Journal of Alternative Medicine Research
Volume 1, Issue 4, pp.439-444
ISSN: 1939-5868

Human development XVII: Jerne's anti-idiotypic network theory cannot explain self-nonself discrimination

Søren Ventegodt[*1,2,3,4,5], Tyge Dahl Hermansen[1], Isack Kandel[6,7] and Joav Merrick[5,7,8,„9]

[1]Quality of Life Research Center, Classensgade 11C, 1 sal, DK-2100 Copenhagen O, Denmark;
[2]Research Clinic for Holistic Medicine and
[3]Nordic School of Holistic Medicine, Copenhagen, Denmark;
[4]Scandinavian Foundation for Holistic Medicine, Sandvika, Norway;
[5]Interuniversity College, Graz, Austria;
[6] Faculty of Social Sciences, Department of Behavioral Sciences, Ariel University Center of Samaria, Ariel, Israel;
[7]National Institute of Child Health and Human Development
[8]Office of the Medical Director, Division for Mental Retardation, Ministry of Social Affairs, Jerusalem, Israel and
[9]Kentucky Children's Hospital, University of Kentucky, Lexington, United States

Abstract

In this paper we propose that self-nonself discrimination takes place at a supra-cellular systemic level and involves selective activation of immune cell precursors. We discuss this activation, the further differentiation to active lymphocytes, and the following immune response induced by the system permitting all relevant information to be involved in the "decision" process in a dynamic way. We discuss Jerne's immunological network theory based on the capability of self-nonself discrimination and we discuss if his immunological network theory is able to carry out such self-nonself discrimination. We argue that this is not the case. We discuss the immune tolerance that seems not to be transferred with the immune cells, what Jerne's network model involves as a necessity. We discuss Jerne's idiotypical network's capability of being expanded to include T-cells. Also here we argue that this is not the case. Furthermore, We discuss Jerne's own arguments for his immunological network theory and discuss different experiments capability of supporting or rejecting Jerne's immunological network theory. We found that not enough evidence and proof for his model have yet been presented in the forum of discussion or in the scientific literature to support the existence of Jernes network theory. Finally we argue that his model in principle can not explain the immunological self-nonself discrimination.

Keywords: Immunology, self-nonself discrimination, holistic biology, theoretical biology, clinical holistic medicine, public health, T-cells.

Introduction

In this paper we discuss self-nonself discrimination, mainly in the view of the Danish immunologist Niels Kaj Jerne (1911-1994) immunological network theory (1,2). In 1974, Niels Jerne came up with his network theory for the immune system (1). It was an a priori hypothesis that had no experimental foundation. It

[*] **Correspondence:** Søren Ventegodt, MD, MMedSci, MSc, Director, Quality of Life Research Center, Classensgade 11C, 1 sal, DK-2100 Copenhagen O, Denmark. Tel: +45-33-141113; Fax: +45-33-141123; E-mail: ventegodt@livskvalitet.org

was what Jerne himself later called "a preconceived idea" (2). Jerne did take an important step in 1974, because the investigation of systemic information was and is essential. Because the scientific community at that time had no clue about the function of the immune system as a system, Jerne's hypothesis was very well received. Because a network theory was expected at that time, many immunologists did not question the nature of Jerne's theory. The hypothesis was in its basic elements simple and easy to understand, but in its totality impossible to get an overview of, even incomprehensible. Nobody had expected the regulation of the immune system to be simple, and fundamentally Jerne's theory did not deter many immunologists. Today opponents against Jerne's theory reject his network theory as a formal absurdity (3-5), and its spokesmen admit that self-nonself discrimination also in the view of Jerne's theory lack the capability of controlling the network (6). Jerne's network theory only takes care of the regulation of the immune response after activation (when the "choices" has been taken), and a problem concerning the spokesmen is that Jerne rarely cites the experimental results that contradict his network theory (7,8).

According to Klein (9) a network is a possibility, and he discusses the existence of idiotype specific cells (Th-cells). There are as many experiments that confirm the existence of these cells as there are experiments that contradict their existence. We think the existing proof for confirmation of Jerne's network theory has not been sufficient. In this paper we argue that Jerne's network theory is not able to explain the mechanism behind self-nonself discrimination, what our holistic paradigm is (10).

