NEW BIOMEDICAL TECHNOLOGIES

The Use of the Neuronal Net Model Based on Immunological Parameters for Predicting Cancer

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The significance of immunological parameters for the prognosis of prostatic cancer is analyzed using a model of a neuronal net based on combinatorial and geometrical principles. Groups of patients with prostatic cancer with favorable and unfavorable prognosis, with and without metastases, have specific spaces for changes in immunological parameters. By immunological parameters these groups are differentiated from each other and from healthy subjects and patients with prostatitis, prostatic adenoma, and their combinations.

Key Words: *cancer prediction; neuronal net model; prostatic cancer*

The search for prognostic signs of cancer (PSC) of various organs is an important task, since such signs help to properly select therapy and prevent progression of the disease. Although the addition of new molecular biological parameters, which directly or indirectly characterize differentiation, growth rate, and invasiveness of a tumor, to the classical PSC (tumor size, lymph node status, and tumor histology) have provided a better understanding of oncogenesis, the problem of revealing new PSC still remains.

The definition of PSC as a factor associated with the biological characteristics of a tumor that determine its progression and capable of providing information regarding the disease outcome [3,5] is inappropriate, because it is based only on the characteristics of the tumor and ignores the role of the host in the development of the disease.

The characteristics of the host defense system, including the immune system parameters, should be regarded as equivalent candidates for PSC. This requires no special validation and can hardly be disputed. Based on analysis of the immune system parameters, we attempted to predict the progression of cancer and effectiveness of its therapy with the use a neuronal net model.

MATERIALS AND METHODS

The approach is based on expressing the immunological parameters (IP) of normal subjects and patients with cancer of a certain organ as nonoverlapping multidimensional multitudes with due consideration for the great range of values even in health and the long list of parameters. When the convex envelopes for these multitudes are constructed, they can be used for prognosis. With this in mind we used a CORTEX model of the neuronal net, which allows the detection and classification of the slightest interchanges in a great number of examined parameters.

A simple crude architecture of animal cerebral cortex underlies the topology of the CORTEX nodes. Figure 1 is a scheme of CORTEX with three levels (input, output, and block of intermediate layers) and a selective attention module. The intermediate layer nodes are connected with each other within a single

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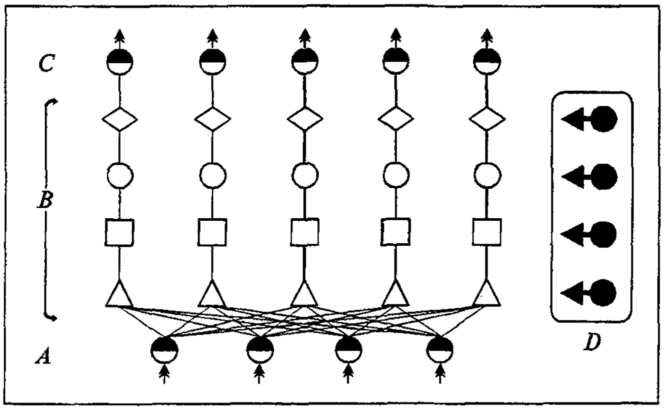

Fig. 1. Scheme of nodes in the CORTEX. *A*) input level; *B*) block of intermediate layers; *C*) output level; *D*) selective attention module. Relationships between the nodes are shown only for the successive computation mode.

column and with the input and output nodes and function independently. The columns in the intermediate layer block represent structural and functional units for transforming the input information, and their number N is the number of object classes singled out by researcher. The maximum number of nodes per column (or levels in the block of intermediate layers) is equal to the number n of input parameters characterizing the objects. On the scheme, the nodes of one layer are shown as the same patterns symbolizing the common type of transforming the input information in this layer and its changes in the hierarchy of the levels.

The column completely transforms the input information from n levels and analyzes it. The ordered totality of the products of parameters in (r/n) combinations represents the parameters of objects at each level, where n is the number of input parameters, and r the order of the node in the column (counted upwards), varying from 1 to n. Each r is associated with its own sum of combinations with the constant number of signs, and hence, for each node of the column an object is described through new (in their number and values) parameters, and at the first level the objects are described by the input parameters. In the case where $n>3$ at the second level of description, the values of the object's characteristics are increased at least twofold in comparison with the initial number of parameters, which is useful and important to attain nonoverlapping convex multitudes occupied by each class of objects. These new parameters of the objects, being hidden in the CORTEX intermediate layers, more precisely describe the objects.

