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FGF21 up-regulates glycolytic proteins for hypertrophic chondrocyte survival under ER stress

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Perturbation of endoplasmic reticulum (ER) homeostasis is associated with various diseases. In a mouse model (13del-tg) for metaphyseal chondrodysplasia type Schmid (MCDS), misfolded mutant Collagen X proteins accumulate in hypertrophic chondrocytes (HCs) triggering ER stress was shown as the molecular basis of the disease. Interestingly, under ER stress, HCs activate a survival signal that also alters the chondrocyte differentiation program in the growth plate, impairing endochondral ossification causing dwarfism. How HCs survive ER stress in this context is unknown. Previously, we showed there is an altered metabolic machinery favoring glycolysis in 13del-tg HCs using a label-free quantitative proteomic approach. Recently, transcriptome analysis identified a marked upregulated expression of FGF21, a novel ER stress target and a key metabolic regulator involved in various metabolic diseases in 13del HCs. However, the role of FGF21 in energy flux maintenance for HCs survival under ER stress has not been studied. Here, in a label-free quantitative proteomic analysis in mice, we showed that FGF21 is required to maintain higher levels of glycolytic proteins in HCs under ER stress for survival, and its inactivation in 13del-tg mice will lead to apoptosis. We found that FGF21 is not required for normal chondrocyte differentiation. Our findings support a switch to rapid energy supply is necessary to sustain pro-survival pathways in HCs to survive under ER stress, and FGF21 have a key role in this switch in activating and/or sustaining an up-regulated glycolytic process required for survival.

Biography

SO K H has completed his Bachelor's degree in Biochemistry from The University of Hong Kong. He is currently pursuing his Master of Philosophy degree under the supervision of Prof. Danny Chan and Dr. Qizhou Lian in the field of Genetics and Skeletal Development at School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong.

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