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The idiotypic network in the regulation of autoimmunity: Theoretical and experimental studies

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ABSTRACT

The regulation of autoimmunity is a key issue in fundamental immunology. Despite outstanding achievements on this front, we currently have more questions than answers. The idea of an immune network as a regulatory mechanism is quite attractive, since it enables us to explain the selectivity (specificity), and moreover the clonality, of the regulation. Nevertheless it remains unclear how this mysterious network of immune cells is organized, how it operates, and how it exerts control over autoimmunity. This article presents an attempt to understand how the immune network functions and how it controls autoreactivity. We present a mathematical model of the immune network that is based on principles of immune network organization and function that we arrived at from a survey of the available literature. To test the principles on which the mathematical model is based, we studied the model and compared the different responses to antigen that it generated with the results obtained from experimental studies of immune response. The modeled kinetics of idiotype and anti-idiotype in response to the administration of antigen are in good agreement with the experimental kinetics of idiotypic and anti-idiotypic antibodies. To obtain evidence of the existence of idiotypic mechanisms for regulating autoimmunity, we studied a mathematical model containing autoclones and compared the model results with data from experimental studies in a model of autoimmune hemolytic anemia in mice. Because the results from the theoretical and the experimental studies coincide, there is justification to conclude that autoreactive lymphocytes are normal components of the immune network within which they are regulated. We discuss a possible molecular/cellular mechanism for negative control of autoreactive cells as affected by anti-idiotypic antibodies.

1. Introduction

The regulation of autoimmunity is a key issue in fundamental immunology. No one today will deny that autoreactive lymphocytes are normal representatives of lymphocyte clones, that they have access to the corresponding autoantigens, and that they exhibit activity under normal conditions (von Boehmer and Waldmann, 2010). Furthermore, Carneiro has suggested that autoreactive lymphocytes be viewed as growth points for the entire lymphocyte network during early ontogenesis, with these lymphocytes ultimately determining the repertoire of the body's lymphocyte receptors for antigen recognition (Leon et al., 1998). The question then arises: how is autoreactive lymphocyte activity regulated such that autoimmune responses remain nonaggressive under normal conditions? Ever since the clonal selection theory was published, researchers have held to the idea that mechanisms exist for the negative regulation of autoreactive lymphocytes. The idea of these mechanisms evolved along two lines. One of them was focused on the search for a special population of cells that provide negative control of autoreactivity. The idea of such cells has gone from "veto" cells to T-suppressor and regulatory T cells. Despite outstanding achievements on this front, we currently have more questions than answers.

The other approach is based on the idea that there is an idiotypic network which itself, as a system, serves as the negative control mechanism (Jerne, 1974). The idea of an immune network as a regulatory mechanism is quite attractive, since it enables us to explain the selectivity (specificity), and moreover the clonality, of the regulation. Clonality of regulation in an immune network is explained by the fact that for a lymphocyte to be recognized as a regulatory target, an idiotype of an antigen-recognition receptor is used that is unique to each lymphocyte.

Outstanding contributions to the development of this idea in the wake of Jerne were made by such scholars as Behn (Behn, 2007), Carneiro (Carneiro, 1997), Cohen (Cohen and Atlan, 1989), Coutinho (Coutinho, 2003a, 2003b), De Boer (De Boer and

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Hogeweg, 1989), Hoffmann (Hoffmann, 1975), Perelson (Perelson, 1989), Rodkey (Rodkey, 1980), Root-Bernstein (Root-Bernstein and Couturier, 2006), Shoenfeld (Shoenfeld, 2004), Schulz (Schulz et al., 2013), Sulzer (Sulzer et al., 1994) The history of how knowledge of the immune network has developed is presented in outstanding survey articles (Behn, 2007; Paul, 1984; Rodkey, 1980). Despite significant achievements, it remains unclear how this mysterious network of immune cells is organized, how it operates, and how it exerts control over autoimmunity. Study of the idiotype-anti-idiotypic network is a complex task that requires mathematical modeling. Theoretical ideas have played a profound role in the development of the idiotypic network theory. Mathematical models can help in the precise translation of speculative ideas into quantitative predictions. They can also help establish general principles and frameworks for thinking (Perelson, 1989).

This article presents an attempt to understand how the immune network functions and how it controls autoreactivity. We present a mathematical model of the immune network that is based on principles of immune network organization and function that we arrived at from a survey of the available literature. To test the principles on which the mathematical model is based, we studied the model and compared the different responses to antigen that it generated with the results obtained from experimental studies of immune response. To obtain evidence of the existence of idiotypic mechanisms for regulating autoimmunity, we studied a mathematical model containing autoclones and compared the model results with data from experimental studies in a model of autoimmune hemolytic anemia in mice. We discuss a possible molecular/cellular mechanism for negative control of autoreactive cells as affected by anti-idiotypic antibodies.

