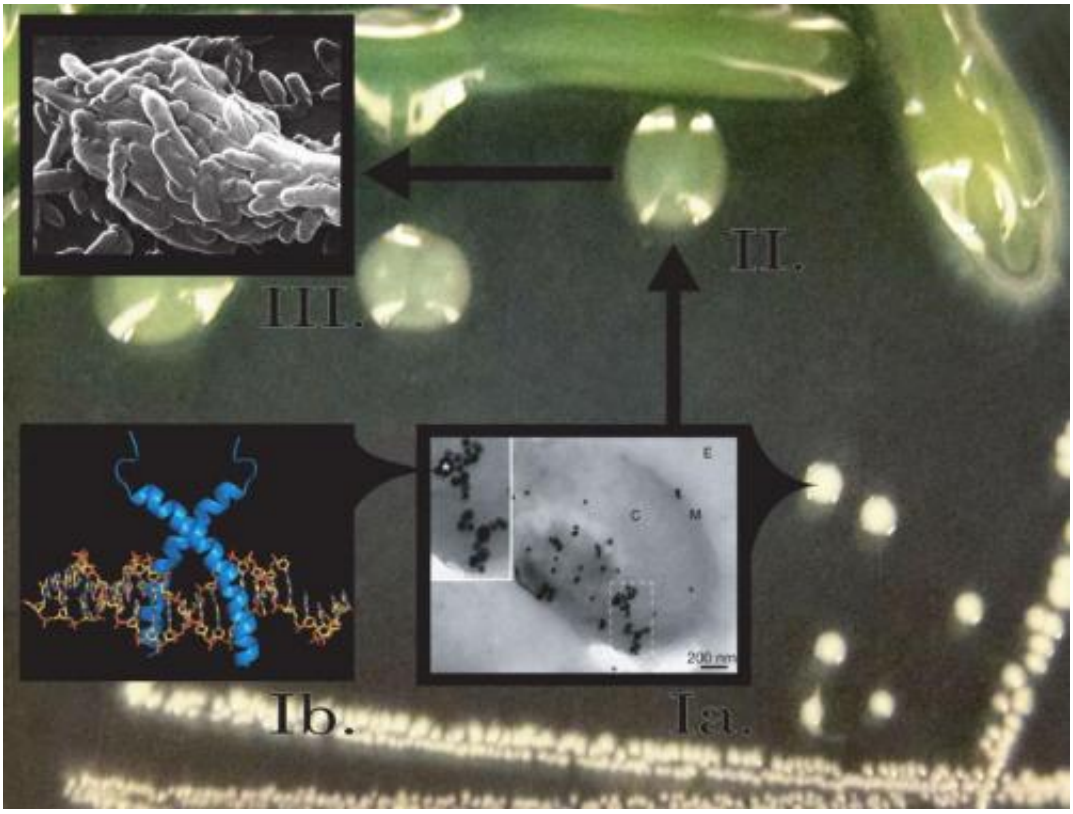
Low-dose natural antimicrobial exacerbates chronic lung infection in cystic fibrosis

April 24 2014



This shows the proposed model of LL-37 induced mutagenesis and mucoid conversion. Step Ia, at low doses LL-37 (*) interacts with *Pseudomonas aeruginosa* and enters bacterial cells, binding to DNA (Step Ib). LL-37/DNA interactions promote mucA mutagenesis and conversion to the mucoid phenotype (Step II). Mucoid *P. aeruginosa* biofilms are now more resistant to killing by lethal levels of LL-37 and are selected for in the CF pulmonary environment (Step III). Credit: Wozniak et. al

Respiratory failure caused by chronic lung infection with *Pseudomonas aeruginosa* bacteria is a common cause of death in patients with cystic fibrosis (CF), a genetic disease that is common in individuals of European descent. A study published on April 24th in *PLOS Pathogens* demonstrates that an antimicrobial peptide produced by human immune cells can promote mutations in the bacterium that make it more lethal.

Daniel Wozniak, from The Ohio State University Wexner Medical Center, USA, and colleagues studied a process called "mucoid conversion", which involves mutations in *Pseudomonas* that produce a sticky sugar coating of the bacteria which makes them more resistant to various treatments. The process is fairly well understood, and involves mutation of a particular *Pseudomonas* gene called mucA. Searching for factors of the human host that facilitate mucA mutation, the scientists found that specific immune system cells called polymorphonucleocytes (or neutrophils), which are present in large numbers in lung cells of patients with CF, can trigger *Pseudomonas* mucoid conversion, and that a specific antimicrobial factor produced by these cells called LL-37 plays a key role.

At high doses, LL-37 can kill bacteria by poking large holes into their cell walls. However, at lower concentrations (which seem to mimic the situation in the lungs of CF patients), the scientists found that some LL-37 molecules can enter the bacterial cells without killing them. Once inside, LL-37 appears to be able to directly interact with and alter the bacterial DNA, leading to mutation of the mucA gene. The resulting mucoid conversion makes the sugar-coated bacteria then resistant to higher doses of LL-37, including doses that would readily kill the "naked" Pseudomonas bacteria prior to mucoid conversion.

The scientists went on to show that LL-37 can induce mutations besides those in mucA in both *Pseudomonas* and *E. coli*, showing that its function as a mutagen is neither restricted to a particular gene nor a

particular pathogen.

Taken together, the results demonstrate that an antimicrobial substance can, at low dose, function as a mutagen that makes bacteria more dangerous. Given that antimicrobial peptides similar to LL-37 are being discussed as promising leads for the development of new antibiotics, the scientists say their data "reinforce how important it is to consider the impact of current and novel treatments and the host immune response on evolution of microbial communities during chronic infections."

More information: Limoli DH, Rockel AB, Host KM, Jha A, Kopp BT, et al. (2014) Cationic Antimicrobial Peptides Promote Microbial Mutagenesis and Pathoadaptation in Chronic Infections. *PLoS Pathog* 10(4): e1004083. DOI: 10.1371/journal.ppat.1004083