Micalis
Microbiologie de l'Alimentation au service de la Santé

Novel antibiotics inferred from a Toxin-Antitoxin module effective against gram-positive and negative multi-resistant bacteria with limited resistance

Brice Felden

Université de Rennes, Inserm BRM 'Bacterial RNAs & Medicine'

Antibiotics are a medical wonder, but an increasing frequency of resistance among most human pathogens is rendering them ineffective. If this trend continues, the consequences for public health and for the general community could be catastrophic. Thus, there is an urgent and growing need for new classes of antibiotics to maintain the advanced medical procedures we now take for granted. The current clinical pipeline, however, is very limited and is dominated by derivatives of established classes. Here, we have exploited our recent identification of a bacterial peptide expressed from a toxin-antitoxin module to transform it into antibiotics active on multi-drug resistant (MDR) Gram positive and negative bacterial pathogens. A new family of peptidomimetics was produced, several effective against methicillin-resistant *Staphylococcus aureus* (MRSA) in mild and severe sepsis mouse models without exhibiting toxicity on human erythrocytes and kidney cells, zebrafish embryos and mice. *In vivo* efficacy was also demonstrated against *Pseudomonas aeruginosa* and MRSA in a mouse skin infection model. Importantly, these compounds did not result in resistance after *in vitro* serial passages and day's exposure *in vivo*. Activity of heptapseudopeptides was explained by the ability of unnatural amino acids to strengthen dynamic association with bacterial lipid bilayers and to induce membrane permeability, leading to bacterial death. Based on structure determination, we showed that cationic domains surrounded by an extended hydrophobic core could improve bactericidal activity. Because two peptide analogs are effective against both MRSA and *P. aeruginosa* in severe sepsis and skin infection models, respectively, we believe these peptidomimetics merit clinical testing.

PLoS Biol. 2019 17(7):e3000337; *Chem Biol* 2015;22(3):329-35; *Nat Struct Mol Biol* 2011;19(1):105-12

Vendredi 24 janvier 2020
14h
Auditorium - Bât. 442
INRA, Jouy en Josas

Invité par Francis Repoila (francis.repoila@inrae.fr)