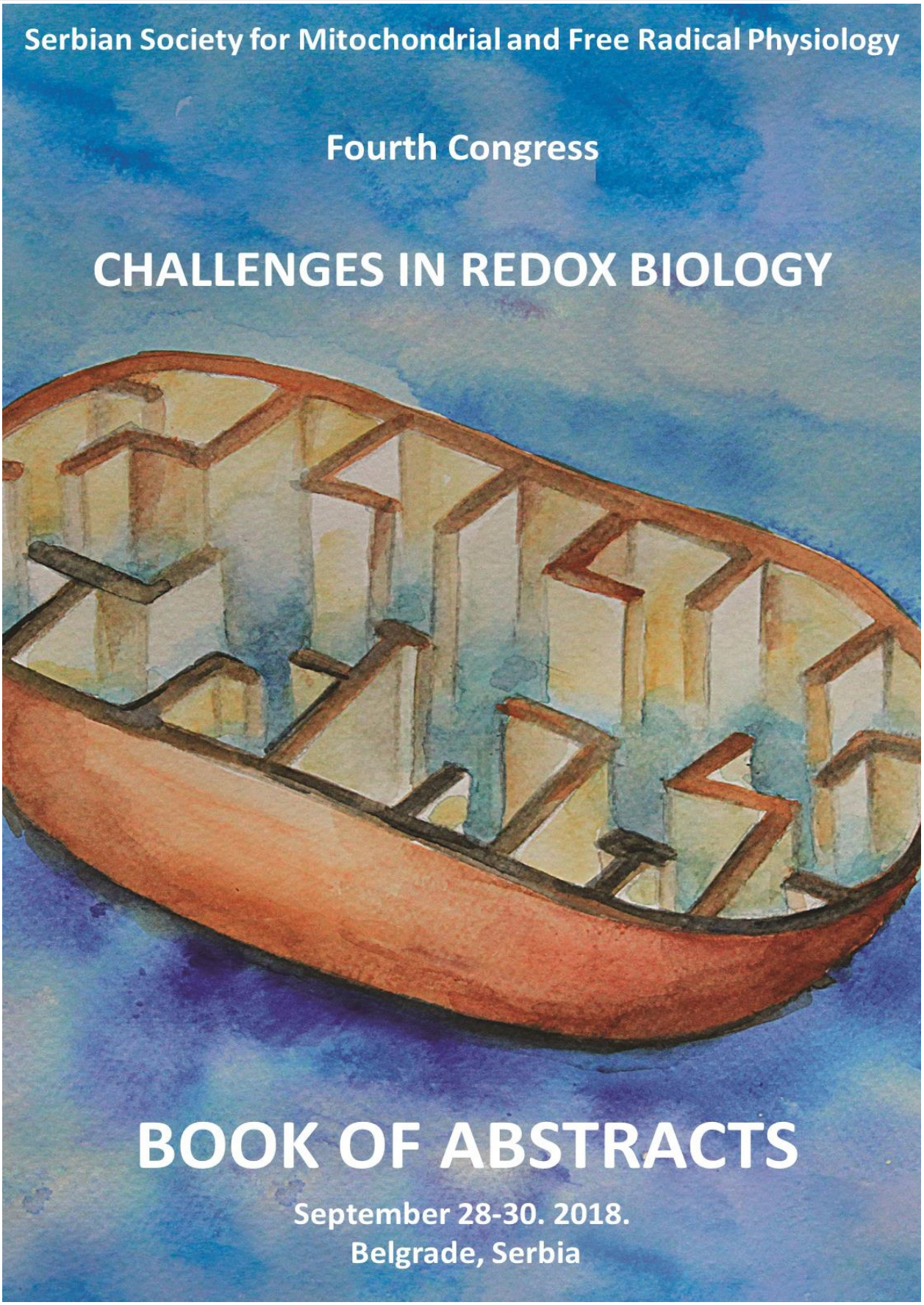

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THE LEVEL OF OXIDATIVE STRESS DETERMINES THE ROLE OF EXTRACELLULAR HMGB1 PROTEIN IN DIABETIC RAT LIVER

Anja Petrović[1], Desanka Bogojević[1], Svetlana Ivanović-Matić[1], Vesna Martinović[1], Aleksandra Korać[2], Sofija Jovanović Stojanov[1], Goran Poznanović[1], Ilijana Grigorov[1]
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Oxidative stress through changes in antioxidative enzyme activities, glutathione metabolism and lipid peroxidation, leads to cell damage and even cell death. These changes are integrated in the pathogenetic mechanisms of the long-term, specific complications of diabetes, such as neuropathy, retinopathy, cardiomyopathy, nephropathy and hepatopathy. Recent studies have shed light on new redox sensitive endogenous targets which are important regulators of oxidative stress-induced damage. HMGB1 is a nuclear chaperone with an inflammatory function when released in the extracellular space. Extracellular HMGB1, through interaction with TLR4 receptors in its oxidized state, and with RAGE in its reduced state, controls the equilibrium between apoptosis and autophagy. HMGB1 is a redox sensitive protein with a potentially harmful role. We therefore analyzed the changes in HMGB1 regulated signaling pathways by immunoprecipitation and Western blot that can lead to cell death or cell survival in the liver of streptozotocin (STZ)-induced diabetic rats during decreased oxidative stress after melatonin administration, and when HMGB1 release was inhibited by ethyl pyruvate. Inhibition of HMGB1 release decreased both apoptosis and autophagy, and supported the unchanged state in liver cells in STZ-treated rats as compared to the control animals. The decrease in oxidative stress achieved with melatonin decreased HMGB1 driven apoptosis but upregulated HMGB1 regulated protective autophagy, mitophagy in particular as the second level of antioxidative defense which was detected by electron microscopy. It provided a selective advantage, minimizing oxidant insults when primary antioxidant activities are compromised during oxidative stress. This adaptation led to improved cell survival in the liver of STZ-treated rats. These results showed that modulation of the role of HMGB1 in the extracellular space that was achieved by a decrease in oxidative stress is more desirable than complete inhibition of its release because HMGB1 has a protective role against oxidative injuries in diabetic liver.