6-month-long fast-food intake is associated with worse metabolic syndrome score and higher ecDNA levels in female rats

Katarína Šebeková[1*], Andrej Feješ[1], Veronika Kunšteková[1], Lucia Mihalovičová[1], Veronika Borbélyová[1]

[1]Institute of Molecular Biomedicine, Medical Faculty, Comenius University, Bratislava, Slovakia

Background: Obesity is a state of chronic low-grade inflammation that may aggravate obesity-associated metabolic complications. Extracellular DNA (ecDNA) is a damage-associated molecular pattern. Its mitochondrial fraction (mtDNA) can activate innate immunity. DNase cleaves ecDNA into shorter, less immunogenic fractions. We hypothesized that in rats with diet-induced obesity, ecDNA, especially of mitochondrial origin, is higher and DNase activity lower than in the controls and that these markers are associated with the cardiometabolic risk estimated as continuous metabolic syndrome score (cMSS).

Methods: Twenty 8-week-old female rats were divided into two groups of similar body weight. The control group consumed a standard rat chow, the experimental group was administered an isocaloric fast-food diet (FFD) with a 3-fold higher fat content. Six months later, cardiometabolic risk factors and markers, circulating ecDNA levels, mtDNA and nuclear DNA genomic equivalents, and DNase activity were determined.

Results: FFD-consuming animals displayed dysmetabolic phenotype characterized by a higher body weight (508±71vs. 417±49 g), blood pressure (SBP: 133±10 vs. 125±3 mm Hg), uricemia (83±23 vs. 52±17 µmol/l), and erythrocyte counts (9.1±0.3 vs. 8.8±0.4x10^9/l) compared with their control counterparts, reflected by a less favorable cMSS z-score (-0.7±1.9 vs. -1.9±1.7). The FFD-consuming rats displayed higher levels of ecDNA (35±6 vs. 28±5 ng/ml). Numbers of mtDNA or nuclear DNA genomic equivalents and the activity of DNase did not differ significantly. The multivariate regression analysis indicated that low DNase activity, high erythrocyte counts, and fasting insulin levels were the main determinants of ecDNA levels, while erythrocyte counts and insulinemia determined numbers of mtDNA genomic equivalents. Low cMSS, ecDNA, and fasting insulin concentrations are associated significantly with higher DNase activity.

Conclusion: Here we show that in female rats, the activity of DNase, erythrocyte counts, and insulin resistance but not obesity or metabolic syndrome score determine ecDNA levels.

Acknowledgment: This study was supported by a grant from the APVV, No. 21-0355