ROS-NLRP3 inflammasome pathway is a critical mediator linking lipid metabolism to macrophage functions

Supported by the National Natural Science Foundation of China, Prof. Gan Lixia's laboratory at the Third Military Medical University and Prof. Yu Liqing at the University of Maryland published their research findings entitled "Macrophage CGI-58 deficiency activates ROS-inflammasome pathway to promote insulin resistance in mice" in *Cell Reports* (2014, 7(1): 223—235).

It is well known that overnutrition activates a proinflammtory program in macrophages to induce insulin resistance (IR). The increased adipose tissue infiltration of inflammatory immune cells, particularly the proinflammatory (M1-like) macrophage is believed to be the primary source of many inflammatory cytokines. Both extracellular signals such as the necrotic adipocytes, damaged endothelial cells, adaptive immune cells and free fatty acids, and intracellular signals such as oxidative stress, endoplasmic reticulum stress and reactive oxygen species (ROS) have been demonstrated to promote the proinflammatory property of adipose tissue macrophages. However, the triggers for the inflammatory activation of macrophages remain incompletely understood. In this study, we tested the molecular mediator and signaling pathways linking intracellular lipid accumulation, one of the most distinguished pathologic features in obesity, to macrophage activation.

Comparative gene identification-58 (CGI-58) is an activator of triglyceride hydrolysis, whose mutations in human cause Chanarin-Dorfman syndrome (CDS), a rare autosomal recessive neutral lipid storage disease characterized by accumulation of triglyceride-rich lipid droplets in most obesity tissues and cell types. Using macrophage-specific CGI-58 knockout (MaKO) mice as a model, we have showed MaKO mice aggravate high fat diet (HFD)-induced glucose intolerance and IR, which is associated with augmented proinflammatory activation of adipose tissue macrophages and systemic inflammation. We have also shown that macrophage CGI-58 deficiency activates NLRP3 inflammasome by inducing ROS accumulation through suppression of PPARγ-dependent mitochondrial function, leading to activation of caspase-1 and subsequently enhanced proteolytic cleavage and secretion of potent proinflammatory cytokines interleukin (IL)-1β and IL-18. Conversely, PPARγ-specific agonist, anti-ROS treatment or NLRP3 silencing prevents CGI-58-deficient macrophages from oversecreting proinflammatory cytokines and from inducing proinflammatory signaling, and prevents exacerbation of inflammation and IR in HFD-fed MaKO mice. Our findings establish CGI-58 as a suppressor of overnutrition-induced NLRP3 inflammasome activation in macrophages. This study directly links a cell's lipolytic factor to its own inflammasome activity.

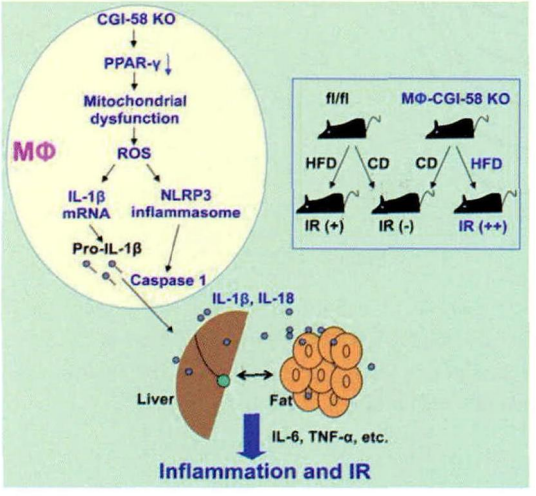

Figure Macrophage CGI-58 promotes HFD-induced insulin resistance by activating ROS-NLRP3 inflammasome pathway through suppression of PPAR-γ-sustained mitochondria function.