that NAb, by interacting with molecules and cell involved in the function of various biological systems that compose the organism, contribute to the general homeostasis of the organism.

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