Pathogen blocks host innate immunity by arginine GlcNAcylation of death domains in death receptor pathways

The research group led by Prof. Shao Feng, who is funded by the National Science Fund for Distinguished Young Scholars, published their new research findings in an article "Pathogen blocks host death receptor signaling by arginine GlcNAcylation of death domains" in *Nature* (**2013**, 501(7466): 242–246). The research was carried out at the National Institute of Biological Sciences (NIBS), Beijing, where Prof. Shao holds an investigator position since 2005.

Many Gram-negative bacterial pathogens harbor a type III secretion system (T3SS) that injects virulence effectors into eukaryotic cells to manipulate host defense pathways. Revealing the functional mechanism of important T3SS virulence effectors at the molecular level is critical for better understanding and combating against infectious diseases. NleB is a T3SS effector protein conserved in multiple diarrhea-causing pathogens, such as Enteropathogenic *E. coli* (EPEC), *Salmonella* and *Citrobacter rodentium*, and is required for these pathogens to survive within the host. However, the mechanism of NleB function has been unknown for many years. Dr. Shao and his colleagues discover that NleB harbors an unprecedented GlcNAc transferase activity that modifies a conserved arginine residue in death receptors (tumor necrosis factor receptor 1 (TNFR1) and FAS) and their downstream adaptors (TRADD, FADD and RIPK1). In infected host cells, NleB-catalyzed arginine glycosylation disrupts homotypic/heterotypic death domain interactions between the receptor and its adaptors. The activity of NleB not only blocks TNFR1 complex assembly and TNF-induced cell death, but also inhibits FAS ligand and TRAIL-induced cell death by preventing FADD-mediated death inducing signaling complex (DISC) formation (Figure **A**). Furthermore, in the mouse model of EPEC infection, the GlcNAc transferase activity of NleB is required for bacterial escape from host innate immunity as loss of NleB catalytic activity renders the bacteria incapable of colonization in the mouse colon (Figure **B**). It is also interesting to note that NleB-modified arginine in FAS is frequently mutated in autoimmune lymphoproliferative syndrome (ALPS), confirming its importance in immunity.

This study for the first time reports that bacterial pathogen directly targets the death receptor complex with a novel argnine GlcNAc transferase activity. The mechanism of action of NleB represents not only a new paradigm in bacterial counteracting host defenses but also a previously unappreciated posttranslational modification in eukaryotic signaling regulation.

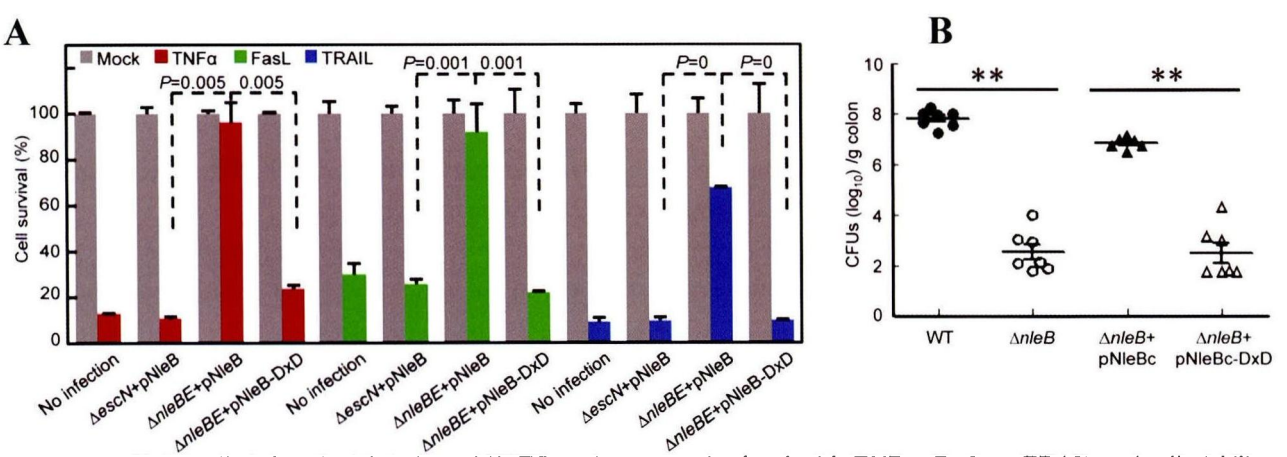

Figure **A** HeLa cells infected with indicated EPEC strains were stimulated with TNFα, FasL or TRAIL and cell viability was determined by measuring ATP levels. **B** 5-6-week-old C57BL/6 mice were orally gavaged with indicated *C. rodentium* DBS100 strains. Bacterial colonization of the intestine 8 days post-infection is shown as the mean ± s. e. m. of $\log_{10}$ CFU/g colon ($n > 6$).