Understanding key features of CRISPR/Cas system induction through modeling

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Bacterial immune systems, such as CRISPR/Cas or restriction-modification systems, critically affect bacterial pathogenicity by reducing the flow of genes between bacteria. Additionally, non-canonical functions of CRISPR/Cas, such as regulation of endogenous gene expression, which has a crucial role in virulence, was recently discovered. Both CRISPR/Cas and its components are typically silent under normal conditions, and a major question in understanding CRISPR/Cas functioning is how the expression of this normally silent system is induced, which is very hard to directly experimentally observe. Consequently, CRISPR/Cas induction mechanism is currently unknown, and the main goal of this work is to use computational modeling to understand the role of the key features in CRISPR/Cas induction and to propose a realistic experimental model for the system induction. The first key feature of CRISPR/Cas expression is cooperative transcription repression, with both CRISPR and cas promoters being silenced by cooperatively acting global repressors under standard conditions. On the other hand, transcription regulation of some restriction-modification (RM) systems, which is also exhibited through cooperative binding of transcription regulators, has been studied in detail. Based on similarities in transcription regulation mechanisms, and putative functional constraints on the dynamics of these two bacterial immune systems, in this work we use transcription control of a well-studied RM system as a proxy for a much less understood control of CRISPR/Cas system. The second key feature of CRISPR/Cas expression is fast non-specific degradation of pre-crRNA, which was (surprisingly) shown to be necessary for generating large number of

crRNAs, from small pre-crRNA amounts. Through computational modeling we show that both of these key system features are responsible for a fast (switch-like) transition of the system from "OFF" to "ON" state, which is typically associated with evading the autoimmune response and with efficiently protecting bacterial cell against the infection by foreign DNA. Furthermore, we observe that the cooperative transcription regulation qualitatively leads to a cross-over to the regime where at higher pre-crRNA processing rates the transcript generation approaches the limit of (an infinitely abrupt) system induction. Finally, we show that a more realistic model of CRISPR/Cas induction, where Cas proteins and pre-crRNA are gradually synthesized, still leads to the dynamics of crRNA synthesis capable of protecting the host cell.

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