Séminaire

Institut de Biologie Structurale

CONFÉRENCIER INVITÉ

Vendredi 06 Novembre 2020 à 11h

Salle des séminaires IBS

Institut de biologie structurale - 71 avenue des Martyrs CS 10090 38044 Grenoble Cedex 9 - T.+33 (0)4 57 42 85 00

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Phages revenge: Cas9 allosteric inhibition by the anti-CRISPR protein AcrIIA6

The battle for survival between bacterial viruses (bacteriophages or phages) and their prey leads to a continuous evolutionary arms race. Bacteria have evolved sophisticated defense mechanisms to thrive in virus-rich ecosystems, including the well-known CRISPR-Cas9 adaptive immune system. In parallel, phages have developed counter-attack strategies to overcome their host's defenses, including diverse anti-CRISPR proteins that inactivate CRISPR-Cas immunity. Anti-CRISPR proteins do not share much resemblance with each other and with proteins of known function, which raises questions relating to their mode of action. Moreover, these proteins have rapidly garnered interest as they form a promising reservoir of biotechnological tools to fine-tune CRISPR-Cas9-based gene edition, and as useful addition to phage therapy.

In this context, we embarked on the structural and functional characterization of the anti-CRISPR protein AcrIIA6, which inhibits *Streptococcus thermophilus* Cas9 (St1Cas9), combining cryo-electron microscopy, *in vitro* analyses of macromolecular interactions, and functional assays in cells. The AcrIIA6 molecular mechanism is unique: we showed that AcrIIA6 acts as an allosteric inhibitor and induces St1Cas9 dimerization. AcrIIA6 affects St1Cas9 conformational dynamics, which reduces St1Cas9 binding affinity for DNA and prevents St1Cas9 binding to its target within cells. These findings led us to identify a natural St1Cas9 variant resistant to AcrIIA6, illustrating anti-CRISPR-driven mutational escape and molecular diversification of Cas9 proteins.

Hôte : Cécile Breyton (IBS/groupe Membane & Pathogènes)

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Contactez O. Cavoret (au moins 48h à l'avance) - T. 04 57 42 87 04 - email : ibs.seminaires@ibs.fr