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shift. This in our opinion may lead to future structural damage. On the other hand, breakage of Z disk parallel orientation can by provoked by functionality loses of structural proteins, such as titin.

Photo 4. Pathological changes in Z disks (x6000 magnification)

These data allow as to conclude that acute muscle ischemia results in severe morphofunctional loses in single muscle filaments and with time will lead to full loss of the muscle ability to contract. Morphofunctional studies of ischemized muscles in parallel with contraction dynamics recordings can not only reveal the pathological status but also determine ischemia damage stage.

THE RENOPROTECTIVE EFFECTS OF STATINS: CASE STUDY OF MUSCLE DAMAGE RESULTING FROM EXPERIMENTAL CRASH SYNDROME

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It is known that damage to striated muscle cells (rhabdomyolysis) may be caused by traumatic destructions of skeletal muscles, and also toxic effects of certain drugs. Specifically, rhabdomyolysis is closely associated with myoglobinuria that reduces renal blood flow, activates vasoconstrictive factors in kidneys, increases intratubular pressure, and also provokes the imbalances in prooxidant/antioxidant balance on the background of progressive of renal ischemia.

Rhabdomyolysis may be caused by different medicinal agents, including statins. As follows from routine medical practice, the number of cases of renal failure in the patients who received statins is low (no more than 0.3 – 0.6 cases per 1 million of prescriptions). Further, on the occasion of statin administration in permitted dosages, the reduced functions of kidneys and development of renal failure were significantly more often observed in pa-

tients who received placebo (0.8%) as compared to those treated with statins (0.5%). What is more, based on the results of 21 randomized clinical trials with statins, myopathy occurred in 5 and rhabdomyolysis in 1.6 cases per 100 thousand patients a year, respectively. The risks of rhabdomyolysis emergence depend significantly on the interactions between medicinal agents, especially, their effects on metabolism of cytochrome system and also binding with the glucuronic acid. The alternatives of statin myopathy include depletion of the mevalonic acid metabolites, reduced levels of ubiquinone level, the effects on chloride channels, high lipophilicity of certain statins and their easy penetration into myocyte membranes.

Notwithstanding a possibility for rhabdomyolysis, in has been found that statins had a positive effect on renal functions. Specifically, based on some experimental and clinical research studies its was found that on the occasions of postischemic and toxic acute renal failures (ARF) the statins were efficient to improve the renal functions of patients due to their effects on inflammatory mechanisms, the NO system, and also prooxidant and antioxidant systems.

Based on several current data available we may argue that statins do not cause direct nephrotoxic impact, and their administration, as a rule, is not a cause for any acute or chronic renal failure. Actually, as of today, we consider the cases of development of rhabdomyolysis as exceptions; however, it should be noted that the effects of statins on renal functions in myoglobinuric ARF are still not clearly understood.

Our research study was targeted at the examination of development of rhabdomyolytic ARF in rats; specifically, we initiated the appearance of ARF in its myoglobinuric form by injection of a 50% glycerol solution intramuscularly at a dose of 10 ml/kg, which is an experimental analogue of crash syndrome. Further, as a preventive measure, the statins (atorvastatin, lovastatin, and simvastatin) were introduced intragastrically at 10 mg/kg daily for 3 days before the ARF simulation. The renal functions were assessed 24 hrs after completion of ARF simulation.

As has been found in our experiments, 24 hrs after injection of 50% glycerol solution statin-treated rats featured improvements in the excretory functions of kidneys; the latter fact was demonstrated by an increased glomerular filtration rate and reduced proteinuria. Characteristically, the best results were found with lovastatin which caused an increase of diuresis, higher rates of glomerular filtration and levels of creatinine excretion.

Furthermore, we have found a number of favourable changes concerning the effects of studied medicinal agents on antioxidant/prooxidant system. To illustrate: the preventive administration of two statins (atorvastatin and simvastatin) at the 24th hour of the experiment has demonstrated considerably reduced levels of malonic dialdehyde in the tissues of kidneys and increased activity of glutathione peroxidase and higher levels of the SH-groups in blood plasma.

It should be emphasized that the renoprotective effects of statins compare well with those of the quercitin drugs (Zamorskii I.I., Goroshko O.M., 2010).

Relying on our data, we may conclude that under conditions of experimental rhabdomyolysis certain of studied statins (atorvastatin, lovastatin, and simvastatin) did not cause any aggravation of ARF. Quite the reverse, they have shown renoprotective properties, and they significantly reduced proteinuria. It is worthy of note that atorvastatin and simvastatin show rather high renoprotective properties due to improved prooxidant/antioxidant balances; alternatively, lovastatin improved the excretory function of kidneys.

REGULATION OF CENTROSOMAL PROTEINS BY PROTEIN KINASE LOSK

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Microtubules in interphase cells provide tracks for intracellular transport, ensure proper interaction with the substrate and govern cell polarization and motility. Their radial organization is established as a result of nucleation and anchoring of microtubules at the centrosome. Dozens of centrosomal proteins can be divided into several groups according to their function: those that ensure structural integrity, nucleation, capping of microtubule minus-ends, attachment of microtubules to the pericentriolar material, delivery of all these proteins to the centrosome and regulation in response to signaling events. Protein kinase LOSK was shown to be required for maintenance of microtubule radial array. Here we report its direct and indirect targets among centrosomal proteins. We demonstrate that dynactin (cofactor of dynein motor protein) is phosphorylated by LOSK and targeted to the centrosome, where it is responsible for microtubule anchoring. We provide the first evidences that dynactin is involved in microtubule organization independently of its transport functions: phosphorylation by LOSK does not affect transport of other dynein-driven centrosomal proteins, but is ultimately required for microtubule anchoring. We also reveal a new target of LOSK - a structural protein of pericentriolar material called PCM-1. Its centrosomal location is disturbed in cells with inhibited LOSK. However, the observed effect is independent of dynactin phosphorylation. Overall, we assume that LOSK governs microtubule organization by a direct phosphorylation of dynactin and by modulation of PCM-1 localization. Thus, microtubule radial array results from a coordinated interplay between scaffolding, transport and regulatory proteins.