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## The wonder world of microbial viruses

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### Abstract

The first congress on Viruses of Microbes took place at the Institut Pasteur in Paris, France, on 21–25 June 2010. The advances in genomics and metagenomics reported at this meeting reveal striking and unexpected complexity of the virus world. Viruses, in particular viruses that infect prokaryotes and unicellular eukaryotes, are emerging as the most abundant class of biological entities on earth and a major evolutionary and geochemical force.

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The congress in Paris was far more than a run of the mill scientific conference. In fact, it was a veritable celebration of the current renaissance of virology. A decade ago, the study of microbial viruses, that is, viruses infecting prokaryotes and unicellular eukaryotes, was a rather moribund field, notwithstanding all the glorious history of bacterial viruses as early models of genetics and molecular biology. The vibrant meeting of over 400 researchers at the Institut Pasteur is the best testimony to a complete change of the fortunes in this area.

The venue chosen for this historic meeting was more than appropriate: it was the Institut Pasteur, where in 1915–1917 Felix d’Herelle discovered viruses infecting bacteria (roughly simultaneously with and independently of Frederick Twort in England), which he named bacteriophages [1]. Although the term is still very much in use, it was emphasized by several speakers during the congress that the traditional divide between bacteriophages and viruses of eukaryotes is counter-productive on at least two accounts. First, over the last few years, the rapid progress in the study of archaeal viruses, notably spearheaded by Pasteur’s very own scientists – and organizers of the congress – David Prangishvili and Patrick Forterre, revealed a new dimension of the virus world, indicating that the appropriate demarcation lines should separate viruses of archaea, bacteria and eukaryotes; a special domain of viruses for each domain of cellular life [2]. Viruses of Archaea were highlighted in several presentations during the congress, particularly, in the fascinating report of Prangishvili that showcased the unusual shapes of archaeal virus particles and also emphasized their unfamiliar genomic landscape, with very few genes having detectable homologs. This work was complemented by the reports of Mark Young (Montana State University, Bozeman, MT, USA) and Claire Geslin (University of Brest, France) that dramatically expanded the known genomic diversity of archaeal viruses. Second, the divide between viruses that infect cells of different domains is certainly porous: indeed, there are numerous evolutionary links between bacterial viruses and viruses of eukaryotes. These connections point to key contributions of bacteriophages to the origin of the viruses of eukaryotes as emphasized in

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the reports of Arcady Mushegian (Stowers Institute of Medical Research, Kansas City, MO, USA) and Valerian Dolja (Oregon State University, Corvallis, OR, USA).

d'Herelle was not just an outstanding microbiologist but also a visionary whose ideas on the evolution of life were far ahead of his time and appeared quite extravagant. He speculated that the bacteriophages that he discovered might represent relics of the earliest stages of evolution, an idea that subsequently was abandoned as ridiculous once it became obvious that viruses were obligate intracellular parasites. Nowadays, however, d'Herelle's insights seem to be returning in a modern form. Dolja, in his talk coauthored with Eugene Koonin (National Center for Biotechnology Information, NIH, Bethesda, MD, USA) discussed an evolutionary scenario according to which virus-like entities, in particular, genetic elements with RNA genomes, inhabited networks of inorganic compartments at hydrothermal vents and indeed might have preceded the first cells and played a central role in their emergence [3]. As in the days of d'Herelle, this scenario remains speculative but is, of course, better steeped in facts and might be the most realistic available narrative on the origin of cellular life. Quite different in terms of details, but perhaps similar in spirit, is Forterre's hypothesis on the independent origins of DNA genomes and replication in the three domains of cellular life as a result of infection of primordial RNA cells by DNA viruses [4].

Arguably, the beginning and still the most spectacular manifestation of the current virus renaissance is the discovery of the amazing giant viruses of amoebas. The prototype giant virus, the mimivirus, with its 1 Mb genome, exceeds many bacteria in the particle and genome size [5]. This discovery blurred the formal distinction between viruses and cells and caught the imagination of many biologists, leading to a renewed, lively discussion of the origins of viruses and even the definition of an organism and the rather notorious question of whether or not viruses are 'alive' [6,7]. These fundamental subjects were notably discussed in the lecture of Forterre who proposed the concept of the 'virocell', a new entity that emerges when an infecting virus subverts the functional systems of an infected cell for viral reproduction. Unlike a virus particle, the virocell seems to possess all features of a living organism.

