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ClC-3 Enhances Visceral Adipocyte Hypertrophy and Adipose Tissue Inflammation linking Obesity-Induced Insulin Resistance

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Background and Objective: We have previously found that chloride channel/antiporter ClC-3 gene knockout alleviates lipid and glucose disorders in mice model with type 2 diabetes. The present study was designed to verify the role of ClC-3 in adipocyte hypertrophy and adipose tissue macrophage (ATM) inflammation during obesity.

Methods: We measured the ClC-3 expression and fat cell size in omental fat tissues from Chinese women with body mass index (BMI) from 16.0 to 28.4 kg/m^2. The adipocyte cell size, ATM-mediated inflammatory phenotype switch and TLR-4/NF**κ**B inflammatory signaling pathway was examined in visceral adipose tissue from ClC-3$^{-/-}$ and wild-type mice fed with high-fat diet (HFD) using micro-CT, histological, cellular, and biochemical molecular approaches.

Results: The expression of ClC-3 mRNA and protein upregulated in omental fat tissues of obese women and has a strong positive correlation with BMI and adipose cell size. In HFD-induced obese mice, ClC-3 protein significantly increased as early as 4 weeks after HFD initiation. ClC-3$^{-/-}$ mice exhibited a dramatic decrease in HFD-induced body weight gain; VAT accumulation, adipocyte size enlargement or increased percentage of large adipocytes in VAT, as well as an improvement of obesity-induced metabolic disorders. ClC-3 deficiency also reduced obesity-induced ATM recruitment and accumulation, M1-like macrophage polarization and expression of pro-inflammatory cytokines through the TLR-4/NF-κB signaling pathway. In THP-1 differentiated cells *in vitro*, ClC-3 knockdown dramatically reduced LPS-induced NF-κB activation and TLR-4 expression, while overexpression of ClC-3 did the opposite.

Conclusion: The upregulation of ClC-3 gene may contribute to obesity-induced adipose tissue dysfunction by promoting adipocyte hypertrophy and ATM inflammation, suggesting a therapeutic potential of inhibiting ClC-3 for obesity-related metabolic disorders.

Biography:

Xiaomiao Zhao, MD., Ph.D., an associate professor and associate chief physician of reproductive endocrine and advisor of Ph.D candidate, the vice president of Youth Committee of the Chinese OB/GT Committee of International Health Care Exchange and Promotive society. She has completed her M.D. at the age of 24 years and Ph.D at 30 years from Sun Yat-Sen University in Guangzhou, China and postdoctoral studies from Cedars-Sinai medical center, USA. Her research interest is in the field of reproductive endocrinology, mainly in polycystic ovary syndrome, androgen excess, insulin resistance, IVF, poor responder for ovary stimulation. Until now, Dr. Zhao has grown up to be the outstanding person of the field of reproductive endocrinology and leads the PCOS study group to the innovative science research, and has great performance of the clinical practice in IVF center. She has published more than 53 papers, among which, over 24 papers in reputed English journals (e.g. Fertility and Sterility, Clinical Endocrinology, International of Caner, and International Journal of Cardiology, etc.) and serving as a reviewer of International Journal of Cancer, JCEM and endocrinology. She takes charge of 11 research grants as a PI in China.