Structural Basis of Gabija Bacterial Defense System

Prokaryotic organisms have evolved sophisticated immune systems for self-protection to resist bacteriophage invasion. With further research on prokaryotic immune systems, several important molecular biology tools have been developed, including the widely used restriction endonuclease in molecular cloning experiments and the CRISPR-Cas system in gene editing.

Many prokaryotic immune system-related genes with unknown functions exist within the genomes of bacteria and archaea. Among them, the Gabija gene is one of the prevalent anti-phage defense genes found in more than 15% of sequenced bacterial and archaeal genomes. The Gabija system comprises two components: GajA and GajB. GajA has been identified as a sequence-specific dependent DNA-nicking endonuclease, with its endonuclease activity being strictly regulated by nucleotide concentration. GajB is hypothesized to be a Uvrd-like helicase. The Gabija system endows Escherichia coli with robust immunity against bacteriophage infection, but the assembly of molecular machinery and structural basis of the Gabija system remain to be revealed.

On January 29, 2024, Dr. WEI Taotao's group at the Institute of Biophysics, Chinese Academy of Sciences, in collaboration with Dr. MA Jun's group, published a research paper entitled "*Structural and biochemical insights into the mechanism of the Gabija bacterial immunity system*" in *Nature Communications*. The paper reports the structure of the Gabija octameric complex, providing a comprehensive understanding of the molecular mechanism underlying the immune defense facilitated by the Gabija system.

The Gabija complex comprises four GajA and four GajB, forming an octamer structure, as shown in Figure 1. Initially, GajA molecules form a tetramer as the core component of the Gabija complex, while four GajB proteins bind individually to the periphery of the complex. Experimental evidence demonstrated that GajA or GajB alone in bacteria is insufficient to resist phage invasion; only the intact Gabija system can render bacteria to resist phage infection, emphasizing the crucial role of the 4:4 assembly of the GajA/B complex in phage defense.

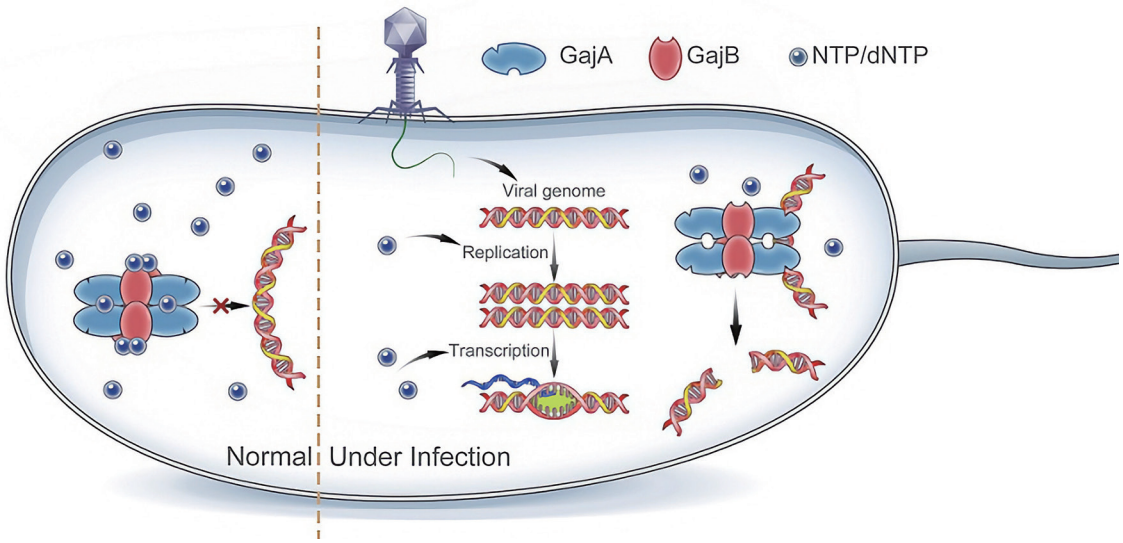

Figure 1. The Gabija complex octameric ring structure. (Image by IBP)

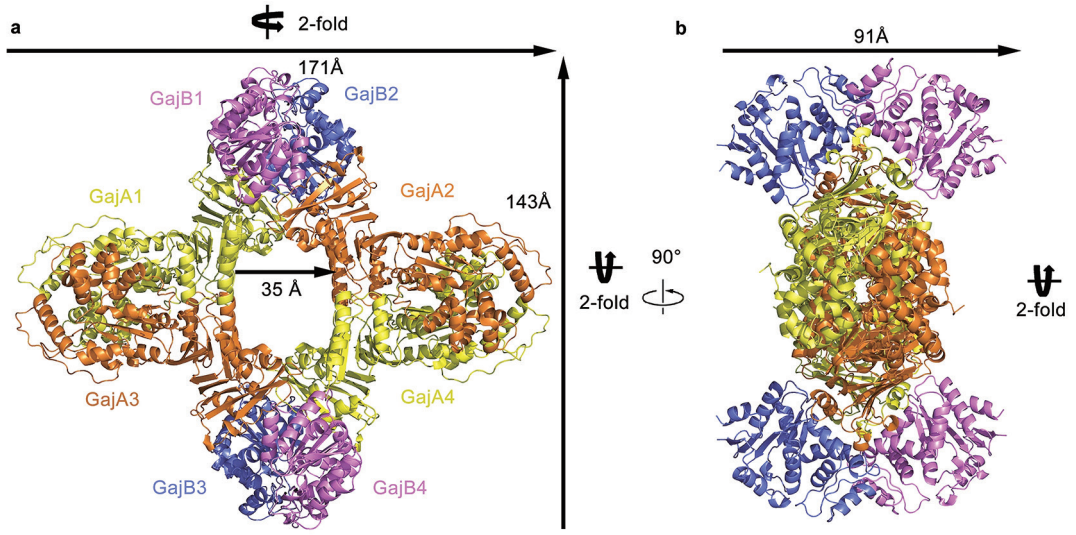

Figure 2. The Gabija system facilitates the molecular mechanism underlying the immune defense. (Image by IBP)

The study also revealed that the Gabija complex possesses sequence-specific DNA endonuclease activity and prefers circular DNA substrates. Gabija complex endonuclease activity is more sensitive to nucleotide concentration than the GajA protein alone. The results imply that by responding to the concentration of intracellular nucleotides, GajB serves as a sensor of cellular energy status and precisely regulates the endonuclease activity of the GajA protein.

Based on cryo-EM structure analysis and biochemical experiments results, the study proposed a model for the antiviral mechanism of the Gabija immune system: under normal physiological conditions, high intracellular concentrations of NTP and dNTP inhibit the endonuclease activity of the Gabija complex. However, under bacteriophage invasion conditions, replication and transcription of viral DNA deplete intracellular NTP and dNTP, rapidly activating the Gabija complex. This complex first cleaves circular DNA to inhibit bacteriophage DNA replication, thereby blocking phage amplification, as shown in Figure 2.

Article link: https://www.nature.com/articles/s41467-024-45173-7.

Contact:
Dr. WEI Taotao
Institute of Biophysics, Chinese Academy of Sciences
Beijing 100101, China
Email: weitt@ibp.ac.cn

(Source: IBP)