Study Reveals How Multiple Viruses Can Determine Bacterial Cell Fate

September 15 2008

School of Biology assistant professor Joshua Weitz developed a model that shows that when multiple viruses infect a host cell, those viruses can make a collective decision rather than behaving as they would individually. (Georgia Tech Photo: Gary Meek)

(PhysOrg.com) -- A new study suggests that bacteria-infecting viruses – called phages – can make collective decisions about whether to kill host cells immediately after infection or enter a latent state to remain within the host cell.

The research, published in the September 15 issue of the Biophysical

Journal, shows that when multiple viruses infect a cell, this increases the number of viral genomes and therefore the overall level of viral gene expression. Changes in viral gene expression can have a dramatic nonlinear effect on gene networks that control whether viruses burst out of the host cell or enter a latent state.

“What has confounded the virology community for quite some time is the observation that the cell fate of a bacteria infected by a single virus can be dramatically different than that infected by two viruses,” said Joshua Weitz, an assistant professor in the School of Biology at the Georgia Institute of Technology. “Our study suggests that viruses can collectively decide whether or not to kill a host, and that individual viruses ‘talk’ to each other as a result of interactions between viral genomes and viral proteins they direct the infected host to produce.”

To study viral infections, Weitz teamed with postdoctoral fellow Yuriy Mileyko, graduate student Richard Joh and Eberhard Voit, who is a professor in the Wallace H. Coulter Department of Biomedical Engineering, the David D. Flanagan Chair Georgia Research Alliance Eminent Scholar in Biological Systems and director of the new Integrative BioSystems Institute at Georgia Tech.

Nearly all previous theoretical studies have claimed that switching between “lysis” and “latency” pathways depends on some change in environmental conditions or random chance. However, this new study suggests that the response to co-infection can be an evolvable feature of viral life history.

For this study, the researchers analyzed the decision circuit that determines whether a virus initially chooses the pathway that kills the host cell – called the lytic pathway – or the pathway where it remains dormant inside the host cell – called the lysogenic pathway.

When the lytic pathway is selected, the virus utilizes bacterial resources to replicate and then destroys the host cell, releasing new viruses that can infect other cells. In contrast, in the lysogenic pathway, the viral genome inserts itself into the bacterial genome and replicates along with it, while repressing viral genes that lead to lysis. The virus remains dormant until host conditions change, which can result in a switch to the lytic pathway.

The decision of the genetic circuit that controls whether a virus initially chooses lysis or lysogeny is not random. Instead, cell fate is controlled by the number of infecting viruses in a coordinated fashion, according to the new study, which was funded by the Defense Advanced Research Projects Agency, the National Science Foundation and the Burroughs Wellcome Fund.

“In the case of perhaps the most extensively studied bacteriophage, lambda phage, experimental evidence indicates that a single infecting phage leads to host cell death and viral release, whereas if two or more phages infect a host the outcome is typically latency,” explained Weitz, who is a core member of the new Integrative BioSystems Institute at Georgia Tech. “We wanted to know why two viruses would behave differently than a single virus, given that the infecting viruses possess the same genetic decision circuit.”

To find out, the researchers modeled the complex gene regulatory dynamics of the lysis-lysogeny switch for lambda phage. They tracked the dynamics of three key genes – cro, cI and cII – and their protein production. The decision circuit involved both negative and positive feedback loops, which responded differently to changes in the total number of viral genomes inside a cell. The positive feedback loop was linked to the lysogenic pathway and the negative feedback loop was linked to the lytic pathway.

With a single virus, cro dominated and the lytic pathway prevailed. If the

number of co-infecting viruses exceeded a certain threshold, the positive feedback loop associated with cI dominated, turning the switch to the lysogenic pathway. The differences in bacterial cell fate were stark and hinged upon whether or not one or two viruses were inside a given cell.

The researchers found that the cII gene acted as the gate for the system. Increasing the number of viruses drove the dynamic level of cII proteins past a critical point facilitating production of cI proteins leading to the lysogenic pathway.

“The decision circuit is a race between two pathways and in the case of a single virus, the outcome is biased toward lysis,” explained Weitz. “In our model, when multiple viruses infect a given cell, the overall production of regulatory proteins increases. This transient increase is reinforced by a positive feedback loop in the latency pathway, permitting even higher production of lysogenic proteins, and ultimately the latent outcome.”

The central idea in the model proposed by Weitz and collaborators is that increases in the overall amount of viral proteins produced from multiple viral genomes can have a dramatic effect on the nonlinear gene networks that control cell fate.

“Many questions still remain, including to what extent subsequent viruses can change the outcome of previously infected, but not yet committed, viruses, and to what extent microenvironments inside the host impact cell fate,” added Weitz. “Nonetheless, this study proposes a mechanistic explanation to a long-standing paradox by showing that when multiple viruses infect a host cell, those viruses can make a collective decision rather than behaving as they would individually.”

Provided by Georgia Institute of Technology