A new type of DNA phosphorothioation-based antiviral system in archaea

With the support by the National Natural Science Foundation of China, the research team led by Prof. Chen Shi (陈实) at the Key Laboratory of Combinatorial Biosynthesis and Drug Discovery Ministry of Education, School of Pharmaceutical Sciences, Wuhan University, discovered a new type of DNA phosphorothioate (PT) modification-based antiviral system in archaea, which was published in *Nature Communications* (2019, 10: 1688).

PT modification is a newly identified DNA structural alteration in which the non-bridging oxygen in the DNA sugar-phosphate backbone is replaced by sulfur. This unusual oxygen-sulfur swap occurs in a sequence-selective and R_P configuration-specific manner governed by gene products of the *dndABCDE* cluster. To understand this unusual sulfur-containing DNA modification, Prof. Chen's group has conducted extensive investigations towards its physiological functions. The sulfur-for-oxygen substitution confers nuclease resistance to PT linkage. In some bacteria, PTs constitute a defense barrier resembling the methylation-based restriction-modification system, in which PT serves as a recognition tag allowing discrimination between self and non-self DNA, and DndFGH acts as the restriction cognate to attack non-PT modified foreign DNA. Moreover, Chen's group has found that PT modification has evolved additional functions including the epigenetic control of gene expression and the maintenance of cellular redox homeostasis. These findings were published in *PNAS* in 2017 and 2018, respectively.

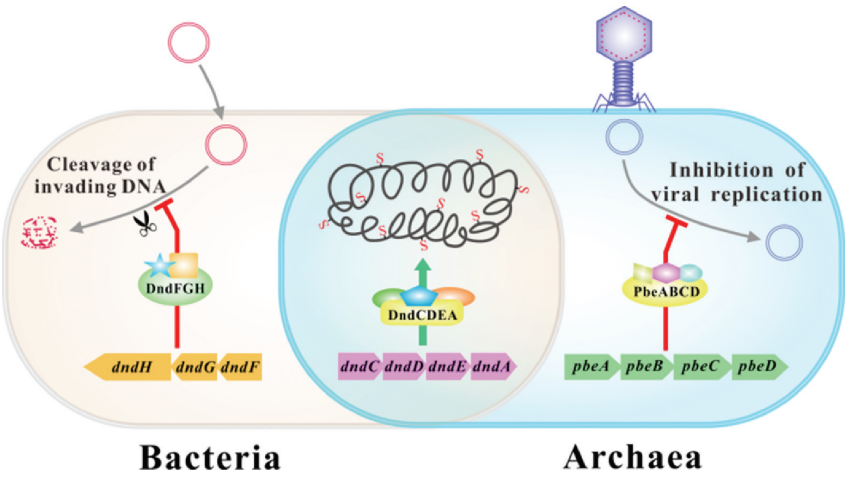

Figure The different genetic organizations and antiviral mechanisms of PT-based DndFGH and PbeABCD defense systems.

In spite of the extensive studies in bacteria, no PT systems have been investigated in the archaea domain. Although categorized as prokaryotes, archaea have the genetic features more similar to those of Eukarya than to those of bacteria. For example, archaea wrap their DNA into histone-DNA complexes with the same geometry as DNA in the eukaryotic nucleosomes. In this work, they reported a new archaeal defence system that involves DndCDEA-specific DNA PT modification and the PbeABCD-mediated halt of virus propagation. PbeABCD is a new set of PT-related restriction proteins, which shares no sequence homology to DndFGH in bacteria but is capable of inhibiting viral DNA replication. Interestingly, unlike the discrimination and cleavage of non-PT-modified invasive DNA by DndFGH, DndCDEA-PbeABCD does not exert its defense function via the degradation or cleavage of viral DNA, expanding the known arsenal of defence systems as well as our understanding of host-virus interactions.