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The role of antibiotic resistance mobile genetic element MCR-1 in enhancing bacterial survival in macrophages

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ABSTRACT

Background: Antimicrobial resistance (AMR) determinants such as mobile colistin resistance (MCR-1) that encodes colistin resistance are increasingly spreading in healthcare-associated and community-acquired infections.[1] Colistin, a cationic peptide antibiotic, resistance is encoded by the MCR-1 gene that functions as phosphoethanolamine (PEA) transferase which adds a PEA moiety to lipid A head group rendering it resistant to host antimicrobial cationic peptides (AMPs).[2,3] The given hypothesis is that MCR-1 harboring bacteria survive longer in macrophages by evading AMPs. This study aims to investigate the role of MCR-1 in enhancing bacterial survival in macrophages.

Methods: Eight *E. coli* strains were used in the study in which 4 strains were MCR-1 positive and 4 strains were negative. MCR-1 was confirmed by Polymerase Chain Reaction (PCR), and colistin and polymyxin minimal inhibitory concentrations (MICs) were determined using the microdilution method. Macrophage bactericidal assay was employed to examine bacterial survival using adherent murine RAW264 macrophages in an in-vitro bacterial infection model. Briefly, Macrophages were infected with *E. coli* strains at a multiplicity of infection (MOI) of 50 for 1 hour. The survival of bacteria associated with macrophages was quantified by agar plating method to calculate colony forming units (CFU/ml). Cytokines released from infected macrophages were quantified using ELISA method respectively.

Results: Colistin MICs for MCR-1 positive *E. coli* strains were > 25 μg/ml, whereas MCR-1 negative *E. coli* MICs < 6.2 μg/ml. *E. coli* strains encoding MCR-1 survived significantly more in association with macrophages ($p = 0.024$) compared to MCR-1 negative *E. coli* strains. Further, *E.coli* strains encoding MCR-1 induced slightly less IL-1β release from infected macrophages compared to *E. coli* strains without MCR-1 ($p = 0.05$). Taken together, the data suggest that MCR-1 enhanced bacterial survival in association with macrophages and modulated innate immune responses which may lead to treatment failure.

Conclusion: MCR-1 encoding *E. coli* strains conferred resistance to colistin and survived more in association with macrophages.

Keywords: Antimicrobial resistance, Colistin, *E.coli;* MCR-1, Macrophage

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