Bacillus bombysepticus α-toxin binding to G protein-coupled receptor kinase 2 regulates cAMP/PKA signaling pathway to induce host death

With the support by the National Natural Science Foundation of China and 973 Program, Lin et al. from the State Key Laboratory of Silkworm Genome Biology, Southwest University, reported the impact and mechanism of *Bacillus bombysepticus* (Bb) α-toxin in GRK2-mediated GPCR desensitization that regulates cAMP/PKA signaling to induce host death. Their work has been published in *Plos Pathogens* (2016, 12(3): e1005527).

Bacterial pathogens target cells, leading to abnormal division or death, through receptor-mediation and receptor-disruption of the essential cytosolic function. This is an efficient and widespread mechanism of microbial pathogenesis. Lin et al. found that a new bacterial toxin-*Bacillus bombysepticus* (Bb) α-toxin was lethal to its host *Bombyx mori*, and demonstrated that Bb α-toxin directly bound to G protein-coupled receptor kinase 2 (BmGRK2) to promote death by affecting G protein-coupled receptor (GPCR) signaling pathways. This mechanism involved the stimulation of $G_{\alpha s}$, increased level of cAMP, and activation of protein kinase A (PKA). Activated cAMP/PKA signal transduction altered downstream effectors that affect homeostasis and fundamental biological processes, disturbing the structural and functional integrity of cells and resulting in death. Conversely, when cAMP/PKA signaling transduction was prevented by inhibitions, the pathogenicity of Bb α-toxin was substantially reduced. The discovery that a toxin-induced host death is specifically linked to a GRK2-mediated signaling pathway reveals a now model to subvert host processes by bacterial toxins. The characterization of host genes whose expression and function are regulated by Bb α-toxin and GRK2 may offer a deeper understanding of the pathogenesis of infectious diseases caused by pathogens that elevate cAMP. Furthermore, this might be extended to other microbial pathogenesis and assist in designing new or safer strategies against pathogens.

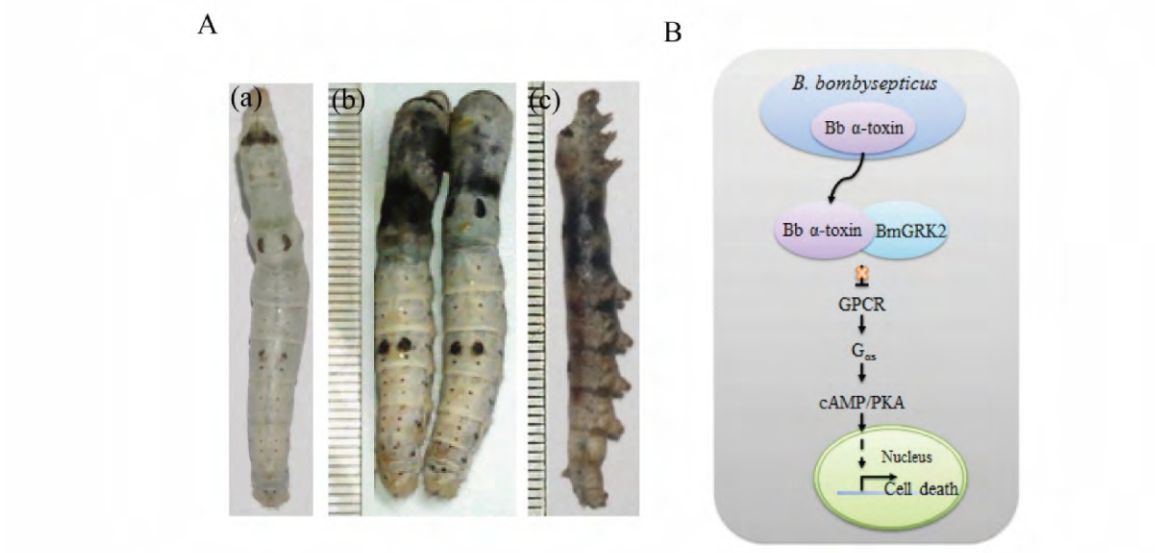

Figure A schematic representation of the model for the action of Bb α-toxin. A. *Bb* infection causes silkworm, *B. mori*, death. B. Bb α-toxin bound to BmGRK2 affects the modulation of the GPCRs signaling pathway that influences cAMP/PKA signaling. In turn, PKA activation alters effectors that disturb homeostasis and many fundamental biological processes, which destroy midgut cells and induce larvae death.