

## Simulation of the Interferon-Mediated Protective Field in Lymphoid Organs with Their Spatial and Functional Organization Taken into Consideration

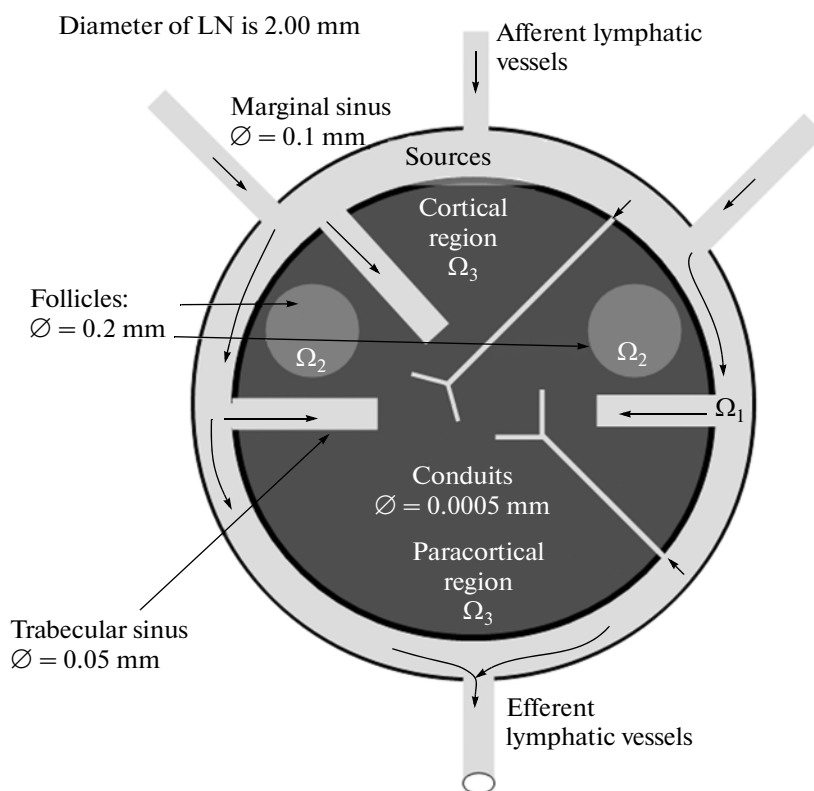
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The development of antiviral immune responses occurs in the lymph nodes (LNs) that drain the affected organ and in other secondary lymphoid organs [1]. The three-dimensional structural and

functional organization of the LNs meets the task of maintaining the optimal conditions for the development of immune responses. In particular, in the LNs, viruses interact with the antigen presenting cells



**Fig. 1.** The biological scheme of the structural and functional organization of the LN. The main areas represented at the scheme are related to the marginal sinus and conduits ( $\Omega_1$  region), B-cell follicles ( $\Omega_2$  region), and T-cell cortical and paracortical regions ( $\Omega_3$  region).

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(APCs), which is followed by presentation of viral antigens to T lymphocytes of the corresponding specificity for recognition. This function is performed by macrophages and conventional dendritic cells. Their protection against cytopathic viruses before the antigen-specific immune response is provided by interferon alpha (IFN- $\alpha$ ) secreted by the plasmacytoid dendritic cells (pDCs).

