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NEWS AND COMMENTARY

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Endosymbiosis: past and present

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Discoveries reported in PLoS Biology have opened up a promising new front in the battle against the human suffering caused by parasitic nematodes. Foster and colleagues (2005) have completed the genome sequence of a bacterium, *Wolbachia* sp., found in a nematode that infects humans and causes elephantiasis. According to the World Health Organization, 138 million people are infected with these nematodes and many more are at risk. Analysis of this genome could provide new potential drug targets and shed light on endosymbiont evolution.

Remarkably, it is the bacteria that have been implicated as the principal cause of acute inflammatory filarial disease, rather than the nematode itself (Taylor, 2003). These bacteria may be essential for their nematode hosts (Fenn and Blaxter, 2004), in contrast to the case of many arthropods, in which *Wolbachia* are considered parasitic and can be removed by the use of antibiotics. For nematodes, the evidence is less clear-cut: the worms tend to perform poorly when treated with antibiotics, yet evolutionary analysis indicates repeated losses in nature.

New evidence comes from a genome project. Sequencing of the genome of the parasitic nematode *Brugia malayi* by the Filarial Genome Project (Blaxter *et al*, 1999) also provided data for the associated *Wolbachia*, whose sequence Foster *et al* (2005) have completed. The data show that, despite substantial genome degradation, the nematode's *Wolbachia* sp. retained a surprising number of metabolic pathways in comparison to known parasitic endosymbionts.

We can now understand the effect of antibiotics on nematode development and fertility, because *Wolbachia* sp. provides vitamins, nucleotides and heme to its host: the host appears to have become dependent on its *Wolbachia*. In return, it receives amino acids, which it can no longer make because (with one exception) it has lost every gene involved in their synthesis. It is particularly the provision of heme to its host that might open the way for potential new drug targets to combat human filarial disease.

Bacterial endosymbionts such as the *Wolbachia* sp. are surprisingly widespread: an estimated 15–20% of all insect species contain endosymbiotic bacteria. Compared to bacteria, eukaryotes are severely limited in their biochemical repertoire. For this reason, it has been assumed, eukaryotes have engaged in symbioses with bacteria. Yet, in many cases, the bacterial symbiont appears to parasitize its host. The initial events leading to a successful symbiosis are not known but they could have been parasitic in nature, that is, the bacterium benefited. Later on, due to loss of redundant metabolic pathways caused by individual gene loss, this initial parasitic symbiosis may have turned into a mutually beneficial interaction. In support of this scenario is the discovery that some nonmotile endosymbionts contain genes that encode parts of a flagellar apparatus on their genomes and certain pathogenic bacteria excrete virulence factors via the flagellar export apparatus. A similar mechanism was possibly involved in the early events leading to the endosymbiosis. Why these genes have not yet been lost or changed into pseudogenes in 'friendly' bacteria remains an open question.

One common characteristic of all endosymbionts is their reduced genome size. The average bacterial genome is about 2 Mb (this is probably an underestimate, since most sequenced genomes are from pathogenic bacteria, which have smaller genomes). Most bacterial endosymbionts have smaller genome sizes ranging from 0.6 to 1 Mb. The trend to decrease genome size is confirmed by smaller genomes of older primary endosymbionts compared to later secondary endosymbionts, such as those found in many insect groups. Evolution of reduced genome size could be explained by the loss of genes involved in the production of resources that are supplied by the host's nutrient-rich environment. Those genes that do persist appear to code for metabolic pathways essential for maintaining the symbiotic relationship: for example, in the form of amino acid metabolism in the well-studied aphid endosymbiont *Buchnera*, or nucleotides and cofactors for the *Wolbachia* sp. of filarial nematodes. Such enormous genome reductions of course have one unavoidable result: the endosymbiont is completely dependent and would not be able to survive outside the confines of its host.

Although most well-studied examples of endosymbiosis are a few hundred million years old, they are relatively recent on an evolutionary timescale. Much older and more important endosymbioses are among us: mitochondria and plastids are the results of earlier endosymbiotic events. Mitochondria are believed to be in the order of 2 billion years old while plastids are about 1.5 billion years old. The disintegration of the genomes of their once free-living contributors has gone much further than those of endosymbiotic bacteria (Gray, 1999). Although the genome sizes of the mitochondria and plastids can be as large as 0.5 Mb, there is no correlation between genome size and gene content. Organellar genomes contain a maximum of about 250 genes, but the average number of genes is only 40. The remainder of the genomes is currently thought to consist of noncoding 'rubble'. The number of genes is dramatically smaller than their closest free-living relatives, alpha-proteobacteria and cyanobacteria, which contain a few thousand genes at least. Not all of these genes have simply been lost: many have been transferred to the nucleus (Kurland and Andersson, 2000; Martin *et al*, 2002). The products of some of these genes are targeted back to their original environments.

There are differences, though, between the bacterial symbionts, and mitochondria and plastids. While the latter are found in all cells of their hosts, the former are only found is certain specialized cells called bacteriocytes. So, it does not seem likely that *Buchnera* will end up as an amino-acid-producing organelle. Another group of organelles that have an endosymbiotic origin are hydrogenosomes and mitosomes, which are found in a huge variety of anaerobic microbial eukaryotes where they play important, but not completely understood, roles in the metabolism of the cell. The difference between them is that the hydrogen-producing hydrogenosomes do play a role in energy production while mitosomes do not. Despite some recurring attempts to suggest otherwise (see Gray, 2005), most authors nowadays believe these organelles to be related to mitochondria (van der Giezen *et al*, 2005). Most hydrogenosomes and mitosomes have taken genome

reduction to the extreme and have completely lost their organellar genome and as such are an interesting example of extreme integration of an endosymbiont into its host.

Comparative analyses have been extremely helpful in understanding the relationship between hydrogenosomes and mitosomes to mitochondria. In addition, the bacterial origin of mitochondria and plastids has been unequivocally proven using comparative genomics. Therefore, the continued sequencing effort aimed at modern bacterial symbionts will provide more data to understand the powers that drive the evolution of genome reduction and are valuable as such. Whether claims that such sequencing efforts will be turned into actual drugs remains to be seen.

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Further Reading

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