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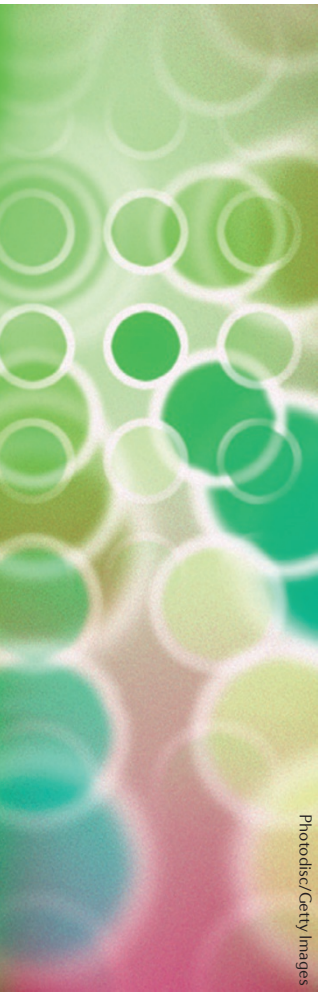

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MICROBIAL GENETICS

Amplified origins of antibiotic resistance

Many bacteria activate a state of 'competence' in response to antibiotic treatment, in which they have an increased ability to take up exogenous DNA and can thereby acquire antibiotic resistance genes. Key genes that are required for competence induction (*com* genes) have been characterized, although how they mediate competence seems to depend on the type of antibiotic used. A new study shows that competence in response to various antibiotics that induce replication stress occurs through an increase in copy number of *com* genes near the replication origin.

Slager *et al.* studied the response of *Streptococcus pneumoniae* (which causes pneumonia and other diseases) to the bacterial DNA polymerase inhibitor 6-(*p*-hydroxyphenylazo)-uracil (HPUra). The resulting replication stress caused competence, as shown by the transcriptional induction of competence genes and by the ability to import and integrate exogenous DNA. From a global analysis of the transcriptional response to HPUra, the authors found that it was specifically genes proximal to the DNA replication origin (*oriC*) that were upregulated, including known *com* genes.

Interestingly, fluorescence microscopy and DNA copy-number analysis showed that HPUra slowed replisome progression away from *oriC* while allowing repeated firing of new DNA replication at *oriC*, thus increasing the copy number of *oriC*-proximal genes relative to genes elsewhere on the chromosome and providing an explanation for their selective transcriptional upregulation. Further evidence for this mechanism came from engineered strains, in which moving *com* genes away from *oriC* blocked antibiotic-induced competence, whereas additional copies of *oriC*-proximal *com* genes speeded up the response.

The authors investigated the generality of this mechanism by analysing the genomes of different bacterial species and their responses to a range of antibiotics. They found that *com* genes are frequently *oriC*-proximal, and that *oriC*-proximal genes increase in both copy number and transcriptional output in various species in response to different replication-stress-inducing antibiotics. This occurred even for antibiotics that work through distinct mechanisms from HPUra, such as the DNA gyrase inhibitor ciprofloxin and the ribonucleotide reductase inhibitor hydroxyurea.

This study indicates that the evolutionarily conserved genomic locations of *com* genes may provide an intrinsic and robust mechanism to promote bacterial survival and resistance to diverse antibiotics. It will be interesting to see whether such knowledge can guide the choices of clinically administered antibiotics to minimize resistance.

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ORIGINAL RESEARCH PAPER Slager, J. *et al.* Antibiotic-induced replication stress triggers bacterial competence by increasing gene dosage near the origin. *Cell* **157**, 395–406 (2014)