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Commensal probiotic bacteria affect host cellular lipid metabolism through various cellular metabolic pathways: Role of mTOR, FOXO1, and autophagy machinery system

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Abstract

Aim & Backgrond: Although *in vivo* studies revealed that lactic acid bacteria (LAB) of the natural intestinal microflora prevent metabolic diseases through the control of host energy metabolism, the precise molecular bases have not been fully elucidated. As mechanistic Target of Rapamycin (mTOR) signalling and autophagy machinery system negatively cross-regulate each other's outcome and regulate cellular lipid metabolism, we investigated the influence of *Bifidobacterium breve (B.b)* and *Lactobacillus rhamnosus GG* (*LGG)* on mTOR signalling and inflammation/metabolic markers in three-dimensional (3D) cell culture systems. ***Methods:*** The cell culture system that we used included triple co-culture model of T84 intestinal epithelial cells (IECs) with human monocyte-derived 3D macrophages (HMDMs) and hepatocyte-derived 3D HepG2 cells. Monolayer barrier integrity was assessed by measuring TEER and leakage of LPS. Cell-based ELISA and Western blot (WB) were used to assess expression of IL-1β, IL-6, IL-8, TNF-α, CB1, forkhead box protein O1 (FOXO1), phosphenolpyruvate carboxykinase (PEPCK), G6Pase, mTOR, adhesion molecules (VCAM-1, ICAM-1), autophagy markers (LC3-I, LC3-II, Beclin-1, p62) as well as mTOR kinase activity and cellular triglycerides(TG). Autophagy was also quantitatively assessed by fluorescence microscopy and Tecan GENios Multi-Detection Microplate Reader. DNA-binding activity, nuclear translocation of NF-*κ*B (I*κ*Bα degradation, expression of p50/p65 subunits), and NF-*κ*B-dependent luciferase activity were assessed using EMSA, WB and a TECAN GENios microplate reader respectively. ApoC-III gene expression was assessed by qRT-PCR. FOXO1/mTOR siRNA was used to silence FOXO1 and mTOR gene. ***Results:*** LAB inhibited oleate/LPS-induced IL-1β, IL-6, TNF-α, and cellular TG, accompanied by reduction of mTOR and FOXO1 activity and enhanced occurrence of autophagy, as manifested by increased LC3-II/LC3-I ratio and decreased expression of Beclin-1 and p62. ***Conclusion:*** We describe a new mechanism whereby LAB prevent high fat diet/endotoxin/inflammation-mediated disruption of normal cellular lipid metabolism by inhibiting mTOR/FOXO1/NF-*κ*B activity and enhancing the occurrence of autophagy. This may be a molecular basis by which LAB enhance intrinsic cellular tolerance against excess calorie consumption and participate in homeostatic regulation of metabolic processes *in vivo*.