Researchers study the pathobiology of antibiotic side reactions

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You get an infection, you are given penicillin—and then you could get hemorrhagic diarrhea. This rare but extremely unpleasant side reaction can be related to the enterotoxin tilivalline produced by a regular intestinal bacterium. Austrian scientists have now scrutinized the toxin's biosynthetic pathway and presented the results in the journal *Angewandte Chemie*. Their findings give important insights in the pathobiology of antibiotic side reactions and unveil the multifunctionality of bacterial toxins.

Some bacteria are sensitive to penicillin, others are not. When patients take antibiotics to destroy harmful microorganisms, their own intestinal microbiota suffers. If the introduced imbalance leads to an overgrowth of bacteria producing toxins themselves, intestinal and metabolic disorders can follow. In an interdisciplinary collaboration, Ellen Zechner of the University of Graz, Austria, and her colleagues have researched the role of penicillin-resistant Klebsiella oxytoca enterobacterium in antibiotic-associated hemorrhagic colitis (AAHC).

They first identified a metabolite tilivalline as a critical enterotoxin, which in higher doses, damages the intestinal epithelium and can induce colitis. Surprisingly, tilivalline shares its chemical structure with a class of soil bacteria metabolites called pyrrolobenzodiazepines, which are in clinical trials for their antitumor properties. After having identified the gene cluster for tilivalline synthesis, the scientists performed comprehensive biomolecular and molecular genetic experiments to track down the complete biosynthetic pathway of tilivalline.

Tilivalline itself lacks the DNA-damaging activity of its antitumor antibiotic relatives because the chemical site crucial for DNA interference is blocked. However, Zechner and colleagues found that the source of the blocking, an indole, only enters the biosynthetic pathway at its end. The tilivalline precursor without the indole, which was then named tilimycin, was shown to be a more potent cytotoxin than tilivalline. Surprisingly, the final addition of the indole to tilimycin occurs spontaneously, without the help of any enzyme. "Klebsiella oxytoca is able to produce two pyrrolobenzodiazepines with distinct functionalities depending on the availability of indole," the scientists stated. Indole occurs naturally in the human gut.

Both outcomes, the elucidation of the biosynthetic pathway and the discovery of tilimycin as a stable intermediate metabolite that is even more toxic to human cells, have important physiological and pharmacological implications. First, the better understanding of the AAHC pathogenesis may lead to new treatment schemes and strategies to avoid or alleviate antibiotic side reactions. And second, the unusual Klebsiella pathway to the anticancerogenic structures can inspire scientists to develop new approaches for producing anticancer drugs.

More information: Elisabeth Dornisch et al. Biosynthesis of the Enterotoxic Pyrrolobenzodiazepine Natural Product Tilivalline, *Angewandte Chemie International Edition* (2017). DOI: 10.1002/anie.201707737

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