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INFLUENCE OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME ON THE DEVELOPMENT OF OXIDATIVE STRESS DURING SIMULATION OF CHRONIC ALCOHOL INTOXICATION IN RATS

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Sepsis is an important predictor of mortality among patients with alcoholic liver disease. About 60% of patients with alcoholic hepatitis have signs of systemic inflammatory response syndrome (SIRS) [1]. Increased susceptibility to bacterial infections in patients with severe alcoholic hepatitis is due to endotoxin-induced inhibition of neutrophils and lymphocytes [2]. Another important pathogenetic mechanism for the development of complications of alcoholic hepatitis is the penetration of lipopolysaccharide (LPS) through the intestinal barrier [3]. LPS through TLR4-dependent cascade stimulates Kupffer cells to release reactive oxygen species and a number of pro-inflammatory cytokines [4]. Ethanol metabolism also leads to the formation of reactive oxygen species. Chronic alcohol abuse and LPS can lead to free radical liver damage, but the question of their combined effects on the liver remains unclear.

The *aim* of our study was to analyze changes in the development of oxidative stress in the liver of rats with chronic alcohol intoxication against the background of systemic inflammatory response

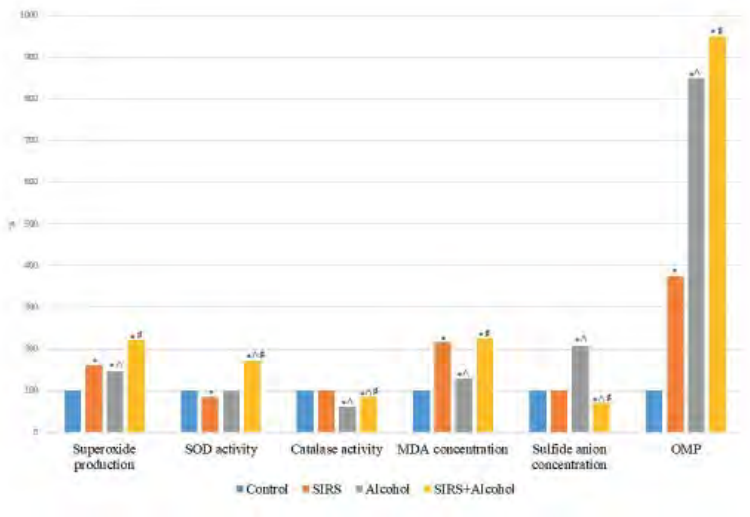

Fig. **Changes in the liver of rats under the conditions of modeling alcohol intoxication on the background of systemic inflammatory response syndrome**

* — $P < 0.05$ in comparison to the control group, ^ — $P < 0.05$ in comparison to the SIRS group, # — $P < 0.05$ in comparison to the alcohol group.

syndrome based on the study of catalase and superoxide dismutase activity, concentration of malonic dialdehyde, oxidatively modified proteins and sulfide anion and superoxide anion production.

Methods. Experimental studies were performed on 12 male Wistar rats weighing 180–220 g. Animals were divided into two groups: 1 — control and 2 — animals, on which we simulated alcoholic hepatitis and SIRS [4]. The activity of catalase (Korolyuk MA, 1988) and superoxide dismutase (SOD) (Brusov OS, 1976), the concentration of malonic dialdehyde (MDA) (Gérard-Monnier D, 1998), oxidatively modified proteins (OMP) (Dubinina OY, 2001), sulfide anion (Sugahara S, 2016) and superoxide anion production were studied in the rat liver homogenate (Kostenko VO, 2000). The obtained results were subjected to statistical processing using the Mann-Whitney test.

Results. Analyzing the development of oxidative stress in the liver of rats, on which we simulated the combined effects of SIRS and prolonged alcohol intoxication, we found that the activity of SOD increased by 1.72 times ($P < 0.05$), and catalase decreased by 1.18 times ($P < 0.05$) compared with the control group (Figure). The production of superoxide anion radical in the liver of rats increased 2.21 times ($P < 0.05$) in the group of animals with combined exposure to bacterial LPS and alcohol intoxication compared to control. The concentration of MDA increased 2.25 times ($P < 0.05$), and OMP by 9.5 times ($P < 0.05$) compared with control group. The concentration of sulfide anion in the liver of rats under the conditions of modeling the combined effects of SIRS and alcohol intoxication decreased by 1.44 times ($P < 0.05$) compared with the control.

Discussion. Stimulation of rat organism with bacterial LPS on the background of excessive alcohol intake leads to increase of superoxide production against the background of antiradical protection imbalance, accompanied by lipid peroxidation and oxidation of proteins.

Hydrogen peroxide, which is excessively formed under the action of SOD and is not completely utilized by catalase, reacts with ions of metals of variable valence, forming highly reactive hydroxyl radicals, which are powerful initiators of lipid peroxidation. Lipid peroxidation is the most important reaction involved in alcohol-induced liver damage through the formation of toxic aldehydes, including MDA. Acetaldehyde is also able to promote the formation of cross-links between DNA strands and create links between proteins and DNA, which causes replication and mutation errors in oncogenes or oncosuppressor genes with genotoxic, mutagenic and carcinogenic effects [3]. Given the powerful antioxidant properties of sulfide anion, a decrease in its concentration under the combined effects of chronic alcohol intoxication and stimulation of the organism with LPS may indicate depletion of the antioxidant potential of the liver.

Conclusions. Modeling of alcohol intoxication against the background of systemic inflammatory response syndrome leads to oxidative damage to lipid and protein structures of the liver due to increased production of superoxide anion radical and imbalance of antiradical protection.

Key words: alcoholic hepatitis, systemic inflammatory response syndrome, oxidative stress.

The authors state that they have no conflict of interest.

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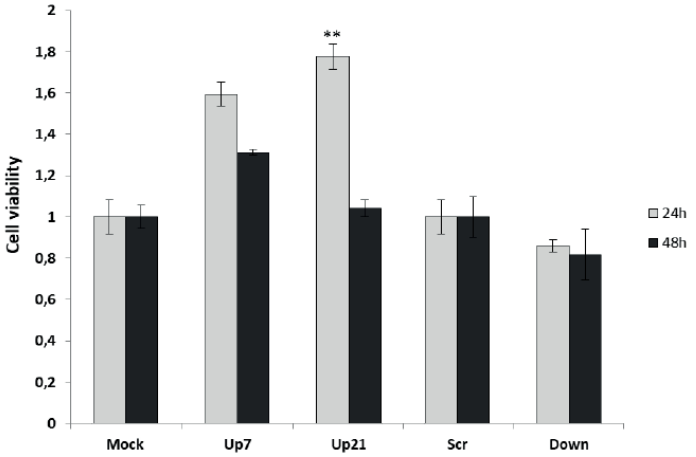

Fig. **Adaptor protein Ruk/CIN85 modulates viability and motility rate of mouse melanoma B16 cells depending on its expression level:**
A — cell viability; *B* — motility rate. (Up7, Up21 – subclones of B16 cells verexpressing Ruk/CIN85 and corresponding control Mock cells; Down – B16 cells with down-regulation of Ruk/CIN85 and corresponding control Scr cells).
$M \pm m$, $\boldsymbol{n} = 3$, *,** $P < 0.05$ to Mock and Scr.

The authors state that they have no conflict of interest.

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