Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome

With the support by the National Natural Science Foundation of China, the research team led by Prof. Wang Di (**王迪**) at the Immuno metabolism Lab, Institute of Immunology, Zhejiang University School of Medicine, uncovered the mystery of Bile Acids control inflammation and metabolic disorder, which was published in *Immunity* (2016, 45: 802—816)).

The metabolic disorders are some of the most serious threats to public health in the world, and the incidence of metabolic disorders such as obesity, type 2 diabetes and atherosclerosis has increased considerably in recent decades. The key feature of metabolic disorders is the chronic inflammation. The inflammasome is a cytosolic multimeric protein complex which can affect infection and inflammation. The activation of inflammasome influences many metabolic disorders. Wang's group has found that the NLRP3 inflammasome plays a key role in host defense against pathogens and inflammation.

More interestingly, they demonstrate that, as a diverse class of endogenous cholesterol-derived molecules, bileacids inhibit NLRP3 inflammasome activation via the TGR5-cAMP-PKA axis. TGR5 bile acid receptor-induced PKA kinase activation led to the ubiquitination of NLRP3, which was associated with the PKA-induced phosphorylation of NLRP3 on a single residue, Ser291. Furthermore, this PKA-induced phosphorylation of NLRP3 served as a critical brake on NLRP3 inflammasome activation. In addition, *in vivo*, bile acids and TGR5 activation blocked NLRP3 inflammasome-dependent inflammation, including lipopolysaccharide-induced systemic inflammation, alum-induced peritoneal inflammation, and type-2-diabetes-related inflammation. These exciting results suggest that TGR5 might be a promising target for the treatment of NLRP3 inflammasome-related inflammatory diseases.

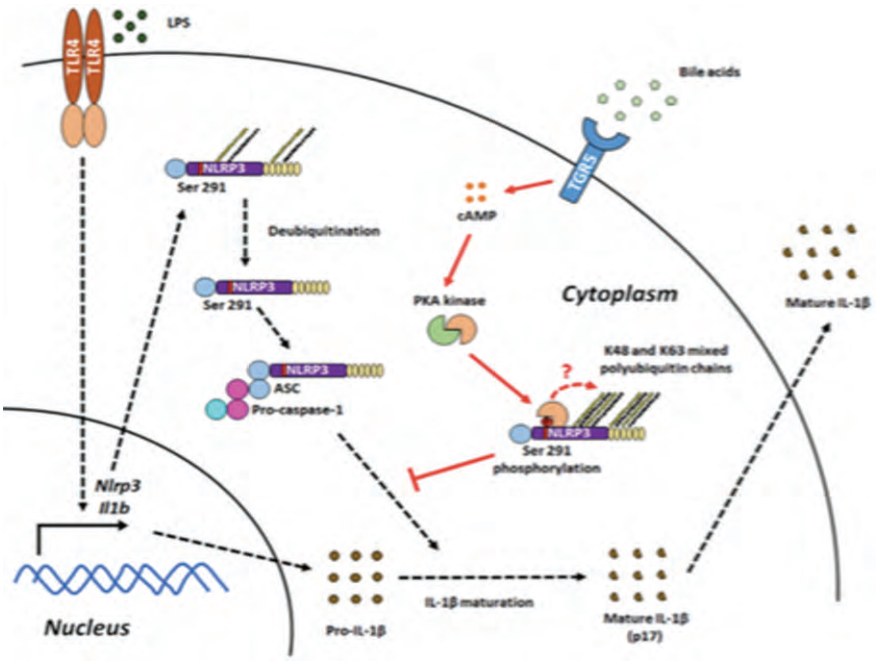

Figure Bile acids inhibit NLRP3 inflammasome activation via the TGR5-Camp-PKA axix.