A Cardiolipin-Specific Peptide Ameliorates Obesity and NASH through Mitochondrial Function Restoration

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Obesity is a disease characterized by the accumulation of fat in cells and an abnormal increase in weight due to intake of more calories than consumption of them. This fat accumulation in liver cells is the main cause of nonalcoholic fatty liver disease (NAFLD). Even though the disease does not have any pathological symptoms, NAFLD can progress to more severe forms of liver diseases, such as nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and cancer. However, there are currently no FDA-approved drugs to treat NAFLD and NASH. Mitochondrial dysfunction is strongly associated with the development and progression of NAFLD, and the significant decline in mitochondrial function in fatty liver cells is closely related to the low expression of cardiolipin (CL), a specific phospholipid necessary for maintaining the structure and function of inner membrane of mitochondria (IMM). When CL is oxidized and pathogenically remodeled, protein complexes in IMM cannot carry out their roles properly, generating dysfunctional mitochondria and progressing NAFLD to NASH. We have been developing a CL-specific peptide, CMP3013, which can bind to normal or oxidized CLs in IMM, converting leaky to rigid IMM, correcting mitochondrial dysfunction. Treatment of this peptide to high-fat diet induced mouse showed a significant reduction of weight and inflammatory fatty liver damages in liver cells. Since the CL-specific peptide strongly bind to CLs, it prevents the escape of CL molecules from IMM to cytosol for inflammasome formation, which is known as an essential event from NAFLD to NASH. Taken together, we have shown that the CL-specific peptide can be a plausible therapeutic against obesity related NASH.