Jerne's network model

Jerne (1) at first defined a few concepts: the antigen determinant he called the epiotope, and the antibody combining site he called the paratope. Each individual antibody molecule carries a specific paratope, but also a number of its own specific determinants that under specific circumstances are able to give an immune response. These are situated at the variable part and are called idiotopes (idios = self). Jerne assumes that the existence of identical paratopes not necessarily means that the two antibodies have the same idiotopes. He furthermore assumes that each antibody recognizes through its paratope and is recognized through all its idiotopes.

Jerne emphasized, that the resulting network implies both free and cell bound Ig, why the B-cells are involved. He mentioned that Myeloma Ig gives idiotypespecific tolerance, when it is administered untreated in a mouse, while the polymerised or modified Myeloma Ig gives anti-idiotypic antibody response. From this he concludes, that the B-lymphocyte can react with response or with tolerance at the Ig (this is not a logical consequence but seems very reasonable). He further mentions, that most of the experiments suggest that B-cells become suppressed, when a paratope of an alien Ig finds an idiotope at the B-cell (but the evidence seems weak). Finally, Jerne (1) emphasized the importance of suppression: "I have become increasingly convinced of its lymphocytes", he wrote.

Experiments with tolerance induction show that a cell also can become suppressed when it meets the specific epiotope for which it has a paratope, wherefore the inhibiting forces in the network seem to outdo the activating forces. Jerne imagined a dynamic equilibrium, where the immune cells through inhibition are prevented from working, except when they are needed. Jerne mentioned the problem of low-dose tolerance and wrote that the concentration of Ig-idiotopes maybe exceed the threshold of low-dose tolerance. The low-dose interval, however, seemed to be 106-1012 epitopes pr. ml., while the average of Ig-idiotopes taken as an average of some millions, is about 1010. This value should furthermore be adjusted in a downward direction for the peaks of specific Ig's formed in connection with an immune response. Thereby the idiotopes seem to fall within the low-dose tolerance interval. From this we conclude that the immune system has an eigen-behaviour and constantly reacts towards itself.

In figure 1 for each Ig plotted a paratope (P) and an idiotope (I) are also. P(Ig1) (also referred to as AB1 below) recognizes the antigen (E) (left). But, at the same time, the paratope P(Ig1) fits to an idiotope I(Ig2) on the Ig2. P(Ig1) have its own idiotope I(Ig1) that is recognized on P(Ig3). To a stranger epitope E, a set of Ig's (P-I) exists with different affinity.