In addition to transformation of the initial information in accordance with the combinatorial rule for the level (r level) in which they are located, the nodes in a column make the convex envelope for the training sample of objects of a class and for "filtration" of the needed objects through this convex envelope. If the object with transformed parameters belongs to a multidimensional multitude, limited by convex envelope plotted by the node, it is released to the output level, i.e., it is identified. Each node of the output layer represents only one class and is connected only with the column filtering the objects of this class only.

CORTEX may operate in the training and autotraining mode. Let us analyze the first regime, as a simpler one. The idea of recognition is based on positioning the classes of objects in convex multidimensional multitudes; therefore, two situations are possible: multitudes of different classes intersect or not. The second situation appears to be ideal, and hierarchical processing of input information used by CORTEX is aimed at attaining it. If as a result of CORTEX training the objects of each class in the corresponding columns have a convex multitude not intersecting within the layer at at least one node and the new analyzed object belongs to one of such a multitude, this new object is identified as belonging to the class occupying this convex multitude. The selective attention module is intended for detecting the first of such multitudes (node) and arrest of further computations for this object. In alternative cases an appropriate voting strategy is used.

To demonstrate the prediction of cancer development and effectiveness of its therapy, we used the published clinical data on prostatic adenoma and cancer [1,2] kindly provided by Dr. V. A. Savinov. Among the characteristics of the immune systems of patients and healthy controls were the concentrations of immunoglobulins A, M, and G, circulating leukocytes and lymphocytes and their ratios, and functional parameters of their response to stimulation. The IP of patients with prostatic diseases (adenoma, cancer, prostatitis, and their combinations) were comparable. The number of patients in the groups varied from 28 to 163. The control group consisted of 35 subjects. The model of CORTEX neuronal net was realized in the successive computations mode using C++.

RESULTS

The diagnostic validity of the laboratory data is often low because of their unspecificity and wide range even in health. Immunological parameters are phone to circadian fluctuations and age-related changes. A multidimensional description of the immune system (more than 20 characteristics were used in our study) showed that each group of patients and normal subjects could be clearly distinguished by its nonintersecting multidimensional multitude of combinations of IP changes. We tested our model in predicting prostatic cancer because the available clinical data permitted a paired comparison and demonstrated that multidimensional description of the immune system helps detect the slight interrelated changes in IP.

Specifically, groups of patients with prostatic cancer with favorable and unfavorable prognoses, with and without metastases, had special spaces of IP changes, and by the totality of IP these groups could be differentiated from each other and from groups of normal subjects and patients with prostatitis or prostatic adenoma or combinations thereof.

The IP of patients with prostatic cancer treated by immunocorrecting drugs were used to check whether effective therapy changed IP so that they "migrated" into another multidimensional multitude. Comparison of IP in patients with prostatic cancer before and after administration of BCG vaccine or placental suspension showed that both agents "transformed" IP in the patients into other multidimensional multitudes, causing improvement of clinical status and suppressing tumor development. It has been demonstrated for prostatic cancer that the model of the neuronal net permits the use of IP for predicting the course of the disease and results of its therapy.

The sum of IP can be characterized as a system or PSC, with which the complex of evaluation criteria required from PSC may be attained [1,2]. The system of IP does not contradict the PSC associated with biological characteristics of a tumor but supplements them by reflecting the degree of host defense against a developing tumor and the effectiveness of therapy. In future, with the development of molecular immunotherapy (for example, drug targeting or injection of lymphocytes loaded with genes coding for the cytokines triggering the antitumor reactions) the significance of IP as a PSC system will increase and, probably, the IP system will surpass the PSC associated with the biological characteristics of a tumor, because by the methods of molecular immunotherapy it is possible to block the development of cancer even at its late stages, and the assessment of the immune status will be most important.

Among the advantages of IP is the possibility of their accurate quantitative description, which permits wide use of methods of man-made intellect for deriving new valuable information from IP system without resorting to additional experimental studies. It is due to these features that methods of man-made intellect, specifically, the neuronal net models, are widely used in theory and practice [4].

The results of using IP as a system of PSC should be regarded only as preliminary and a stimulus for their active use in oncology with a greater clinical database. This is quite possible within the framework of international oncological programs.

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