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Ginseng extract protects against tacrolimus-induced pancreatic beta cell injury by regulating autophagy

Sun woo LIM[1], Yoo JIN[1], Kang LUO[1], Long JIN[1], Jian JIN[1], *Chul woo YANG[2]

[1]Transplant Research Center, St. Mary, Korea,South, [2]Division of Nephrology, Department of Internal Medicine, St. Mary's Hospital, The Catholic University of Korea, Korea,South

Objectives : Growing evidence suggests that regulation of autophagy may be an effective approach to protect beta cells against various extra-/intracellular stimuli. We previously demonstrated that long-term treatment of calcineurin inhibitor causes excessive autophagosome burden and impaired autophagy clearance in pancreatic beta cells. This study investigated the effect of Korean red ginseng extract on autophagy modulation focused on oxidative stress.

Methods : The rat insulinoma cell line INS-1 was treated with Tac (40 ug/mL) and KRGE (100 pg/mL) with or without 3-methyladenine (3-MA, 10 mM) or bafilomycine A1 (BA, 2nM) for 6h. Mice were treated with Tac (1.5 mg/kg, subcutaneous) and KRGE (0.4 g/kg, orgal gavage) for 4 weeks. The effect of KRGE on Tac-induced diabetes was evaluated by assessing intraperitoneal glucose tolerance test, plasma insulin level, beta cell area, and 8-hydroxy-2'deoxyguanosin in serum and islet. Autophagy and mitochondria functions were examined by measuring either microtubule-associated protein 1 light chain 3 beta expression, the number of autophagic vacuoles, and lysosome function or oxygen consumption and mitochondrial membrane potential.

Results : In vitro study, we evaluated the effect of KEGE on Tac-induced autophagic cell death, and found that KRGE decreased autophagosome formation and improved lysosomal degradation, accompanied by improved beta cell viability and insulin secretion. 3-methyladenine (3-MA), an inhibitor of autophagosome, reduced Tac-induced beta cell injury, but bafilomycin A (BA), an inhibitor of lysosomal function, abolished the protective effects of KRGE. In mitochondria, Tac treatment impaired mitochondrial oxygen consumption, ATP production, and increased reactive oxygen species production. But, KRGE improved these parameters and this effect was enhanced by 3-MA treatment, but decreased by BA treatment. In mice with Tac-induced diabetes mellitus, KRGE attenuated hyperglycemia, restored islet size, and reduced oxidative stress. Electron microscopy showed that KRGE attenuated the formation of autophagic vacuoles and restored the number of insulin granules.

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Conclusions : These findings indicated that KRGE has benefit effect against Tac-induced pancreatic islet injury by reducing the burden of autophagosomes and activation of autophagosome clearance, and this protective effect involves the protection of mitochondria.

Keywords : Korean red ginseng; autophagy; tacrolimus; diabetes mellitus; mitochondria function