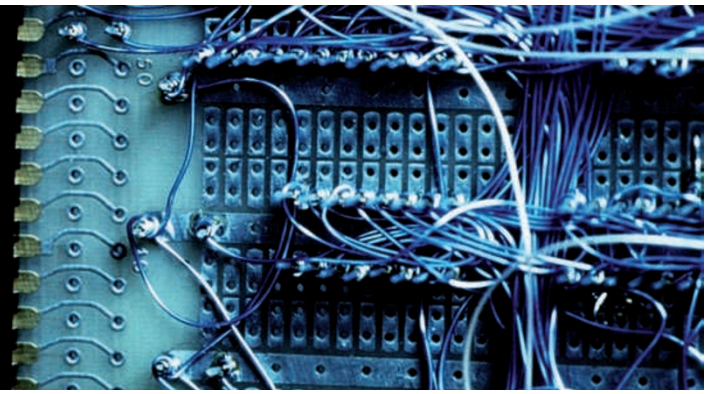
SYSTEMS BIOLOGY

Small genome, complex regulation

Three papers describe transcriptomic, metabolic and proteomic analyses of *Mycoplasma pneumoniae*, which has one of the smallest genomes among self-replicating bacteria. These studies reveal a surprising degree of complexity at each level, which is not only informative about life with a reduced genome but also provides insights into the regulation of cellular functions in bacteria.

M. pneumoniae, which causes an atypical form of pneumonia, has a genome of just 816 kb — much smaller than the genomes of laboratory favourites such as *Escherichia coli*, which span several thousands of kilobases. Güell and colleagues looked at *M. pneumoniae* transcriptional output, combining three transcriptomic approaches: spotted arrays, strand-specific tiling arrays and deep RNA sequencing. They identified 117 new transcripts, most of which were non-coding. The high proportion of genes that produce antisense transcripts (13% of the total) was surprising; the authors suggest that these transcripts have roles in regulating gene expression, predominantly through mechanisms that involve dsRNA.



Other transcriptomic insights add to the picture of regulatory complexity. For example, not all genes in an operon are expressed coordinately; instead genes in internal positions can be repressed or activated in response to changes in growth conditions. Many *M. pneumoniae* genes were also found to produce alternative transcripts.

Yus and colleagues used a combination of manual curation and experimentation to define the complete metabolic network of *M. pneumoniae*. Compared to bacteria that have larger genomes, *M. pneumoniae* has a higher proportion of multifunctional enzymes and a smaller number of interconnected and parallel pathways, suggesting that it has a streamlined metabolism. However, the bacterium can respond nimbly to changing conditions, suggesting economy of function without penalties at the level of robustness and adaptability. This flexibility is achieved using a smaller number of transcription factors than are present in bacteria with larger genomes, possibly due to complex transcriptional, post-translational and signalling-based regulation.

At the proteomic level, Kühner and colleagues used affinity purification combined with mass spectrometry to characterize protein complexes. By capturing information for 85% of predicted soluble *M. pneumoniae* proteins, the authors generated a wealth of new information. Among this was further evidence for multitasking: a high proportion of proteins take part in multiple complexes. Interestingly, gene expression analyses and genome organization generally did not predict these interactions, highlighting the importance of proteomic studies.

As well as showing how a small genome can be used to maximum effect, these studies have more general implications for understanding bacterial biology. For example, the complexity of the *M. pneumoniae* transcriptome is more similar to eukaryotes than expected, suggesting that similar studies are warranted in other bacteria.

Louisa Flintoft

ORIGINAL RESEARCH PAPERS Kühner, S. *et al.* Proteome organization in a genome-reduced bacterium. *Science* **326**, 1235–1240 (2009) | Yus, E. *et al.* Impact of genome reduction on bacterial metabolism and its regulation. *Science* **326**, 1263–1268 (2009) | Güell, M. *et al.* Transcriptome complexity in a genome-reduced bacterium. *Science* **326**, 1268–1271 (2009)
FURTHER READING Sorek, R. & Cossart, P. Prokaryotic transcriptomics: a new view on regulation, physiology and pathogenicity. *Nature Rev. Genet.* 24 Nov 2009 (doi:10.1038/nrg2695)