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Okayama University research: Friend to Foe—When Harmless Bacteria Turn Toxic

(Okayama, 27 November) **In a study recently published in *PLoS Pathogens*, researchers at Okayama University reveal novel mutations which transform bacteria into infectious bugs that are resistant to antibiotics.**

Not all bacteria are naturally infectious. Several strains of innocuous bacteria turn infectious over their lifespan. However, the mechanisms by which such bacteria acquire pathogenic properties (known as virulence in microbiology terms) are still a mystery. Now, a research team led by Professor KAITO Chikara from Okayama University has identified specific gene mutations which drive this deadly switch in the microorganisms.

The researchers employed a non-pathogenic strain of *Escherichia coli*, bacteria commonly used in the laboratory, and exposed them to mutation-inducing processes. The bacteria were subsequently injected into silkworms. After multiple rounds of mutagen exposure, the *E.coli* started swiftly killing the worms, turning 500 times more lethal at a certain point. A closer look at the DNA of this dangerous strain revealed mutations in a protein known as the lipopolysaccharide (LPS) transporter. The LPS transporter resides on the bacterial membrane and funnels LPS, a bacterial toxin, from within the cell onto its surface. To understand how these mutations were linked to bacterial toxicity, the mutant *E.coli* were treated with host antimicrobial peptides or antibiotics. These antimicrobial molecules, however, did not hamper the growth of the mutant bacteria suggesting that the mutants had developed resistance against host immune response and antibiotics.

Bacteria store an arsenal of chemicals on their surface within small vesicles. The mutant *E.coli* had an abundance of such vesicles which were also rich in LPS. It thus seemed that the bugs had developed a clever mechanism to expel toxins and chemicals out of the cell. The team then analysed the LPS transporter to investigate whether its mutations played a role in this regard. Indeed, the structure of the LPS transporter was found altered in the mutant strains. A plug which keeps the channel of the transporter closed, appeared defective. Lastly, to see whether similar mutations in the LPS transporter occur naturally, the team examined bacterial samples taken from patients. As expected, these samples contained similar mutants of *E.coli* which were also resistant to antimicrobials. Mutations in the LPS transporter were thus conferring bacteria with crafty mechanisms to stay alive and infect host cells.

“These findings suggest that non-pathogenic bacteria can gain virulence traits by changing the functions of essential genes, and provide new insight to bacterial evolution in a host environment,” conclude the researchers. Information on such toxic mutations in bacteria are vital for diagnosing infections and developing appropriate antibacterial drugs.