2. Material and methods

2.1. Construction of a mathematical model of an immune network

We constructed a mathematical model of the immune network based on the principles in Jerne's theory (Jerne, 1974) and on Köhler's principle of the identity of idiotype and paratope, which introduces symmetry into the system of idiotype-anti-idiotype interactions and suggests that the active site of the anti-idiotypic lymphocyte receptor and the antigen are structurally similar (Köhler et al., 1989), as well as on the known phenomenology of immune responses.

The model is a system of discrete equations describing an idiotypic network with a specific geometry. The main element of the model is a clone of lymphocytes possessing the idiotype (Id) and having its own number, which distinguishes it from other clones (I1, I2,…,I*n*). All of the clones are involved in idiotypic interactions, forming a continuous network for which the geometry can be defined arbitrarily. In the simplest cases it is a linear chain where for each idiotypic clone there are two anti-idiotypic clones. The length of the chain is arbitrary; the numbering of the clones is sequential from beginning to end; and the last clone in the numbered sequence is connected with the first, closing the chain into a ring.

At each point in time, the lymphocyte clone is characterized by an "activity" value (U). Conventional units (c.u.) were used to measure the "activity" value. Lymphocyte activity in the model is a quantitatively expressed capability to respond to an activating signal and to transmit this signal to other cells via anti-idiotypic interactions. In the actual immune system, the activity value (U) corresponds to the increase in lymphocyte proliferative and functional activity. For example, for B lymphocytes, functions of "activity" are the rate of proliferation, the number of antibodies the lymphocytes produce, and memory cell formation as part of the immune response.

The connections established between the idiotypic clone and the anti-idiotypic clone have the following properties.

1. The interacting clones are capable of mutual stimulation, since they are antigenic to one another. This type of connection is defined in the model as direct connection ($F1$) (Fig. 1). The magnitude of the effect exerted on the cell depends both on the activity of its neighbor (anti-idiotype) and on the difference between the activity of the neighbor (anti-idiotype) and the cell's own activity.
2. Clones are capable of specific interactions via a feedback system ($F2$) (Fig. 1). Feedback is provided by anti-idiotypic antibodies or by the anti-idiotypic lymphocytes that form as a result of activation and proliferation. The magnitude and character of the effect in the feedback system ($F2$) depend on the activity of the cell receiving this connection. The feedback is negative, limiting the activity of the idiotype, if the latter is in a state of high activity; conversely, if the activity of the idiotypic clone is low, when the clone is exposed to the anti-idiotype, its activity would increase.
3. All of the established connections are symmetrical and are present simultaneously. The effect of interaction via direct connection ($F1$) and feedback ($F2$) is a change in cell activity (U).

The state of the network is defined as the result of the interaction between the clones. In response to each activity state, there will be a specific effect resulting from the actualization of all of the connections at that time point. In the absence of a signal (antigen), a steady state is established for an indefinite period of time as a result of the interaction between the clones. The level of activity, however, remains constant. This condition can be called the initial (or virgin) network state. Since the model is nonlinear, there may be a large number of such states.

The interaction between cells occurs at time (t), with a single stage in the interaction—during which the antigenic signal is transmitted one step further along the network from the initial stimulated clone—being used as the conventional unit (c.u.) of time. At the subsequent (second) time point, the signal is transmitted to the next element in the network, and this is the next stage in the interaction of the initial pair. Thus, for each time point, an interaction takes place between all of the "neighbors" in the

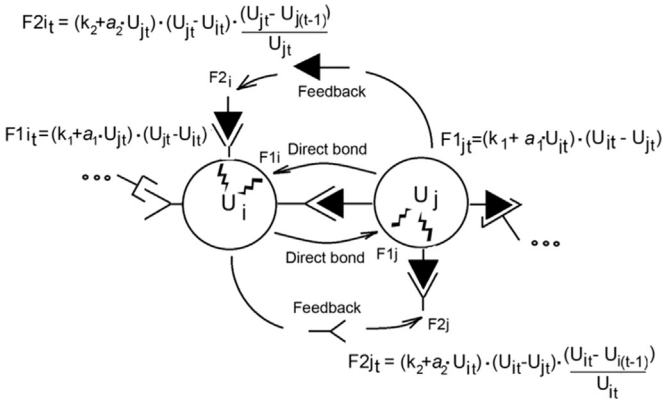

Fig. 1. Diagram illustrating the idiotype-anti-idiotype interactions between cells established in mathematical model of the immune network. One pair of interacting cells is presented. U_i is the activity of clone i, U_j is the activity of clone j, $F1_i$ is the strength of the activation signal to clone i from clone j when interacting via direct connection, $F1_j$ is the strength of the activation signal exerted on clone j by clone i when interacting via feedback, $F2_i$ is the strength of the feedback exerted on clone i by clone j, $F2_j$ is the strength of the feedback exerted on clone j by clone i.

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