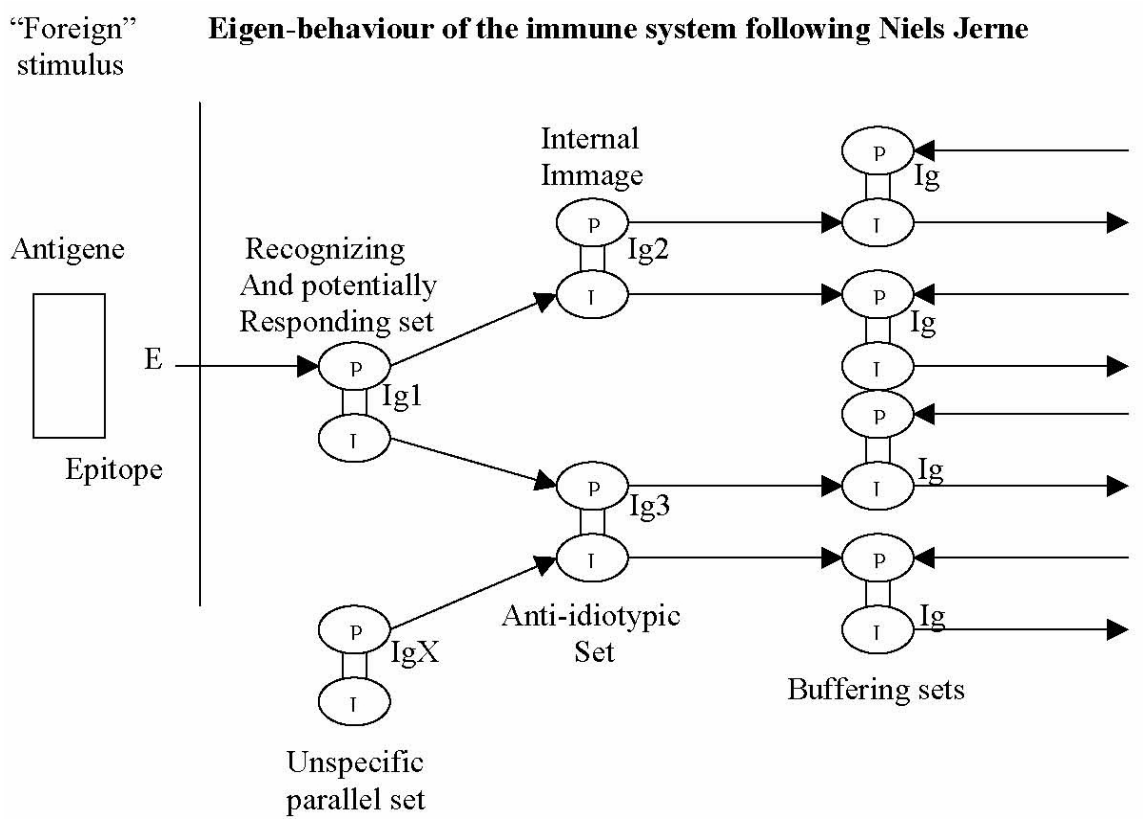

Figure 1. A model of Niels Jerne's immunological network modified from (1). For each Ig a paratope (P) and an idiotope (I) are plotted. P(Ig1) recognizes the antigen (E). The paratope P(Ig1) fits to an idiotope I(Ig2) on the Ig2. P(Ig1) have its own idiotope I(Ig1) that is recognized on P(Ig3). To a foreign epitope E, a set of Ig's (P-I) exists with different affinity produced through an immune response. A modification of Jerne [1] (figure 7).

These affinities can be produced through an immune response. They recognize a great amount of idiotopes said to be the E's "inner picture". These Ig's have a huge amount of idiotopes (I's) that are recognized by an extended set of paratopes (P's).

Jerne argued that the inner picture may have the same effect as the presentation of an outer antigen, and therefore may stimulate the B-lymphocytes. The extended set that recognizes the Ig-idiotopes, on the other hand, should be inhibiting. However, the immune system is after this in a stage of extended suppression that has to be overcome through an outside stimulus, the antigen. This may be the first step in an immune response and may correspond to a suddenly miss of AB1, because this then, is tied to the antigen. This leads to absence of inhibition on a part of the inside picture, that has to be activated to give an increased response. Simultaneously, the Ig's that were stimulated by inhibiting the AB1 should be further inhibited by now. Following Jerne, this should stimulate the immune response against the foreign antigen. Another set that inhibited this set, should be inhibited itself, etc. etc.. The activated inner picture, have an inner picture itself that have to be activated, etc. etc.

After this the strengthened inner picture uninhibited provoke an activation (and propagation?) of AB1-cells that may soon exist in huge amounts. Jerne thought that this reinforcement would tend against counteracting the mentioned avalanche in such way that the network attempts to regain its balance. But we ask how this should be able to happen. The enforcement has exactly come through as a consequence of the unbalance in the system. So, will it be able to bring it in balance again? We do not think so. Analogically, this could be compared to a man that, to find the balance again, grabs the stone he caused to unbalance and just has lost. However, Jerne criticizes his own hypothesis for lack of precision, and admitted that it is not clear what elements that are activated, and which that are inhibited, and why.

