Development of autophagy enhancer as a novel therapeutic agent against metabolic syndrome/diabetes through interdisciplinary approach

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Autophagy is a critical regulator of cellular homeostasis dysregulation of which is associated with diverse diseases. We screened a chemical library from Korea Research Institute of Chemical Technology for novel autophagy enhancers employing a *Renilla luciferase-LC3* reporter construct. An autophagy enhancer (MSL) increased LC3-I to -II conversion without mTOR inhibition. Autophagy enhancer activated calcineurin through direct binding, and induced dephosphorylation/nuclear translocation of transcription factor EB (Tfeb), a master regulator of lysosomal biogenesis and autophagy gene expression. Autophagy enhancer accelerated intracellular lipid clearance, which was reversed by lalistat 2 or *Tfeb* knockout. Autophagy enhancer also attenuated IL-1β release and caspase-1 cleavage after treatment of macrophages with palmitic acid plus LPS, indicating reduced inflammasome activation. Further, autophagy enhancer reduced expression of TNF-α, IL-6 and pro-IL-1β mRNA, which was independent of inflammasome activation. Decreases in cytokine mRNA expression were due to attenuated NF-κB activation by autophagy enhancer, which in turn resulted from enhanced calcineurin activity. Autophagy enhancer administration improved metabolic profile of *ob/ob* mice and ameliorated inflammasome activation, which was accompanied by induction of Tfeb target genes such as lysosomal genes, autophagy genes and mitochondrial genes. A chemically-modified autophagy enhancer with increased microsomal stability (MSL-7) improved glucose profile not only in *ob/ob* mice but also in mice with diet-induced obesity. Our data indicate that our novel autophagy enhancers could be new drug candidates for diabetes or metabolic syndrome with lipid overload.