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First-ever blueprint of a minimal cell is more complex than expected

EMBL and CRG scientists reveal what a self-sufficient cell can't do without

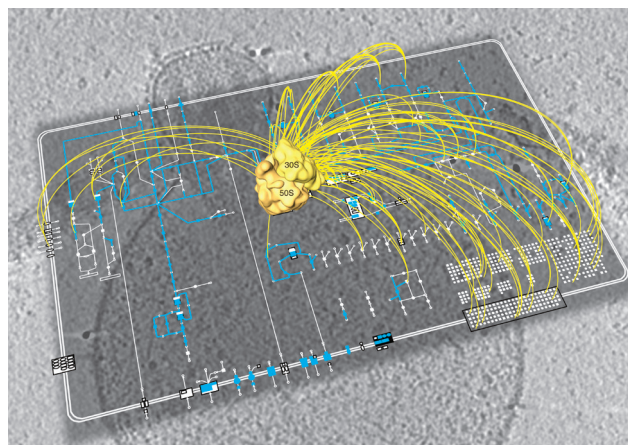
Heidelberg, 27 November 2009 - What are the bare essentials of life, the indispensable ingredients required to produce a cell that can survive on its own? Can we describe the molecular anatomy of a cell, and understand how an entire organism functions as a system? These are just some of the questions that scientists in a partnership between the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, and the Centre de Regulació Genòmica (CRG) in Barcelona, Spain, set out to address. In three papers published back-to-back today in *Science*, they provide the first comprehensive picture of a minimal cell, based on an extensive quantitative study of the biology of the bacterium that causes atypical pneumonia, *Mycoplasma pneumoniae*. The study uncovers fascinating novelties relevant to bacterial biology and shows that even the simplest of cells is more complex than expected.

Mycoplasma pneumoniae is a small, single-cell bacterium that causes atypical pneumonia in humans. It is also one of the smallest prokaryotes – organisms whose cells have no nucleus – that don't depend on a host's cellular machinery to reproduce. This is why the six research groups which set out to characterize a minimal cell in a project headed by scientists Peer Bork, Anne-Claude Gavin and Luis Serrano chose *M. pneumoniae* as a model: it is complex enough to survive on its own, but small and, theoretically, simple enough to represent a minimal cell – and to enable a global analysis.

A network of research groups at EMBL's Structural and Computational Biology Unit and CRG's EMBL-CRG Systems Biology Partnership Unit approached the bacterium at three different levels. One team of scientists described *M. pneumoniae*'s transcriptome, identifying all the RNA molecules, or transcripts, produced from its DNA, under various environmental conditions. Another defined all the metabolic reactions that occurred in it, collectively known as its metabolome, under the same conditions. A third team identified every multi-protein complex the bacterium produced, thus characterising its proteome organisation.

“At all three levels, we found *M. pneumoniae* was more complex than we expected”, says Luis Serrano, co-initiator of the project at EMBL and now head of the Systems Biology Department at CRG.

When studying both its proteome and its metabolome, the scientists found many molecules were multifunctional, with metabolic enzymes catalysing multiple reactions, and other proteins each taking part in more than one protein complex. They also found that *M. pneumoniae* couples biological processes in space and time, with the pieces of cellular



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This image represents the integration of genomic, metabolic, proteomic, structural and cellular information about *Mycoplasma pneumoniae* in this project: one layer of an Electron Tomography scan of a bottle-shaped *M. pneumoniae* cell (grey) is overlaid with a schematic representation of this bacterium's metabolism, where blue indicates interactions between proteins encoded in genes from the same functional unit. Apart from these expected interactions, the scientists found that, surprisingly, many proteins are multifunctional. For instance, there were various unexpected physical interactions (yellow lines) between proteins and the subunits that form the ribosome, which is depicted as an Electron microscopy image (yellow).

machinery involved in two consecutive steps in a biological process often being assembled together.

Remarkably, the regulation of this bacterium's transcriptome is much more similar to that of eukaryotes – organisms whose cells have a nucleus – than previously thought. As in eukaryotes, a large proportion of the transcripts produced from *M. pneumoniae*'s DNA are not translated into proteins. And although its genes are arranged in groups as is typical of bacteria, *M. pneumoniae* doesn't always transcribe all the genes in a group together, but can selectively express or repress individual genes within each group.

Unlike that of other, larger, bacteria, *M. pneumoniae*'s metabolism doesn't appear to be geared towards multiplying as quickly as possible, perhaps because of its pathogenic lifestyle. Another surprise was the fact that, although it has a very small genome, this bacterium is incredibly flexible and readily adjusts its metabolism to drastic changes in environmental conditions. This adaptability and its underlying regulatory mechanisms mean *M. pneumoniae* has the potential to evolve quickly, and all the above are features it also shares with other, more evolved organisms.

“The key lies in these shared features”, explains Anne-Claude Gavin, an EMBL group leader who headed the study of the bacterium's proteome: “Those are the things that not even the simplest organism can do without and that have remained

untouched by millions of years of evolution – the bare essentials of life”.

This study required a wide range of expertise, to understand *M. pneumoniae*'s molecular organisation at such different scales and integrate all the resulting information into a comprehensive picture of how the whole organism functions as a system – an approach called systems biology.

“Within EMBL's Structural and Computational Biology Unit we have a unique combination of methods, and we pooled them all together for this project”, says Peer Bork, joint head

of the unit, co-initiator of the project, and responsible for the computational analysis. “In partnership with the CRG group we thus could build a complete overall picture based on detailed studies at very different levels.” Bork was recently awarded the Royal Society and Académie des Sciences Microsoft Award for the advancement of science using computational methods. Serrano was recently awarded a European Research Council Senior grant. ●

Source Articles

Kühner *et al.* Proteome organization in a minimal bacterium. *Science*, 27 November 2009.

Güel *et al.* Frequency of alternative transcripts and antisense RNA in bacteria reveal high regulatory complexity. *Science*, 27 November 2009.

Yus *et al.* Integrative analysis of metabolism and its regulation in a small bacterium. *Science*, 27 November 2009.

About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 20 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and associate member state Australia. Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. EMBL's International PhD Programme has a student body of about 170. The Laboratory also sponsors an active Science and Society programme. Visitors from the press and public are welcome.

About CRG

The Centre for Genomic Regulation (CRG) is an innovative biomedical research centre, created in 2000 by initiative of the Catalan Government. It is a unique centre in Spain, based on a non-bureaucratic organization research model, whose objective is to pursue excellent basic research in biomedicine and, particularly, in the genomic and proteomic fields. The CRG is part of the Barcelona Biomedical Research Park.

About the EMBL - CRG Systems Biology Research Unit

For the emerging academic field of systems biology, it is often important to use genomics and proteomics approaches, data resources and computer simulations in combination with detailed experimental testing. The partnership between EMBL and the CRG aims to help to advance the understanding of complex biological systems, as it combines EMBL's expertise in computational biology with the CRG's know-how in specific areas of genomics and proteomics. Thus, this partnership will allow scientists to better understand some of the key aspects of human health.

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