Not a Simple Life

(Dec. 4th, 2009) Hooray for systems biology! A joint effort between research groups from the European Molecular Biology Laboratory (EMBL) in Heidelberg and the Centre for Genomic Regulation (CRG) in Barcelona brought us a little closer to understanding the minimal genetic requirements for sustaining life.

The perfect model organism to study the bare essentials of life was quickly found in the bacterium, *Mycoplasma pneumoniae,* whose genome had already been sequenced in 1995 by the Richard Herrmann group at the *Centre* for *Molecular Biology* Heidelberg (*ZMBH*). Due to its parasitic lifestyle, this not so pleasant fellow (it causes atypical pneumonia) has lost a lot of its genetic information during evolution -- only about 800 kbps are left to-date. Thus, *Mycoplasma pneumoniae* harbours one of the smallest genomes that still allows for auto-replication and which clearly makes it a prime candidate for the study. Moreover, even though never found freely living "in the wild", the bacterium can be grown successfully on rich medium in the lab.

Research groups at the EMBL and CRG have now studied the prokaryote on three different levels: (1) transcription, (2) metabolism and (3) protein organisation and interaction – in order to get a more or less complete picture of how *Mycoplasma* manages to stay alive. Luis Serrano, group leader at the CRG and one of the co-initiators of the project, explains the holistic approach, "[…] in order to understand the basics of a living device, we must go further and undertake a global analysis at every level: from genomics to metabolomics, including gene expression profiling, proteome assessment, survey of the protein-protein interactions and so on."

Within the "*Mycoplasma* Consortium", six groups worked towards the final goal: Luis Serrano's group at the CRG and from the EMBL the groups under Peer Bork, Rob Russell Anne-Claude Gavin, Bettina Boettcher and Achilleas Frangakis. The fruits of all their labour can now be marvelled at in the current issue of *Science* (vol. 326), where the consortium has published three articles back-to-back (*Kühner et al.*, p. 1235; Güell *et al.*, p. 1263; Yus *et al.*, p. 1268).

Now for the results. With its degenerate genome, no one expected *Mycoplasmas* life to be too complicated but the opposite turned out to be true. Thus, it seems like the fewer genes you have the more complex regulatory mechanisms you need to invent and, ultimately, stay alive.

That's what Güell *et al.* unexpectedly figured out when they analysed the bacterium's highly dynamic transcriptome. Operon internal genes were found to be contextually repressed or activated, suboperons gave rise to alternative transcripts and the expression of 13% of all coding genes were presumably regulated by antisense transcription, a double-stranded RNA-based regulatory mechanism also observed in eukaryotic cells.

Yus *et al.* validated predicted metabolic pathways and their directionalities to create a metabolic map containing 189 reactions. They found that 25% of the enzymes involved were multifunctional, performing multiple tasks. Moreover, the group observed coordinated changes in gene expression along the growth curve and under various metabolic stress conditions. Interestingly, *Mycoplasma* also easily adapted its gene expression to various carbon sources.

This versatility and the quick and complex transcriptional response to external stimuli was the most surprising finding because *Mycoplasma* lacks the majority of transcription factors found in other bacterial strains, only eight have been identified so far. Thus, Güell and Yus speculate that a combination of transcriptional regulators, posttranslational modifications and small molecules (metabolites, chemical messengers) are involved in the regulation of gene expression.

Last but not least, Kühner et al. fiddled with the proteome organisation. By processing 10,477 mass spectrometry samples, the group found that more than 90% of all soluble proteins are part of functional protein complexes, of which, similarly to eukaryotes, 47% form homomultimers. Most proteins have multiple roles, too and thus participate in different cellular processes. Another unexpected finding was that despite the simple genomic organisation it is impossible to predict, which proteins actually interact with each other in real life.

Thus, this simple, genome-reduced bacterium turned out to be much more complicated and similar to a eukaryotic cell than even the most daring researcher could have imagined. There's a lot more to this *Mycoplasma pneumoniae* than just 816 kbps; a highly dynamic transcriptome with intricate regulatory mechanisms, multifunctional proteins, including enzymes - all are needed for keeping the tiny creature with only a few genes alive and, in addition, it also allows the bacterium to rapidly adapt to environmental and metabolic changes. And so, this pathogenic guy was good for something after all: gaining new insight into the real complexity of life.

Kathleen Gransalke

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