Multidrug resistance plasmids commonly reprogramme expression of metabolic genes in *Escherichia coli*

Rebecca J Hall, Ann E Snaith, Matthew JN Thomas, Michael A Brockhurst, Alan McNally

1Institute of Microbiology and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2T. 2Division of Evolution and Genomic Sciences, University of Manchester, Manchester, M13 9PT.

*Hall et al. bioRxiv* 10.1101/2023.11.06.565804

**INTRODUCTION**

Multidrug resistant *Escherichia coli* is a leading cause of global mortality. Transfer of multidrug resistance (MDR) plasmids, encoding beta-lactamases, carbapenamases, and colistin resistance genes, is driving rising incidences of nosocomial and community infection. Acquiring MDR plasmids causes transcriptional disruption, but less is understood about the pathways impacted or what drives differential gene expression in response. Here, we ask:

1. Is the transcriptional response to MDR plasmid acquisition plasmid-specific?
2. Are there parallelisms across the transconjugants in the pathways particularly impacted by plasmid acquisition?

**RESULTS**

Transcriptional response to MDR plasmid acquisition is plasmid-specific

Differentially expressed genes enriched in transport and metabolic functions

Fig 1. Genes significantly upregulated (orange) and downregulated (blue) across the eight transconjugants. There is considerable variation between transconjugants, suggesting the response is plasmid-specific.

A proposed requirement for arginine

Fig 3. Genes upregulated (circle) or downregulated (square) across all transconjugants involved in arginine transport and biosynthesis. Genes in the pathway converting glutamate to arginine are upregulated, and genes in the pathway converting arginine into glutamate/succinate are downregulated.

Convergence in the downregulation of methionine transport and metabolism

Fig 4. Genes related to methionine transport and metabolism were significantly downregulated upon acquisition of an MDR plasmid. No genes in this pathway were significantly upregulated.

**CONCLUSIONS**

1. The transcriptional response to MDR plasmid acquisition is plasmid-specific but with significant convergence.
2. Metabolic pathways are particularly impacted by incoming MDR plasmids, with a notable downregulation of genes involved in methionine transport and biosynthesis.
3. Acquisition of an MDR plasmid may result in the diversion of resources away from the TCA cycle.

**METHODS**

Eight different MDR plasmids conjugated into *E. coli* MC1655. Immediate transcriptional response measured by RNA-Seq.

**ACKNOWLEDGEMENTS**

RJH was supported by a University of Birmingham College of Medical and Dental Sciences Research Development Fund award, and by a NERC grant [NE/T01301X/1] awarded to AM.