Regulation of Immune Responses by Anti-receptor Antibody

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ABSTRACT

A new function of antibodies in the regulation of immune responses is proposed. Antibodies have specific variable sequence determinants which are detected by anti-idiotypic antisera. Anti-idiotypic antibodies can suppress the production of the complementary idiotypic antibody and are, therefore, specific anti-receptor antibodies. Experiments in inbred mice have shown that mutual and reciprocal functional interactions of idiotype and anti-idiotype can occur. These findings give evidence for regulatory mechanisms in the expressions of immune clones by complementary idiotypes.

Introduction

The structure and function of immunoglobulins and their role in the defense against bacterial and viral intruders are known. However, a second function of immunoglobulins is connected intimately with immune defense mechanisms. In fact, it seems that without the second function the immune system could not work properly and thus could not exist.

Each antibody has specific structures which bind the antigen. The specificity and the uniqueness of an antibody are determined by its binding site configuration. Since the experiments of Oudin\textsuperscript{11} and Kunkel\textsuperscript{10} in 1963, it is known that the uniqueness and the specificity of an antibody can be described by a second criteria which does not involve the antigen. These investigators have prepared antisera which were specific for a given antibody or immunoglobulin. The specificity of these antisera was so high that not only the antigen binding specificity but also the donor or the individual animal from which the antibody was obtained could exactly be identified.

Since these specific anti-antibody recognized very unique and individual structural features on an antibody molecule, they were called individual specific determinants or idiotypes. Antibodies which bind to these determinants are called anti-idiotypic antibodies. The sec-
ond function of antibody mentioned earlier deals with its potential to act as an anti-idiotypic antibody or to be the target for recognition as idiotype by another anti-idiotypic antibody. For this biological function, antibody and anti-antibody, i.e., idiotype and anti-idiotype, are present in the same individual, produced by the same individual.

Specific Suppression by Anti-idiotypic Antibody

B-lymphocytes which can be triggered by antigen to produce antibody carry receptors for antigen on their surfaces. These receptors are immunoglobulins in nature and essentially copies of the later synthesized antibodies. Thus, receptors and antibody specific for the same antigen share at least the same combining site structure. It follows from this that anti-idiotypic antibodies which bind specifically to a given antibody also will react with the receptor immunoglobulin of that cell clone which can produce this antibody.

This line of reasoning was used by us and others in designing experimental systems in which an anti-idiotypic antibody suppresses specifically the response to a defined antigen. The simplest model for anti-idiotypic suppression is competition of antigen with anti-idiotypic antibody for the receptor on B-cells (figure 1). Consequentially, anti-idiotypic antibody functions here as anti-receptor antibody. More recently, evidence has been obtained that anti-idiotypic suppression is a complex reaction involving the additional interaction of the Fc-portion of anti-idiotypic antibody with the Fc-receptor on B-cell or macrophages.

Evidence for Regulation by Anti-idiotypic Antibody

Anti-idiotypic suppression offers an attractive model for mechanisms regulating immune responses. Idiotype and anti-idiotype are both immunoglobulins and the mutual affinity of both is based on the complementarity of their binding site structures. Chemically speaking, the affinity of idiotype and anti-idiotype resides entirely in their V-region sequences. Therefore, there is no a-priori reason to designate one antibody the idiotype and the complementary antibody the anti-idiotype. For example, if the idiotype in figure 2 is assigned to the left hand corner, the complementary antibody of the right side becomes the anti-idiotype. However, the model can be reversed to make the idiotype an anti-
idiotype. Transposing this system to the cell receptor level it could work as a closed feedback loop in which the synthesis and the activity of both complementary antibody are controlled.

What is the evidence that such a mechanism might be operating in the regulation of immune responses? The first support for this model comes from the observation that idiotype and anti-idiotype can be made by the same individual. Furthermore, the appearance of idiotype and anti-idiotype occurs sequentially during an immune response. If Balb/c mice are immunized with a phosphorylcholine containing antigen, they first produce antibody against phosphorylcholine (PC) and, subsequentially, anti-idiotypic antibody against the idiotype of the anti-Pc antibody. Recently, a similar sequential appearance of complementary idiotypes has been observed during the

**Figure 3.** Complementary antibody responses. Groups of mice were immunized with phosphorylcholine containing antigen (PC) to produce the anti-PC idiotype or with the anti-PC idiotype to produce anti-idiotypic antibodies. Depending on the timing of immunization both complementary responses can coexist in the same animal (upper panel I) or the first established response suppresses the subsequently induced response (lower panel II). T15 is the idiotype of the anti-PC response.

**Figure 4.** T and B-cells have receptors for antigens which can engage in a functional relationship based on the principle of complementary idiotypes. Therefore, B and T-cells can be paired as B-B doublets or B-T doublets.

**Figure 5.** Dual function of antibody. Cell receptors and antibodies bind to antigen. In addition the antibodies produced by the same cell can also bind to the receptor of another cell. This induces specific suppression of the target cell. It is hypothesized that antibody binding to cell receptors is involved in the regulation of the immune response.
ontogenic development in neonatal Balb/c mice. The serum of newborn Balb/c mice contains, for the first four to five days of life, anti-idiotypic antibodies against the anti-Pc idiotype and from day five on, the anti-Pc idiotype increases steadily while the anti-idiotype disappears. Thus it seems that idiotype and anti-idiotype are constituents of the "naturally" occurring antibodies. At present, the sequential appearance of anti-idiotypic and idiotypic antibodies in the ontogeny of Pc-responsive clones is not understood, but it can be speculated that these early events are important steps for the maturation of the immune response.

To add further evidence for the proposed model of regulation by interacting complementary idiotypes, adult mice were immunized with antigen to produce idiotype or with idiotype to make anti-idiotype. The effect of either response upon the complementary responses was observed. It has been found that a preceding idiotype response spoiled attempts to induce an anti-idiotype response and, vice versa, a preceding anti-idiotype response did not permit a later idiotype production. It can be learned from these findings that the first established response had gained priority of the possible complementary response. However, if both complementary idiotype responses were initiated at about the same time, both responses occurred (figure 3). The priority of the prevailing response is entirely determined by the time sequence of immunization. Thus, it is conceivable that the principle of the priority of the first response plays an important role in the immunological adaptation to environmental stimuli.

The clonal interactions of two complementary antibodies or idiotypes provide the minimum requirements for a functional network of cells and antibodies in the immune system. Recent data allow us to include into this model both B- and T-cells since B- and T-cells can carry either idiotypic or anti-idiotypic receptors (figure 4). So far it is known that anti-idiotypic T-cells can suppress or help idiotypic B-cells. It has also been learned that B-cell products, i.e., antibodies, can stimulate T suppressor cells. From these experiments a new concept emerges: the immune system is under internal self-control including the B- and T-cell compartments.

However, several questions and details in this model are still unanswered and missing. What is the chemical equivalent for idiotype on T-cell receptors? What are the connections between the control of immune responses by the immune response genes (Ir-genes) and the regulation by complementary idiotypes? What are the consequences of having complementary idiotypes for understanding the generation of antibody diversity and evolution of V-genes? It will require more careful experimentation and imagination to reconcile apparent discrepancies in our current thinking on models of immune regulation based on the dual function of antibodies (figure 5).

References