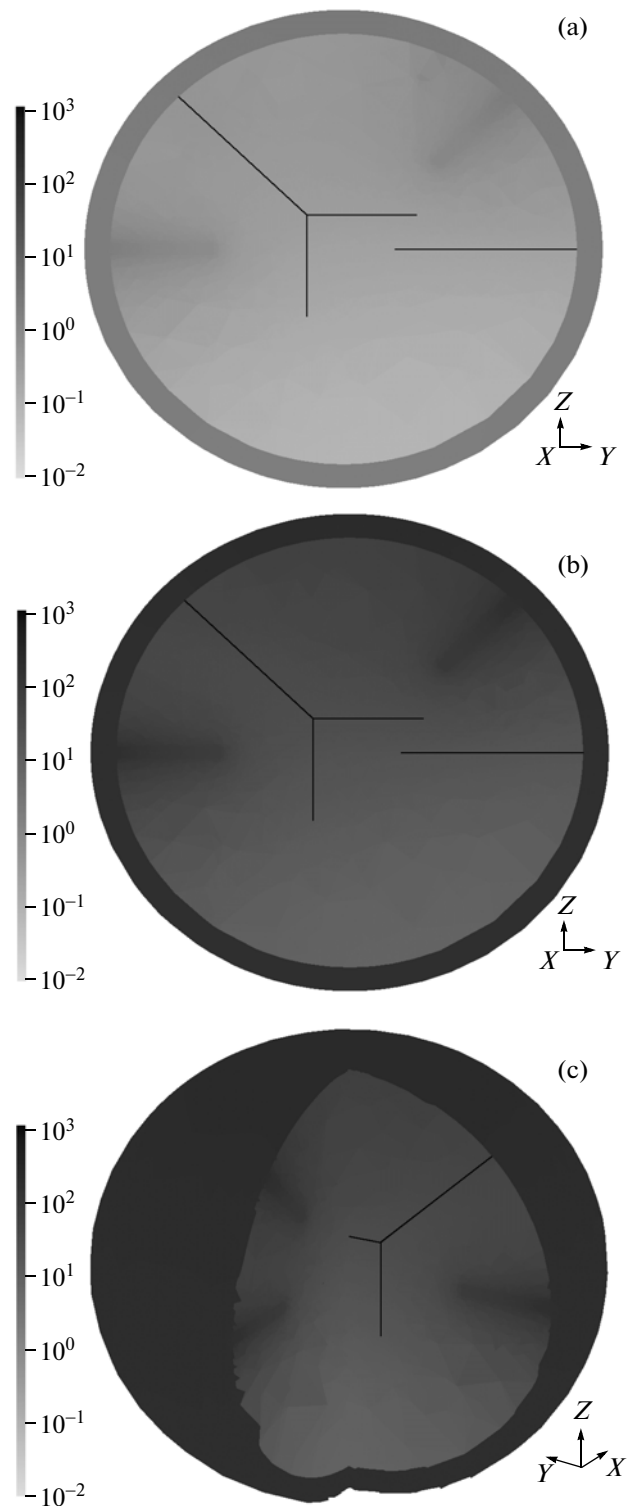
The systemic analysis of the kinetics of an experimental coronavirus infection in mice [2] allowed us to estimate the key kinetic parameters for the reaction of activation and synthesis of IFN- $\alpha$  in response to the coronavirus infection in mouse macrophages and pDCs. In addition, it is predicted that the local concentrations of IFN- $\alpha$  that provide the antiviral protection of macrophages and pDCs are 1 and 45 pg/ml, respectively. However, the empirical analysis cannot provide the information about the particularities of the spatial distribution of interferon in the lymphoid organs in accordance with their structural organization. The only method to study this fundamental aspect of antiviral protection is mathematical simulation that takes into account the three-dimensional architecture of the organs and the diffusion of the humoral factors in their subareas.

To study the stationary distribution of IFN- $\alpha$  in the LN, we used a stationary reaction-diffusion equation for the concentration of IFN- $\alpha$  ( $c(\mathbf{x})$ ); for details, see [3, 4]:

$$-D_i \left( \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) c(\mathbf{x}) + \alpha c(\mathbf{x}) = \sum_{k=1}^M F_k(\mathbf{x}),$$

where  $x \in \Omega_i$ ,  $D_i$  is the diffusion coefficient of IFN- $\alpha$  in the corresponding region  $\Omega_i$ ,  $i = 1, 2, 3$  (all the regions are determined below),  $\alpha$  is the degradation rate of IFN- $\alpha$ . The summand to the right is related to the synthesis of IFN- $\alpha$  by the population of pDCs,  $M$  being the population size. According to [2], the rate of synthesis of interferon by one activated dendritic cell is  $4.4 \times 10^{-4}$  pg/h and the degradation rate of IFN- $\alpha$  is 0.012 1/h. The basic value of  $1.6 \times 10^{-1}$  mm<sup>2</sup>/h, which characterizes the diffusion of myoglobin molecules with approximately the same molecular weight as that of IFN- $\alpha$  [5], was taken as an estimate for the diffusion coefficient of IFN- $\alpha$ .

