**Role of autophagy in the progression from obesity to diabetes**

**–** aggravation of inflammasome activation by metabolic stress **–**

Myung-Shik Lee

Severance Biomedical Science Institute and Dept. of Internal Medicine, Yonsei University College of Medicine

Autophagy, which is critical for the proper function of organelles such as ER, mitochondria and lysosome affects diverse aspects of cellular and whole body metabolism. To study the role of global autophagy insufficiency, particularly that of physiological level, rather than complete autophagy knockout in localized tissues, on the whole body metabolism, we generated mice with global *Atg7* haploinsufficiency (*Atg7*+/- mice). *Atg7*+/- mice did not show metabolic abnormalities, but developed diabetes when crossed with *ob/ob* mice, together with aggravated insulin resistance. Augmented inflammasome activation associated with mitochondrial dysfunction was the culprit leading to enhanced metainflammation and diabetes. To address the role of macrophages in the inflammasome activation associated with autophagy deficiency, we produced mice with myeloid cell-specific deletion of *Atg7* (*Atg7*Lys mice). While *Atg7*Lys mice were metabolically normal, they developed diabetes when bred to ob/w mice (*Atg7*Lys-*ob/ob* mice), accompanied by increases in metainflammation and inflammasome activation in adipose tissue. Here again, mitochondrial dysfunction such as a decrease in NAD+/NADH ratio and increase in intracellular ROS content in autophagy-deficient macrophages was the cause of an increased lipid-induced inflammasome and metabolic deterioration of *Atg7*Lys-*ob/ob* mice. Autophagy enhancers improved inflammation, mitochondrial metabolic profile of obese mice. These results suggest that autophagy is important for the control of inflammasome activation in macrophages in response to metabolic stress, and autophagy deficiency can contribute to the progression of metabolic syndrome associated with lipid injury.