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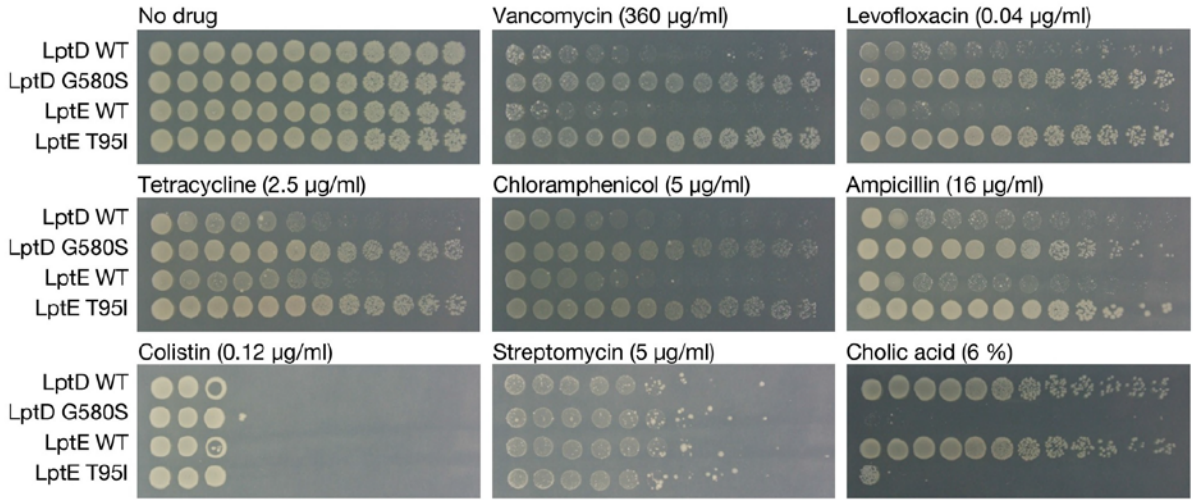
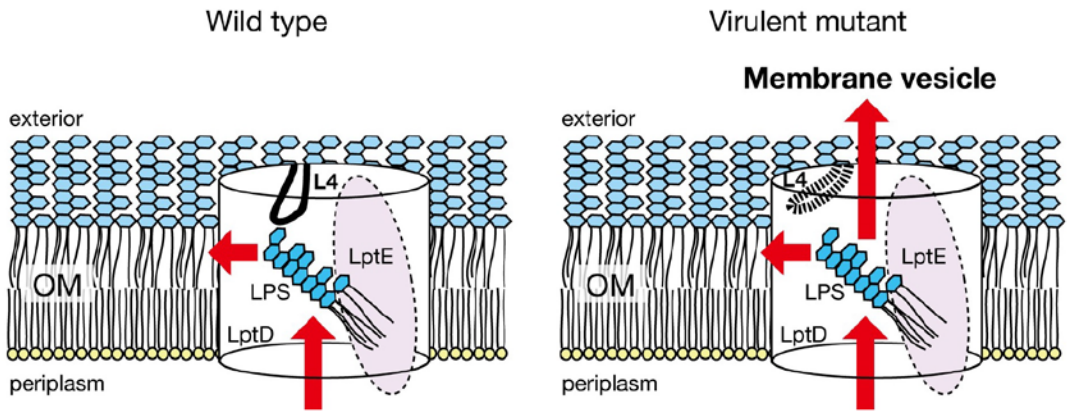
Background

Virulence – A microorganism's ability to infect a host cell is known as virulence. Organisms have varying mechanisms of virulence known as virulence factors. Common virulence factors driving bacterial toxicity are chemicals that help bacteria invade and adhere to host cells or poisons that damage host cells. A thorough understanding of these factors is key to developing strategies for combatting bacterial toxicity.

Lipopolysaccharide (LPS) – LPS is a chemical that forms a major component of the outer membrane of bacteria. Once synthesized within the bacterial cell, it is pushed out through a channel known as the LPS transporter to subsequently reside within the outer membrane. LPS protects the bacterial membrane from foreign attacks and induces responses such as inflammation, fever, and septic shock when bacteria infect hosts. Thus, LPS is a crucial component of the bacterial defense system.





Caption

Top. Mutant bacteria (LptD G580S and LptE T95I) were resistant to common antimicrobial drugs and survived in their presence compared to the nonmutated (LptD WT and LptE WT) strains.

Bottom. A graphical representation of the structural alteration in the LPS transporter induced by the mutations resulting in a rearrangement of the plug (L4) that keeps the channel closed.

Reference

Chikara Kaito, Hirono Yoshikai, Ai Wakamatsu, Atsushi Miyashita, Yasuhiko Matsumoto, Tomoko Fujiyuki, Masaru Kato, Yoshitoshi Ogura, Tetsuya Hayashi, Takao Isogai, Kazuhisa Sekimizu. Non-pathogenic *Escherichia coli* acquires virulence by mutating a growth-essential LPS transporter. *PLoS Pathogens*, 2020 Apr; 16(4): e1008469.
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https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1008469

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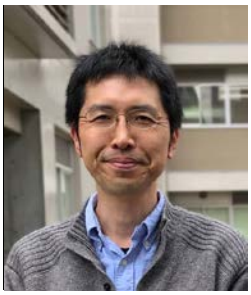

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◆About Okayama University

Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html

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Hirofumi Makino, M.D., Ph.D.
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