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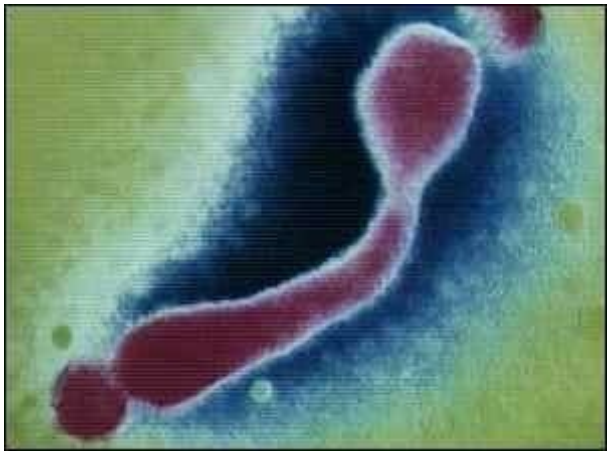
Mycoplasma bacteria as models for minimal cells

Bacteria of the genus Mycoplasma are one of the smallest self-replicating cells and serve as model organisms in synthetic biology research for investigating essential life functions as well as being used as chassis for novel, tailor-made biosyntheses. Researchers from Heidelberg are among the groups who focus predominantly on investigating mycoplasma bacteria as minimal organisms.



Mycoplasma genitalium

Synthetic biology focuses largely on constructing cells with a "minimal genome". Cells with a minimal genome contain only those components that are vital for maintaining life functions; their genome only consists of the genes that are essential for life. The researchers hope that their analyses will provide them with answers to the questions as to what life is, what components are required for survival under defined conditions and what is the evolutionary adaptation of the cells to their environment. In addition, minimal cells will be used as platform for developing new, tailor-made functions. The term "chassis", which comes from the domain of car construction, indicates that synthetic biology is seen as a technical science.

The smallest cells

Bacteria of the genus Mycoplasma are regarded as specifically suitable model organisms for analysing minimal cells and producing them in the laboratory using synthetic biology methods. These days, such model organisms have been very much in the headlines, following J. C. Venter's spectacular news relating to the first laboratory-produced synthetic cell (see article "Engineers of

life"). Venter and his colleagues Clyde Hutchinson and Hamilton Smith had already formulated their objective to synthesise minimal organisms for human use back in 1995 when they published the genome sequence of Mycoplasma genitalium. At that time, the term 'synthetic biology' was not yet in broad use.

In 1995, M. genitalium was considered to be the smallest self-replicating organism. It has a genome of only 580 kbp. However, bacteria with even smaller genomes have since been discovered, including Nanoarchaeum equitans (490 kbp), a tiny microbe discovered in a hydrothermal vent ("black smoker") off the coast of Iceland; Buchnera aphidicola (420 kbp), a symbiont or parasite of plant lice (Aphidae). In 2006, Carsonella ruddii, an endosymbiontic hackberry petiole gall psyllid, was discovered and found to be the bacterium with the smallest genome of any characterised bacteria (160 kbp). The C. ruddii genome is no bigger, and sometimes even smaller, than genomes of certain poxviruses. All these tiny organisms are either symbionts or parasites that are unable to carry out vital metabolic functions such as the synthesis of lipids themselves, but rely on their hosts for the supply of such products. Mycoplasmas have the advantage that they can easily be cultivated in the laboratory in media enriched with serum.

Mycoplasma genitalium vs. Mycoplasma pneumoniae

Prof. Dr. Richard Herrmann, professor emeritus

The sequencing of the M. genitalium genome was the beginning of Venter's minimal genome project, which 12 years later led to the synthesis of the bacterium's genome from prefabricated components. This represents an important milestone in synthetic biology (a term that was coined way back in 1912 by the French biologist Stéphane Leduc (la biologie synthétique), but only became generally known from about 2000 onwards). It is worth noting that in 1996, a group of Heidelberg researchers also sequenced the genome of Mycoplasma pneumoniae. The team led by Richard Herrmann at the Centre of Molecular Biology Heidelberg (ZMBH) took three years to decipher the M. pneumoniae genome, which is 816 kbp in size and encodes 689 proteins of which it was possible to identify the function of 458 proteins.

