THE SEARCH FOR COMPOUNDS TO PREVENT THE CONSEQUENCES OF A CYTOKINE STORM

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The cytokine release syndrome in severe COVID-19 has been documented in many studies. The main pathological role in the development of respiratory distress syndrome, apparently, belongs to IL-6, which is secreted by hyperactivated macrophages. The resulting cytokine storm circulates in other organs and results in multiple organ damage. The aim of this work is to search for substances that reduce the manifestations of the cytokine storm among the newly synthesized compounds.

At the first stage, *in silico*, we built a consensus network model of the effect of new substances on lipopolysaccharide (LPS) intoxication in the IT Microcosm and Statistica programs using supercomputer technology. The formed ensemble of decision rules was used to predict the LPS inhibitory activity of new compounds synthesized by the members of the scientific consortium.

The key mechanism for the development of the cytokine release syndrome is proinflammatory activation (M1 polarization) of macrophages, which was simulated *in vitro* by stimulation of the pool of activated peritoneal macrophages in mice by stimulation of TLR4 receptors with *E. coli* LPS. Several compounds have been identified that suppress the release of cytokines. Prevention of macrophage activation is also confirmed morphologically – compounds, similar to dexamethasone, inhibit the formation of spread forms and pseudopodia of macrophages.

To reproduce the complications characteristic of the severe course of bacterial and viral lung infections, a model of acute lung injury in mice with oropharyngeal administration of LPS was adjusted. In the «Open Field» test, mice from the LPS groups showed a pronounced decrease in motor activity, lethargy, and sedation. The effect of LPS on the motor and behavioral state of animals is reduced by the action of dexamethasone. Analysis of neuroinflammation using electrophysiological studies has shown that LPS causes an increase in low-frequency power, in particular delta power, associated with changes in sleep. Oropharyngeal administration of LPS led to a pronounced increase in the lung permeability index compared to the intact group, while prophylactic dexamethasone administration reduced the permeability of the pulmonary capillaries.

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