Discussion

Does a regulatory, idiotypical network as Jerne's exist? According to our theoretical discussion, it is clear that such a network even if it regulates the ordinary immune response, not is able to make the choice of self-nonself discrimination because it is not perfect since it is able to exclude parts of itself. We think that such network can hardly be expanded to include T-cells. It may be considered which expansions that are theoretically possible. Can the idiotypical network be expanded also to include the lymphocytes with T-cell receptors? The common opinion is yes, but we predict that such expansion would lead to big problems caused by the difference between Ig- (among others) and the T-cell receptor, because the T-cell receptor has a much smaller affinity. But also specially grounded the MHC-restriction. Furthermore, the problem that all information is distributed between cells could be an obstruction for the expansion with T-cells. Because Th- and Tc-cells seem not to communicate directly, the network may happen inside the Th-cell population alone. On the other hand, these cells operate as if they were primed and not as if they were functionally suppressed and only wait for escaping their neighbours to be able to break out in full activity. This means that systemic information cannot be excluded because this seems to be a condition for priming.

The T-cell receptor does not seem to function as if it recognizes idiotypes on other T-cell receptors but as if it read an antigen-determinant in a MHC-site. If this is the case, an idiotypic network can be excluded unless also the T-cell receptors are represented in these sites. But we think this is unlikely. However, a problem is that even if the network on the T-cell level is a system that functions and makes choices, it does not seem to be an idiotypical specific network.

Evidence for the existence of Jerne's network does not seem overwhelming. Holmberg et al (11) thought to have the first direct indication of the existence of a formal idiotypical network. But, everything they have shown is as far we can see that antibodies can react mutually, in a broad way of understanding. This is also the condition of the existence of such a network, but if this network really existed, this would not be enough to confirm if the network has the immunological function as supposed by Jerne. His network is not yet supported by existing data. On the other hand, evidence against Jerne's network exists. As mentioned in the section on the self-Ig's theoretical status of immune response, these are induced by tolerance concerning dose, size, self-nonself status, administration route, and untreated Myeloma-Ig gives a specific idiotype tolerance. Other experiments have shown that antibodies first are able to give an immune response if they are given together with an adjuvant, or if they are tied to an immunogenic molecule (9). This could be the best evidence against Jerne's network theory – it is unlikely that the immune system at all will react on the idiotypes through normal conditions.

In experiments using ongoing (un-physiologic) immunizing, anti-idiotypic antibodies have been formed, but the anti-AB is first created after culmination of the AB's one month later (12). Also idiotype specific antibodies without previous immunizing are identified in vivo. Especially in connection with auto-immunity as the idiotypical antibodies are proposed to regulate (13,14). On the other hand, it can also be the ongoing presence of Ig's that gradually triggers its own immune response analogue to the experiment described below.

In germ free environments the Ig concentration is found to be extremely low (9). This alone, seems to exclude that an idiotypic network should direct the immune system, because such a direction presupposes that the net is present before the release of antigens.

When animals are repeatedly immunized with antibodies the AB1's are first created, then AB2 against AB1, so AB3 against AB2, and AB4 against AB3 etc., then AB3 imitates AB1, and AB2 imitate AB4 (9). This is in contradiction with the idiotypic network that predicts a branch that is able to realize the network. The experiments indicate that the paratope is the most preferred goal for an immune response. If this is the case, it makes the future antibodies insignificant concerning the immune response, simply because AB2 is a copy of the original antigen epitope.

Experiments indicate that everything happening concerning the formation and activation of the immune cells is antigen dependent. According to the network theory this should be net-regulated (9). Many examples exist where anti-idiotypic antibodies alone, have stimulating or inhibiting effects (9). But these

effects can easily be understood if it is assumed that they have exactly the same configuration in the paratope as the original antigenic epitope – in this way the ordinary possibilities for antigenic-response and tolerance-induction appear.

The idiotypical network, apparently, is without experimental evidence and cannot explain the self-nonself discrimination. The only possibility left is to keep going with the remnants and modify the network theory so profoundly that it no longer has any similarities with its beginning point. This has been tried (9,15), but apparently, not with any further luck. As said by Schrödinger "he, that seeks the truth, has to guard himself from ad hoc modifications".

Other previous attempts to make immune regulation happen on the level of organisms (16,17), and seem not very successful. The biggest problem concerning Jerne's network theory is that any useable alternatives do not exist in the literature because people reluctantly reject the existing fundament for the theory if no better has arisen.

