Flippable DNA switches help bacteria resist antibiotics and are more common than thought

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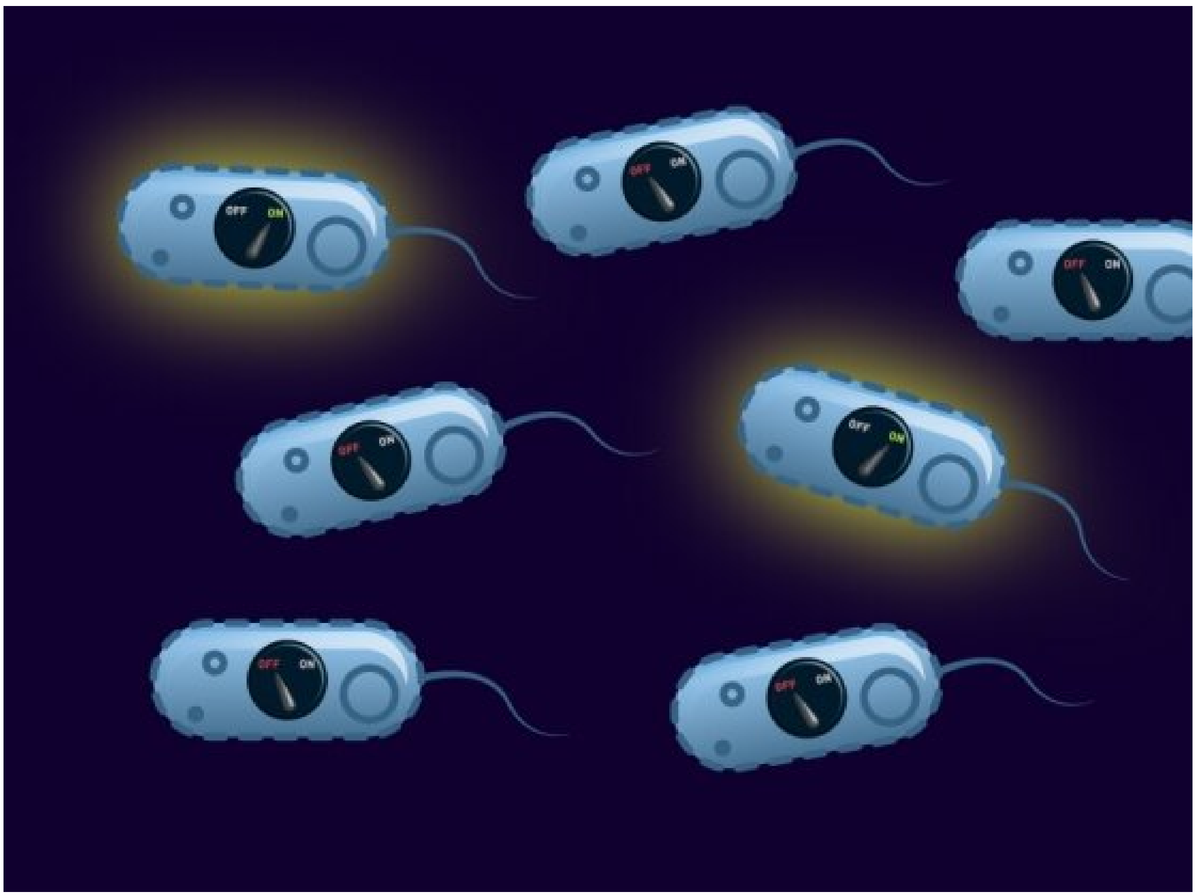

Credit: Susanna M. Hamilton, Broad Communications

Bacteria have a number of well-known tricks available to them to adapt to changing environments, such as mutation and sharing snippets of

DNA with each other. Less studied is a mechanism that allows bacteria to hedge their bets against rapid environmental changes by fine tuning their use of particular genes or pathways, a process known as "phase variation."

Phase variation acts through a unique family of bacterial promoters and other gene-regulating DNA fragments called invertons, which can physically flip back and forth in place. When facing forward (relative to the surrounding DNA), these invertible elements turn nearby genes on; when backward, the genes remain off. But little is known about how widespread invertons are within the bacterial world, which bacterial functions they control, and whether an individual person's distinct physiological makeup can affect which invertons bacteria flip on or off.

Writing in *Science*, a team led by researchers from the Broad Infectious Disease and Microbiome Program (IDMP), Massachusetts General Hospital, and the MIT Center for Microbiome Informatics and Therapeutics (CMIT) report that invertons are present in a wide variety of bacteria, make the case that invertons foster antibiotic resistance, and suggest that they may help bacteria adapt to and colonize new hosts.

Invertons, the team noted, are common, particularly among bacterial species found in the human gut. Many help bacteria adjust their interactions with a host's immune system and other aspects of their surroundings by controlling which proteins and other molecules they display on the surface.

They also appear to respond to a bacterial cell's surroundings. For instance, surveys of gut bacteria from microbiome transplants revealed that many invertons flip orientations as they colonize their recipients, further supporting an environmental adaptive role.

In addition, the team spotted many invertons regulating antibiotic resistance genes, with their "off"/"on" ratio changing significantly after drug exposure. In that context, a picture starts to emerge from their data. Within a group of bacteria, an inverton overseeing a resistance gene will be in the "off" position in most cells. (Antibiotic resistance genes often affect vital functions like protein production, and so bacteria keep these gene off most of the time.) However, the inverton will be "on" in a small number of cells, rendering them resistant.

Antibiotic exposure wipes out most of the bacteria in the group, but that small number can replenish the population. After the antibiotic is gone, over time the inverton flips "off" in the majority of the cells.

To come to their conculsions, the researchers examined sequence data from nearly 55,000 bacterial genomes deposited in the National Center for Biotechnology Information, using a bespoke algorithm called PhaseFinder to look for invertons' telltale genomic hallmarks, followed up by laboratory studies. They also sampled bacteria from patients who underwent microbiome transplants.

Taken together, the team's results point to the many parts that invertons play in managing how bacteria and their hosts coexist, and in potentially fostering the rising tide of antibiotic resistance—findings warranting further, deeper study.

More information: Xiaofang Jiang et al. Invertible promoters mediate bacterial phase variation, antibiotic resistance, and host adaptation in the gut, *Science* (2019). DOI: 10.1126/science.aau5238

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