How antibiotic resistant microbes protect themselves from attack of body's defenses
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Klebsiella pneumoniae can cause deadly infections such as pneumonia, wound or bloodstream infections, that are becoming untreatable due to the lack of effective antibiotics due to antibiotic resistance (AMR).

AMR is a major global health threat, accounting for more than five million deaths a year. Public Health England has warned that the lack of effective antibiotics could result in three million routine operations becoming life-threatening.

These findings, published in Cell Reports, represent a step change in the fight against the global pandemic of antibiotic resistant infections and was led by researchers from the Wellcome-Wolfson Institute for Experimental Medicine at Queen's University Belfast and the Trinity Biomedical Sciences Institute at Trinity College Dublin.

The research demonstrates that Klebsiella hijacks a protein from our cells, SARM1, to limit the activation of protective inflammation. Previously, SARM1 was shown to be involved in neurogenerative disease.

Now, researchers demonstrate that Klebsiella induces the expression of SARM1 in macrophages, a type of white blood cell that are crucial for controlling infections. Macrophages kill microorganisms, remove dead cells, and stimulate the action of other immune system cells, to blunt inflammation and to survive inside macrophages, resulting in a protective niche to the action of antibiotics. These findings reveal one of the Achilles heel of our defenses exploited by Klebsiella to survive.

Importantly, researchers have demonstrated that the absence of SARM1 facilitates the clearance of Klebsiella without need of antibiotics in a translational model of human pneumonia. There are anti ASMR1 drugs already under investigation and this research will be the foundation of testing them to treat Klebsiella infections alone or as add-on of antibiotics.

Professor Jose Bengoechea, a world leader in the deadly Klebsiella pneumoniae infection at the Wellcome-Wolfson Institute for Experimental Medicine at Queen's University Belfast, and the lead of the project, explains: "This new research is of great relevance in our understanding of AMR, and marks an advance into the development of so dearly needed future therapeutics.

"Our research uncovered how deadly infections manipulate our cells for their own benefit but, on the other hand, revealed a new target, SARM1, to combat these infections. This research was possible by funding across the island of Ireland,
expanding our research capabilities and strengthen
the area of infection and immunology, which the
recent pandemic has proven to be of critical
importance in public health."

Professor Andrew Bowie, Professor of Innate
Immunology at Trinity College Dublin and a world
expert on innate immunity who has been working to
unlock the role of SARM1 in the regulation of
inflammation, added: "The surprising and
unexpected discovery that Klebsiella manipulates
SARM1 to counteract host defenses came about
from uniting our different expertise and
perspectives on pathogens and host defense which
was made possible by the joint North-South funding
that myself and Professor Bengoechea received
from Science Foundation Ireland and
Biotechnology and Biological Sciences Research
Council."

Dr. Colin Miles, AMR Lead at Biotechnology and
Biological Sciences Research Council (BBSRC),
said: "AMR is a major area of research interest to
BBSRC and U.K. Research and Innovation (UKRI)
as a whole. It has significant societal implications
and I'm pleased to see that a BBSRC funded
collaboration with the Science Foundation Ireland,
led by Queen's, has been able to discover a
fundamental biological process that may ultimately
translate into the reduced use of antibiotics in
certain clinical cases. This is a positive outcome not
only for BBSRC, but for the U.K. Government's
20-year vision for AMR."

**More information:** Claudia Feriotti et al,
Klebsiella pneumoniae hijacks the Toll-IL-1R
protein SARM1 in a type I IFN-dependent manner
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