Giant viruses were one of the key themes at the Paris congress – remarkably, Michael Boyer from Didier Raoult's laboratory at Université de la Méditerranée in Marseille, France, reported the identification of 19 new mimivirus relatives [8], whereas Matthias Fischer from Curtis Suttle's laboratory at the University of British Columbia (Vancouver, BC, Canada) described a more distantly related giant virus that infects the marine heterotrophic flagellate *Cafeteria roenbergensis*. Strikingly and, to some, supporting the idea that viruses are alive, giant viruses have been shown to host their own parasites that reproduce within intracellular virus factories much like the virus reproduces within a cell. The first of these virophages was discovered in association with the mamavirus, a close cousin of the mimivirus [9]. At the Paris congress, the Suttle laboratory (Vancouver, BC, Canada) reported a second virophage that parasitizes on the *Cafeteria* virus. Although the two virophages are approximately the same size, they appear to be genetically unrelated, suggesting that these 'superparasites' evolved independently on multiple occasions.

All the unusual features of the giant viruses notwithstanding, comparative genomic analysis unequivocally shows that they are *bona fide* members of the broad class of nucleocytoplasmic large DNA viruses (NCLDV) of eukaryotes, which includes well-characterized viruses infecting animals (in particular, poxviruses) as well as diverse viruses of unicellular eukaryotes [10]. Comparative genomic analysis of the NCLDV identified a core set of approximately 50 conserved genes that encode the major components of virions and key proteins involved in viral replication and apparently inherited from the ancestral virus. Koonin reported an in-depth study of the NCLDV evolution that supported the

monophyly of this class of viruses but additionally revealed complex histories of many core viral genes that during the evolution of the NCLDV were repeatedly lost and displaced by homologous genes acquired from the host. Boyer described the recently discovered Marseille virus that, like mimivirus and its relatives, was isolated from *Acanthamoeba* and is so different from the rest of the known NCLDV that it is thought to be the first representative of a new virus family [11]. There is little doubt that many more NCLDV including, most likely, new families, will be discovered in the future as indicated by the unexpected presence of numerous sequences representing unknown viruses of this class in metagenomic samples, in particular, from the J. Craig Venter Institute's Global Ocean Survey.

Viral metagenomics certainly was a central topic of the congress as reflected in the keynote lecture of Suttle on marine viromes and the presentation of Forest Rohwer (San Diego State University, CA, USA) on human gut viromes. It is no exaggeration at all that metagenomics and ecological genomics have affected a change in our very perception of the place viruses occupy in the biosphere. Viruses have emerged as the most abundant biological entities on earth, with virus particles outnumbering cells by an order of magnitude, at least, in the ocean. The same applies to the genetic diversity, as viruses carry many more novel, uncharacterized genes than cellular life forms. Furthermore, viruses are now recognized as major agents of biological evolution through their key role in horizontal transfer of genes, as well as geochemical change, because cell lysis by viruses is central to the cycles of the major elements and sediment formation [12].

The giant NCLDV such as the mimivirus and its kin lead the virus world in size but the recently discovered 'jumbo' bacteriophages are not far behind [13]. Roger Hendrix (Phage Institute at the University of Pittsburgh, PA, USA) discussed these viruses of mycobacteria whose genomes, at approximately 0.5 Mb, are several times bigger than those of the textbook bacteriophages and encode a remarkable diversity of proteins with various functions unexpected in viruses, including translation system components.

In a brief report, there is no opportunity to cover all or even most of the diverse and fascinating reports on various aspects of microbial virus biology. It is impossible, however, not to mention the striking advances in viral structural biology that were evident, among other reports, in the keynote lecture of Michael Rossmann (Purdue University, IN, USA) and the presentation of Dennis Bamford (University of Helsinki, Finland). Both speakers emphasized the remarkable unity of capsid structure among viruses from the three domains of cellular life, which is one of the strongest evidence of the evolutionary continuity of the viral world [14].

Compared with genomics, metagenomics and structural biology, traditional molecular biology of viruses was represented rather weakly. However, new systems biology directions such as transcriptomics by deep sequencing and proteomics figured prominently as exemplified by the report of Jean-Michel Claverie (Aix-Marseille University, France) on the mimivirus transcriptome, which revealed a plethora of new genes [15].

Thanks to new generation technologies, the face of virus research has changed almost beyond recognition, and the contours of the virus world emerging from these approaches are far stranger and more complex than anyone could have imagined only a few years ago. The participants of the congress at Pasteur were unanimous in their enthusiasm about making the meeting on Viruses of Microbes a tradition; it is hard to predict what the biggest viral wonders at the next congress are going to be, but there is hardly any doubt that we are in for major surprises.

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