A peptidoglycan storm caused by β-lactam antibiotics' action on host microbiota drives *Candida albicans* infection

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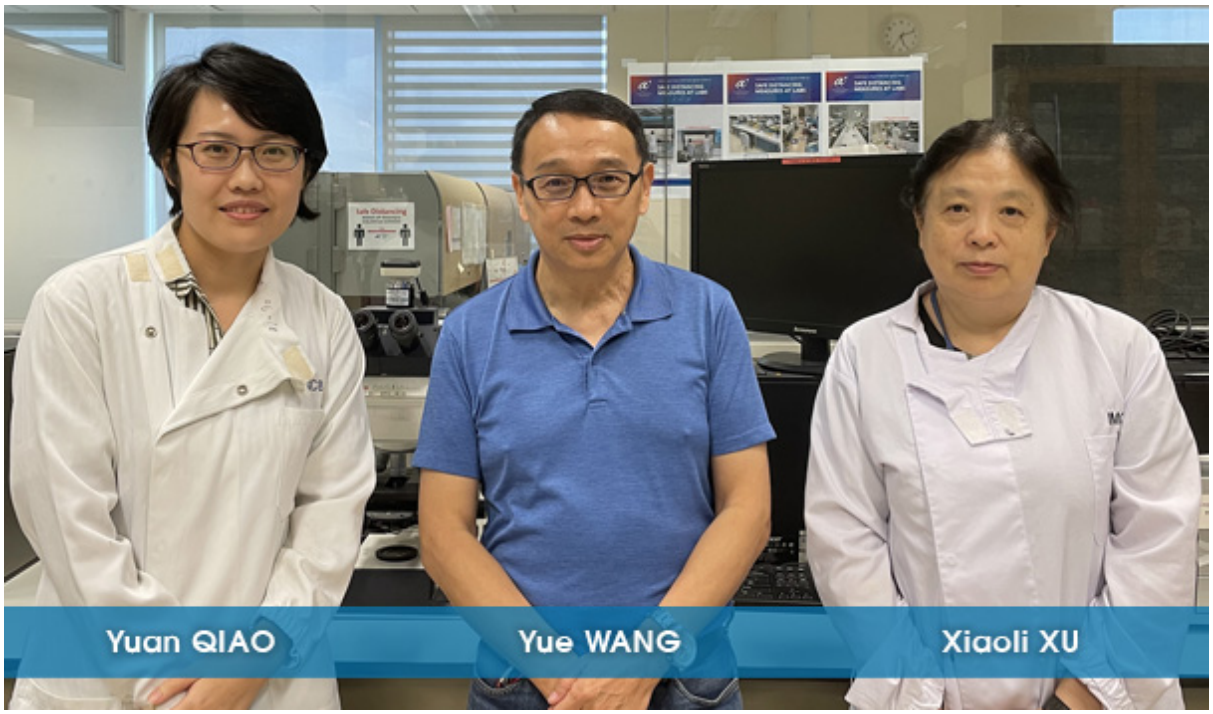

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Abstract

The commensal fungus *Candida albicans* often causes life-threatening infections in immunocompromised patients with high mortality. A prominent but poorly understood risk factor for the *C. albicans* commensal–pathogen transition is the use of broad-spectrum antibiotics. Here, we report that β-lactam antibiotics cause bacteria to release significant quantities of peptidoglycan fragments that potently induce the invasive hyphal growth of *C. albicans*. We identify several active peptidoglycan subunits, including tracheal cytotoxin, a molecule produced by many Gram-negative bacteria, and fragments purified from the cell wall of Gram-positive *Staphylococcus aureus*. Feeding mice with β-lactam antibiotics causes a peptidoglycan storm that transforms the gut from a niche usually restraining *C. albicans* in the commensal state to promoting invasive growth, leading to systemic dissemination. Our findings reveal a mechanism underlying a significant risk factor for *C. albicans* infection, which could inform clinicians regarding future antibiotic selection to minimize this deadly disease incidence.

Figure:

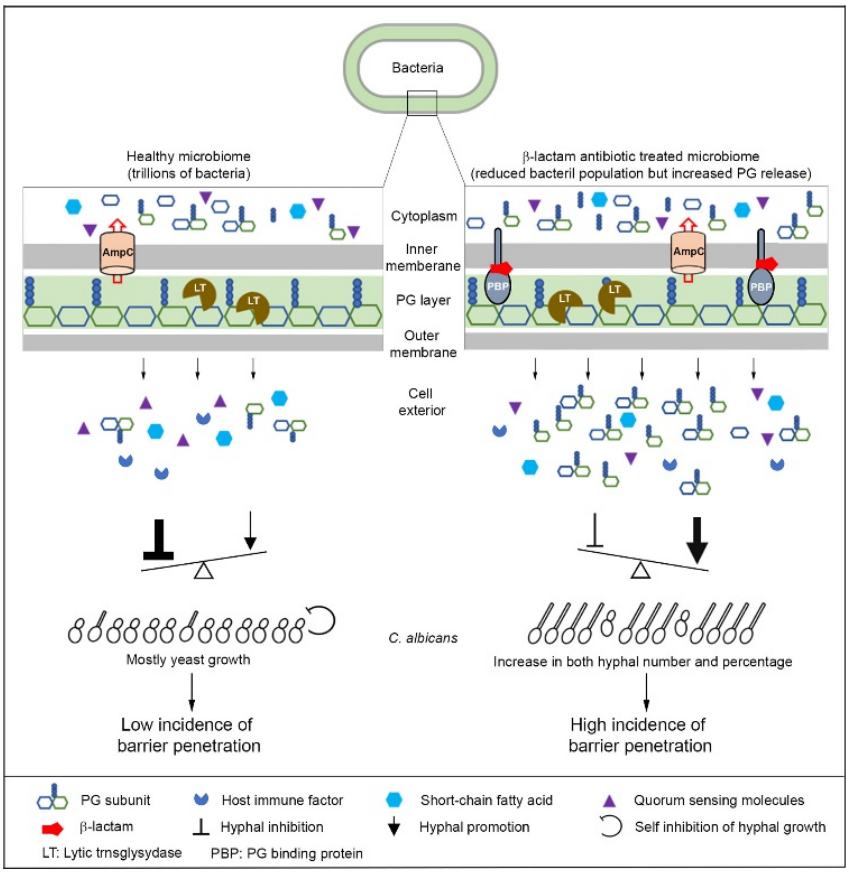

Figure legend: A model depicting the mechanism by which β-lactam antibiotic treatment increases the risk of invasive *C. albicans* infection

The left column depicts the microbiota-*C. albicans* interactions in the GI tract of healthy individuals, where the hyphal growth of *C. albicans* is kept in check by the combined actions of different classes of inhibitory molecules including microbiota-derived quorum-sensing molecules and short-chain fatty acids, host-derived antimicrobial peptides and immune effectors, as well as the self-repression system of *C. albicans*. There is a low incidence of *C. albicans* hyphal growth and mucosal barrier penetration for dissemination. The right column depicts the effects of β-lactam antibiotics on human gut microbiota that tip the balance in favor of *C. albicans* hyphal growth. β-lactam antibiotics the bacterial PGN assembly, which causes the generation of hyphal-inducing PGN subunits and lysis of bacteria cells, resulting in the release of a massive amount of PGN subunits. The β-lactam PGN storm transforms the GI environment from inhibitory to favorable to the hyphal growth of *C. albicans*, thus vastly increasing the number of hyphae and the probability of breaching the mucosal barrier for dissemination.