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The Network Concept and Leukemia

K. Eichmann

Network regulation undoubtedly represents a major mechanism for the maintenance of steady states in the immune system. This is brought out by a large body of experimental evidence suggesting that every antigen-specific element in the immune system – antibody, soluble mediator, or lymphocyte – has its anti-idiotypic counterpart. Thus, the immune system is constructed as a series of idiotypic and anti-idiotypic compartments that regulate one another. The nature of regulation is determined by the effector functions of the antigen-specific elements in each compartment.

Since idiotypic connection is used as a major pathway for the delivery of regulatory signals, it is not surprising that idiotypic or anti-idiotypic reagents are particularly powerful means to artificially manipulate the immune system. A large body of experimental results suggests that with idiotypic and anti-idiotypic antibodies dramatic and persistant changes in immune reactivity can be induced. Furthermore, by choice of the class of antibody changes can be induced such that particular effector functions are altered, whereas others are left untouched. This is in contrast to immune manipulation by antigens and other means in which changes of the immune status are difficult to control.

What this have to do with leukemia? There are at least two ways in which the network concept could become relevant to leukemia. Firstly, one has to consider the possibility that unbalances in network control make certain lymphocytes particularly susceptible to neoplastic transformation. Examples of this appear to be certain groups of mouse myelomas, for example, those with antiphosphorylcholine specificity and T 15 idiotype. These myelomas are found in the collection of Balb/c myelomas at a much greater frequency than would be expected if specificities were randomly distributed. The high frequency of phosphorylcholine specific myelomas is reflected in the normal lymphocyte population of Balb/c mice, and evidence is accumulating at present that this overrepresentation is due to a network unbalance. Thus, network unbalances may be cofactors in neoplastic transformation of lymphocytes.

A second area in which the network concept touches on leukemia relates to therapy. The present state of technology clearly suggests a novel strategy for specific immune therapy of leukemia: normal T cells should be recovered from patients with leukemia and restimulated in vitro with leukemic cells from the same patient. The methods for restimulation should be worked out such that a high proportion of cytotoxic T cells with specificity for idiotypic determinants on the leukemic cells arise. Such cytotoxic cells have been clearly identified by experimentation and their very special property is that they appear to be *functional in vivo*. Cytotoxic cells of all other specificities have been shown to be somehow suppressed in the in vivo situation. Thus, anti-idiotypic cytotoxicity may be the only cytotoxicity that can be exploited to kill neoplastic cells in vivo. After restimulation these cytotoxic cells should then be grown up to large quantities using TCGF technology and reinjected into the same patient.

A further relevant aspect of the network concept is that it reveals any nonspecific manipulation of the immune system to be worthless. Since the immune system is perfectly balanced through idiotypic interactions between its antigen-specific elements, only antigen-specific measures can be expected to

disturb this balance in the direction of the generation of disired effector functions. Non-specific manipulation, such as the so-called immune therapy, can at best change the absolute level of the balance with no functional consequence whatsoever.

Taken together, thinking along the lines of the network concept may open new approaches to the role of immunity in neoplastic diseases. The overall discouraging results from pervious clinical and experimental experience may have been due to our ignorance or negligence of certain basic principles in the way the immune system functions.

Reviews

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