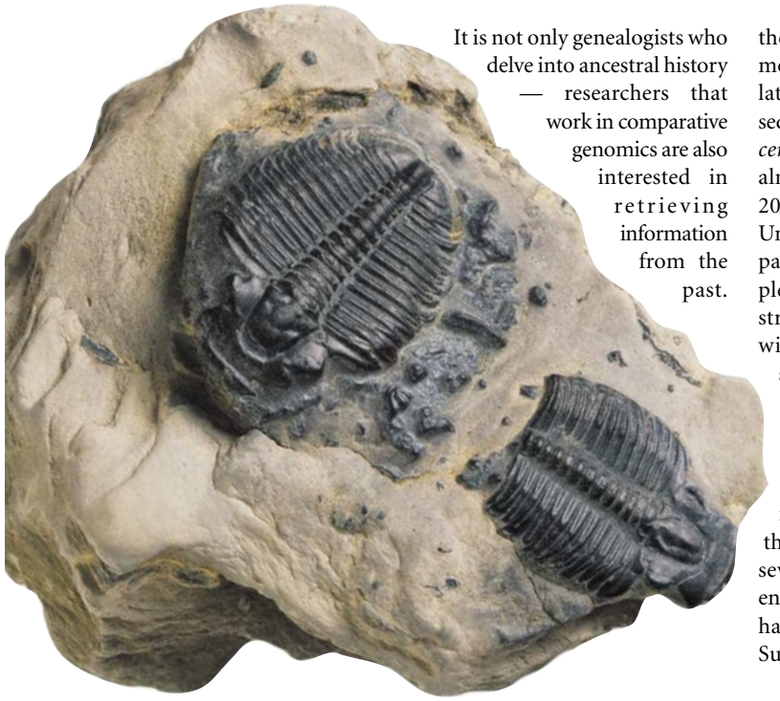
MICROBIAL GENOMICS

Unearthing the past



It is not only genealogists who delve into ancestral history — researchers that work in comparative genomics are also interested in retrieving information from the past. For one pathogen that is in the spotlight, *Bacillus anthracis*, two recent *Nature* papers now provide an insight into its pathogenicity and clues to the lifestyle of its most recent common ancestor.

In the first paper, Read *et al.* show the complete sequence of the chromosome of a *B. anthracis* Ames isolate and compare it with a draft sequence of its close relative *Bacillus cereus* 10987. The Ames isolate is almost identical to that used in the 2001 anthrax postal attacks in the United States. In an accompanying paper, Ivanova *et al*. detail the complete sequence of the *B. cereus* type strain ATCC 14579, and compare it with an earlier draft of the Ames sequence.

The genes that encode the main *B. anthracis* virulence factors — the tripartite toxin and the capsule — are located on the plasmids pXO1 and pXO2. However, these new studies have identified several potential chromosome-encoded virulence factors, including haemolysins and phospholipases. Surprisingly, these chromosomal factors are not unique to *B. anthracis*. Both groups found that most *B. anthracis* chromosomal genes have homologues with high sequence identity in *B. cereus*.

For those scanning the genome with therapeutics in mind, the lack of distinguishing chromosomal features in *B. anthracis* could be disappointing. However, 34 candidate surface proteins were identified that are potential drug targets.

Interestingly, both new genome sequences contained a gene encoding a homologue of enhancin, a metalloprotease that can degrade the mucin layer that is found in insect intestine. Both groups also showed that, compared with other bacilli, *B. anthracis* has more genes that are involved in amino acid and peptide metabolism, more secreted proteases and peptidases, and limited metabolic pathways for carbohydrate catabolism, which point to adaptation to a protein-rich diet. It was previously thought that the most recent common ancestor of the *B. cereus* group (which includes *B. anthracis*) was a benign soil-dweller. So, these

COMPARATIVE GENOMICS

Phage genomics comes of age

Viruses that infect bacteria (bacteriophages) are the most abundant organisms known, and have a powerful influence on microbial evolution through the transfer of genetic material to their hosts. So, it is surprising that despite their extraordinary evolutionary success, little is known about phage genomic diversity.

Now, Pedulla and colleagues have begun to address this imbalance by sequencing and analysing the genomes of ten newly isolated mycobacteriophages, with some unexpected results.

The authors show that each genome consists of a unique assemblage of individual mosaic modules, which often correspond to single genes. Shared sequences that are present at different locations in the phage genomes — such as a 378-bp sequence found in Che8 and Corndog — provide evidence that non-homologous recombination during horizontal gene transfer has been a dominant force in mycobacteriophage evolution.

Highly promiscuous illegitimate recombination might also explain the unexpectedly high mycobacteriophage genomic diversity, by allowing the random recombination of both viral and non-viral DNA. Indeed, approximately 50% of the genes identified by Pedulla *et al.* are entirely novel, many others have no obvious role in viral propagation and several indicate specific new functions of mycobacteriophages in bacterial pathogenesis and human disease.

Although bacterial infections are thought to have a role in the onset of autoimmune infections, there is a weak correlation between these events. The authors strengthen this link by describing a phage gene (*gp220*) that encodes a homologue of the human Ro protein — a main target of the autoimmune response in lupus and Sjogren disease. This viral homologue might act in concert with its bacterial host to stimulate autoimmunity.

The authors also report that phage tape-measure proteins (TMPs) could function as signalling molecules to activate dormant mycobacterial hosts. The TMP of the phage Barnyard contains a 70-residue motif with strong similarity to the resuscitation-promoting factor of *Micrococcus luteus*, which stimulates the regrowth of dormant cells. This is of particular importance in disease bacteria, such as *Mycobacterium tuberculosis*, in which latency and reactivation have a role in infection.

So, by sequencing a relatively small number of mycobacteriophage genomes, Pedulla and colleagues provide many new insights into the genomic diversity of these viruses, and their role in bacterial virulence and host responses to infection. Given the abundance and diversity of this population, it is clear that bacteriophage genomics has a lot more to offer — in genomic terms, the age of the phage is just beginning.

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References and links

ORIGINAL RESEARCH PAPER Pedulla, M. L. *et al.* Origins of highly mosaic mycobacteriophage genomes. *Cell* **113**, 171–182 (2003)

FURTHER READING Campbell, A. The future of bacteriophage biology. *Nature Rev. Genet.* **4**, 471–477 (2003)