Although the morphology of LNs is very complicated [1], taking into consideration the function, we may present the generalized structure of the LN based on the concept of basic blocks (Fig. 1) [6]. The macrophages and dendritic cells are located in the regions of the marginal sinus ( $\Omega_1$ ) under the afferent lymphatic vessels, through which these cells and viruses enter the LN. Then, APCs move to the cortical zone, where they perform their function of induction of antigen-specific immune responses. The regions of a LN that contain T lymphocytes (the cortical and paracortical zones or the  $\Omega_3$  region) are characterized by weak molecular diffusion, which is associated with



**Fig. 2.** Simulation of the stationary distribution of IFN- $\alpha$  in the LN with different amounts of pDCs. The scale of a palette characterizes the concentration of IFN- $\alpha$  in pg/mm<sup>3</sup> ( $10^3$  pg/ml). (a)  $10^2$  pDCs synthesize IFN- $\alpha$ ; (b)  $10^4$  cells synthesize IFN- $\alpha$ ; (c) the regions in which the concentration of interferon is close to the threshold for the protective effect of macrophages (1 pg/ml) in the case of  $10^4$  cells.

poor hydraulic conductivity [7]. Taking this into account, we assume that the diffusion coefficient for the  $\Omega_3$  region is lower by two orders of magnitude than the above mentioned estimation for the  $\Omega_1$  region. The region of lymphoid follicles ( $\Omega_2$ ), which contains B lymphocytes, is intermediate in terms of diffusion processes. Therefore, we assume that the diffusion coefficient for the  $\Omega_2$  region is by one order of magnitude smaller than the baseline one. Since IFN- $\alpha$  has a low molecular weight, the diffusion coefficient in the system of conduits is the same as in the sinusoidal area. The simulation of stationary distribution of IFN- $\alpha$  created by  $10^2$  and  $10^4$  activated pDCs arranged at random, mainly in the upper part of the  $\Omega_1$  region in the LN is shown in Figs. 2a, 2b. The numerical solution for the model predicts that the variation of concentration of IFN- $\alpha$  within the LN is two orders of magnitude, i.e., the compartmentalization of the cytokine occurs due to the diffusion. The inner regions of the LN, where the concentration of IFN- $\alpha$  is close to the threshold concentration of 1 pg/ml with a number of activated pDCs of about  $10^4$  are shown in Fig. 2c.

In this work, the specifics of spatial distribution of IFN- $\alpha$  have been first studied using a mathematical model with the processes of diffusion-reaction and the three-dimensional structural and functional organization of the LN taken into account. It has been shown that the distribution is heterogeneous. There are well-protected areas, such as sinuses and conduits, and the areas where the relative concentration of interferon is decreased by one (follicles) or two (cortical area) orders of magnitude. An up-to-date software package for simulating the stationary distribution of interferon in the LN has been developed. The package includes the following components: the Open CASCADE (<http://www.opencascade.org>) computer-aided design system (CAD); a package of libraries for creation of tetrahedral grids Ani3D [8]; the program for creating CAD models in Open CASCADE and for building a computational grid; a package of libraries MSTK for operating with multidimensional grids; a program for numerical solution of the stationary reaction-diffusion equation [9]; and the GMV program for data visualization [4].

The results of the study allow us to put forward a hypothesis on the process of establishment of viral persistence which is related to the heterogeneity of

spatial distribution of IFN- $\alpha$ . The morphology of secondary lymphoid organs can lead to the formation of poorly protected areas. In these areas, the localization of the cells infected by viruses, such as CD4<sup>+</sup> T lymphocytes in the case of HIV infection or macrophages provides the conditions for the continuation of active infectious processes. The ability of activated pDCs to suppress HIV replication in CD4<sup>+</sup> T lymphocytes, which is related to the synthesis of interferon, has been shown experimentally [10].

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