Conclusion

Jerne criticizes his own hypothesis for lack of precision and admits that it is not clear what elements are activated, and which are inhibited. It seems to be a very bad procedure to change a construction shown not to be in agreement with the experimental facts in fundamental and central fields because it is not obvious that such a network exists. We conclude that no experimental evidence exist for the network theory of Jerne and think that his theory is not able to explain self-nonself discrimination because the immune system apparently not is regulated through an idiotypical network. We also conclude that a network like Jerne's is not able to make the choice of self-nonself discrimination since it is not complete, and we think that it is not plausible to expand it to include the T-cells. We predict that such an expansion would lead to big problems caused by the difference between Ig- and the T-cell receptors.

Some experiments show that antibodies only are able to give an immune reaction together with adjuvants or are tied to an immunogenic molecule. This could be the best evidence against Jernes network theory – it is unlikely that the immune system will react at all to the idiotypes under normal conditions. Because idiotopes seem to fall within the interval of low-dose tolerance we conclude that the immune system has an eigen-behaviour and constantly reacts towards itself.

Acknowledgements

These studies were supported by grants from IMK Almene Fond. Our research in quality of life has been approved by the Copenhagen Scientific Ethical Committee under number (KF)V.100.2123/91.

References

[1] Jerne NK. Towards a network theory of the immune system. Ann. Immunel. (inst. Pasteur) 1974;125C:373-89.

[2] Jerne NK. Idiotypic network and other preconceived ideas. Immunol Rev 1984;79:5-24.

[3] Langman RE, Cohn C. The "complete" idiotype network is an absurd immune system. Immunol Today 1986;7(4):100-1.

[4] Cohn M. Foreword: clippings from one immunologist's journal. In: Langman, RE, ed. The immune system. San Diego, CA: Academic Press, 1989.

[5] Podolsky S, Tauber A. The generation of diversity. Harvard: Harvard Univ Press, 1997.

[6] Paul WE. Fundamental immunelogy. New York: Raven, 1984.

[7] Slaoui M, Urbain-Vansanten G, Demeur C, Leo O, Marvel J, et al. Idiotypic games within the Immune network. Immunol Rev 1986;90:73-91.

[8] KohIer H. Internal antigen and immune network. Proc Soc Exp Biol Med 1985;178(2):189-95.

[9] Klein J. Natural history of the major histocompability complex. New York: John Wiley, 1986.

[10] Ventegodt S, Hermansen TD, Flensborg-Madsen T, Rald E, Nielsen, ML, Merrick J. Human development VII: A spiral fractal model of fine structure of physical energy could explain central aspects of biological information, biological organisation, and biological creativity. ScientificWorldJournal 2006;6:1434-40.

[11] Holmberg D, Holmberg D, Forsgren S, Ivars F, Coutinho A. Reactions among IgM antibodies derived from normal, neonatal mice. Eur J Immunol 1984;14:435-41.

[12] Roitt I, Brostoff J, Male D. Immunology. London: Gower Med Publ, 1985.

[13] Abdou N. The idiotype-antiidiotype network in human autoimmunity. J Clin Immunol 1985;5(6):365-9.

[14] Zanetti M. Idiotypic regulation of autoantibody production. Crit Rev Immunol 1986;6(2):751-3.

[15] Urbain J, Urbain J, Brait M, Bruyns C, Demeur C, et al. The idiotypic network: Order from the beginning or order out of chaos? Curr Top Microbiol Immunol 1985;119:127-42.

[16] Vas NM, Varela FJ. Self and non-sense: An organism¬-centered approach to immunelogy. Med Hypotheses 1978;4:231-67.

[17] Coutinho A, Forni L, Holmberg D, Ivars F, Vas N. From an antigen-centered, clonal perspective of immune responses to an organism-centered, network perspec¬tive of autonomous activity in a self-referential immun system. Immunol Rev 1984;79:151-68.

Submitted: March 05, 2008.
Revised: June 19, 2008.
Accepted: June 29, 2008.