It turned out that all protein-encoding sequences (and more clearly: "open reading frames", ORFs) described for M. genitalium, are also found in the larger genome of M. pneumoniae. Of all other ORFs,

which do not occur in M. genitalium, about 50% turned out to be specific for M. pneumoniae, while others were amplifications of genes. The comparison of the M. pneumoniae and M. genitalium genomes provides valuable information about the vital genome structures and evolutionary adaptations of cells to their environment.

Dr. Peer Bork
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Recently, research groups led by Peer Bork and Anne-Claude Gavin at the European Molecular Biology Laboratory in Heidelberg (EMBL) and by Luis Serrano (now at the Centre Regulacio Genómica, Barcelona, Spain) systematically investigated the regulation of transcription, which depends on the genome structure, the metabolism and proteome organisation. The scientists chose to use M. pneumoniae as a model since it is "complex enough" to survive on its own, at the same time as being small enough and (theoretically) simple enough to represent a minimal cell, and thus enable it to be comprehensively analysed" (EMBL, 27th Nov. 2009).

Dr. Anne-Claude Gavin
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In three articles published in the journal Science, the researchers showed that the bacteria's transcription and its regulation is far more complex than previously assumed. Despite the bacteria's small genomes and the relatively low number of transcription factors, M. pneumonia reacts quite flexibly to even drastically changing environmental conditions. It is not inferior to much larger and more complex bacteria in terms of its adaptation capacity. The researchers also found that a surprisingly large number of proteins had multifunctional properties, including the interaction between protein complexes which they had not expected to find.

No change in the biological world picture

When Craig Venter's team started to focus on the next logical step in their quest to create the first

synthetic bacterial cell they encountered unexpected difficulties once they had succeeded in synthesising the M. genitalium genome, i.e. the inclusion of a synthetic genome into a DNA-free bacterial cell. They found that in contrast to other bacteria, M. genitalium grows very slowly. That is why they finally decided to choose another bacterium for their research. Although M. mycoides has a much larger genome (around 1 mio. kbp), it grows a lot faster. In 2009, the researchers succeeded in transferring this genome into a yeast cell and modifying it. The modified M. mycoides chromosome was subsequently transplanted into a related bacterium, M. capricolum, from which the gene encoding a specific restriction enzyme was removed. After incubation, the researchers obtained cells whose DNA consisted exclusively of DNA originating from the modified M. mycoides genome.

The researchers pursued the same strategy in order to create the completely chemically synthesised M. mycoides genome. The genome was assembled in three stages in yeast cells using specific 1,078 cassettes of DNA that were 1,080 base pairs (bp) long. These cassettes were designed in such a way that the ends of each DNA cassette overlapped each of its neighbours by 80 bp. These cassettes were produced by an American DNA synthesis company (Blue Heron Biotechnology).

This breakthrough "is a very important philosophical step in the history of our species" and "changes my view of life and the way it functions," said Venter in an interview with AFP. However, the experiments will not change the biological world picture of the majority of molecular biologists. This outstanding technical achievement is highly admirable. But the fact that a cell can principally function with either biological DNA or chemically synthesised DNA does not really come as a surprise.

What does minimal mean?

The experiments do not provide us with information on how big a minimal genome needs to be for a cell to live. In their search for the minimal genome, the researchers gradually silenced more and more genes, and found that the cells found some way of remaining alive. At present, 110 kbp is seen as the smallest size at which a cell can survive (the aforementioned bacterium Carsonella ruddii has a 160 kbp genome). Although there is evidence that there is no minimal genome, the genome needs to be redefined depending on the cell under investigation and the conditions to which it is exposed. The huge flexibility and adaptability, which also characterise mycoplasmas, raises further confusing questions in terms of the minimal genome concept.

Publications:

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