Study reveals why certain drug combinations backfire

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Combination drug therapy has become a staple for treating many infections. For instance, doctors treat extensively drug resistant forms of tuberculosis with one drug that breaks down the pathogen's protective barriers and opens the door for another to deliver the deathblow.

Just as some drugs work better together, however, other pairings are counter-productive. "The question we asked was how can it be that two drugs in combination are less effective than one of them alone," said senior author and Harvard Medical School associate professor of systems biology Roy Kishony.

Kishony and his team have found that the answer lies in the way some antibiotic drugs influence a bacterial cell's gene expression levels. Combinations of these altered genetic behaviors can "put the cell in a better position for survival," said Kishony.

The work, which was done in collaboration with Stanford University research associate Selwyn Quan, is described in the November 13 *Cell*.

Kishony's work on drug combinations began in 2006 when his lab found that understanding why certain drugs work well or poorly together can help researchers identify the cellular functions they attack. For instance, drugs that block protein production work poorly with drugs that block DNA replication, but they work well with drugs that weaken the cell wall.

According to first author and research fellow in systems biology Tobias Bollenbach, clinical researchers are primarily interested in drugs that together work better than either alone, and so studies tend to focus on explaining some of the mechanisms behind synergistic drug pairings.

However, ever since the Kishony lab discovered in 2008 that antagonistic drug pairings slow down the evolution of antibiotic resistance, it has become increasingly clear that these drug combinations warrant further study.

To explore the dynamics of these antagonistic drug interactions, Kishony, Bollenbach, and doctoral candidate Remy Chait zeroed in on two classes of antibiotics that suppress one another. One class of drugs he investigated interrupts the replication of DNA and the other blocks the manufacture of proteins. They studied their combined effects on the bacteria Escherichia coli.

Drugs that impede DNA synthesis, such as Ciprofloxacin (a drug rarely used these days), interrupt cell division. As a result, E. coli enters a state of stress.

Normally, when a cell is in a stressful state it responds by trying to repair itself and by scaling back on its other activities, such as production of ribosomes, the molecular machines that manufacture proteins.

But with Ciprofloxacin, the cells try to repair DNA while still producing ribosomes. This is not in the cell's best interest, because making ribosomes uses up cellular resources and creates a surplus of proteins, which is even more costly.

When the team added the additional stress of a protein-synthesis inhibiting drug, such as Tetracycline, instead of causing the cells more trouble, the second drug counteracted the overproduction of ribosomes

and proteins. "Since this other drug inhibits the ribosome, it corrects for the fact that the cell made too many in the first place," said Bollenbach.

The team hypothesized that the second drug restored the cellular equilibrium that the first drug distorted. This enabled the bacteria to flourish in the midst of this dual-antibiotic assault, though it isn't yet mechanistically clear why.

To corroborate these initial findings, the team conducted a second round of experiments in which they impaired the ability of E. coli to produce ribosomes. As a result, the cells could more easily withstand the assault of the first drug, yet succumbed to the second, completely removing the strong antagonism between the drugs.

This work "suggests that there are things about antibiotics and other inhibitors that we never suspected," said University of British Columbia microbiologist Julian Davies, "We are so naive about how drugs work. We are so naive about the activities of these compounds once they are actually in human beings. What I think will be important about this work is that people will be able to design model studies with animals. If one can reproduce these results in animal models, they could be adapted to a human situation."

The discovery has inspired Kishony and his team to ask a more general question about antibiotic interactions. Kishony recently received a federal stimulus grant to pursue a study that explores the genetic determinants of drug interactions more broadly and investigates whether cells can be synthetically manipulated to change the way drugs interact.

"Understanding how cells alter their genetic programs in the presence of antibiotic drugs could provide insights into new ways to discourage the growth of pathogens and encourage the growth of 'good' bacteria in the lab and in the clinic," said Kishony.

Source: Harvard Medical School (news : web)