

The evolution of colistin resistance increases bacterial resistance to host antimicrobial peptides and virulence

Pramod K Jangir^{1*}, Lois Ogunlana¹, Petra Szili^{2,3}, Marton Czikkely², Liam P Shaw¹, Emily J Stevens¹, Yang Yu⁴, Qiue Yang⁵, Yang Wang⁶, Csaba Pál², Timothy R Walsh¹, Craig R MacLean^{1*}

¹Department of Biology, University of Oxford, Oxford, United Kingdom; ²Synthetic and Systems Biology Unit, Biological Research Centre, Eötvös Loránd Research Network, Szeged, Hungary; ³Doctoral School of Multidisciplinary Medical Sciences, University of Szeged, Szeged, Hungary; ⁴Guangdong Provincial Key Laboratory of Veterinary Pharmaceutics Development and Safety Evaluation, South China Agricultural University, Guangzhou, China; ⁵Fujian Provincial Key Laboratory of Soil Environmental Health and Regulation, College of Resources and Environment, Fujian Agriculture and Forestry University, Fuzhou, China; ⁶Beijing Advanced Innovation Centre for Food Nutrition and Human Health, College of Veterinary Medicine, China Agricultural University, Beijing, China

*For correspondence:
jangir.pramod@gmail.com
(PKJ);
craig.maclea@biology.ox.ac.uk
(CRMaclea)

Present address: ¹Biozentrum,
University of Basel, Basel,
Switzerland

Competing interest: The authors
declare that no competing
interests exist.

Funding: See page 15

Preprinted: 12 February 2022

Received: 23 October 2022

Accepted: 05 April 2023

Published: 25 April 2023

Reviewing Editor: Vaughn S
Cooper, University of Pittsburgh,
United States

© Copyright Jangir et al. This
article is distributed under the
terms of the [Creative Commons
Attribution License](#), which
permits unrestricted use and
redistribution provided that the
original author and source are
credited.

Abstract Antimicrobial peptides (AMPs) offer a promising solution to the antibiotic resistance crisis. However, an unresolved serious concern is that the evolution of resistance to therapeutic AMPs may generate cross-resistance to host AMPs, compromising a cornerstone of the innate immune response. We systematically tested this hypothesis using globally disseminated mobile colistin resistance (MCR) that has been selected by the use of colistin in agriculture and medicine. Here, we show that MCR provides a selective advantage to *Escherichia coli* in the presence of key AMPs from humans and agricultural animals by increasing AMP resistance. Moreover, MCR promotes bacterial growth in human serum and increases virulence in a *Galleria mellonella* infection model. Our study shows how the anthropogenic use of AMPs can drive the accidental evolution of resistance to the innate immune system of humans and animals. These findings have major implications for the design and use of therapeutic AMPs and suggest that MCR may be difficult to eradicate, even if colistin use is withdrawn.

Editor's evaluation

Antimicrobial peptides (AMPs) are a class of antibiotics that are inspired by natural components of innate immunity, which raises the specter of bacteria becoming resistant to both. Jangir et al. test this idea and find compelling evidence that a plasmid that encodes resistance to the AMP colistin also increases resistance to AMPs produced by humans, pigs, and chickens, enables the bacteria to grow better in low levels of AMP, and increases bacterial virulence in an insect model of infection. This important study will be of interest to both evolutionary biologists and microbiologists focused on antimicrobial therapy and suggests that the evolution of resistance to these compounds can have collateral effects on immune evasion as well.