RESEARCH SNIPPETS FROM THE MEDICAL WORLD

P Desikan

After bacteriophages, now virophages? A small icosahedral virus, Sputnik, 50 nm in size, has been found associated with a new strain of Acanthamoeba polyphaga mimivirus (APMV). APMV is the largest known virus. It grows only in amoeba and is visible under an optical microscope. Sputnik cannot multiply in Acanthamoeba castellanii on its own. However, it grows rapidly in amoebae coinfected with APMV (Nature 455, 100-104; 4 September 2008). Growth of Sputnik is deleterious to APMV and results in the production of abortive forms and abnormal capsid assembly of the host virus. It is suggested that Sputnik represents a currently unknown family of viruses. Considering its functional analogy with bacteriophages, this virus has been classified as a virophage. It is postulated that virophages could be vehicles mediating lateral gene transfer between giant viruses.

Microbes may be saddled with a serious identity crisis. It is difficult to establish the phylogeny of microorganisms because they are composed of genes that have moved vertically (via inheritance) or horizontally (via lateral transfer mechanisms such as conjugation) or both. A network analysis approach used to estimate the cumulative impact of lateral gene transfer in the genomes of 181 fully sequenced prokaryotes found that approximately 80% of the genes in each genome appear to have been involved in lateral transfer at some point in their history (Proc. Natl. Acad. Sci. U.S.A. 105, 10039, 2008). Hence, well-defined phylogenetic trees, which describe genetic relationships accurately on short-term evolutionary time scales, become rather less clearly delineated when looked at over very long time periods.

Fatal problems encountered in allogeneic stem-cell transplantation include Epstein Barr virus (EBV) reactivation and post-transplant lymphoproliferative disorders (PTLDS). A retrospective analysis in consecutive adult and pediatric EBV reactivations and PTLD over a period of 8.5 years found that the incidence of EBV–PTLD was 1.3%, whereas that of EBV reactivation was 1.8% (Bone Marrow Transplantation, 2008, 42, 181–186). The mortality rates were 82% in patients with EBV–PTLD and 67% in patients with reactivation. This emphasizes the need for standardization and optimization of post-transplant surveillance strategies for EBV.

Antisocial behavior among bacteria is not new. To optimize access to nutrients, some bacteria prevent other microorganisms from invading their space. When two swarms of different Proteus mirabilis strains come into close proximity, motility ceases and a zone of clearance is formed between the two swarms. However, two swarms of the same P. mirabilis strain readily merge to form one swarm. A six-gene cluster that was dubbed idsA–F (for ‘identification of self’) was studied to understand this mechanism (Science 321, 256–259, 2008). The idsD and idsE loci of five different P. mirabilis strains were found to be highly variable, whereas the other ids genes were well conserved. It was, therefore, proposed that idsD and idsE function as ‘biological barcodes’ that allow strains to recognize themselves and prevent mingling. Unravelling this complex mechanism will reveal a fascinating mode of bacterial interaction.

Will early immunization reduce incidence of measles outbreaks? A randomized clinical trial was conducted to examine the protective efficacy of measles vaccination in infants in a low-income country before nine months of age (BMJ. 2008 Jul 24;337:a661). An interim analysis of the trial concluded that, in low-income countries, maternal antibody levels against measles may be low and severe outbreaks of measles can occur in infants before the recommended age of vaccination at nine months. Outbreaks of measles may therefore be curtailed by measles vaccination using the Edmonston-Zagreb vaccine as early as 4.5 months of age.

Generally, prions are limited to a specific host and a few related species. But prions sometimes cross the species barrier to infect new hosts. Notably, prions from cows have hopped to humans, causing Creutzfeldt-Jakob disease (CJD) in 208 people, mostly in the UK. Now, the fear is that there may be other animal prion diseases which could possibly jump to humans. Since prion diseases have long dormant periods, the fact that there are currently no identified human cases of new prion diseases does not necessarily indicate that people will not develop symptoms of new prion diseases in the future. Findings of a study (Cell. 2008 Sep 5;134(5):757-68) show that infectious prion proteins from hamsters can change normal proteins from mice into new, infectious forms of prion – simply by mixing the proteins together in a test tube. The findings suggest that new kinds of prion, with potentially differing characteristics, can be born every time a misfolded prion protein enters a new species.

Neutrophils have an important role in the immune surveillance strategies for EBV.
response against pathogens, but the mechanism by which they mediate their protective effect is poorly understood. A recent study (Nature Reviews Immunology 8, 746, October 2008), shows that, during infection with Toxoplasma gondii, neutrophils migrate to the lymph nodes, where they form dynamic clusters, referred to as swarms. Signals released by these intracellular parasites during their egress from infected cells and by pioneer neutrophils result in the formation of swarms, which remove infected macrophages in the subcapsular sinus of the lymph nodes.

As far as stress busting goes, we could learn a thing or two from microorganisms. They respond to a variety of environmental stresses by upregulating stress-response genes. In many cases the response is coordinated by a multiprotein signaling hub, the stressosome, which integrates multiple inputs to affect a single outcome. In a study, (Science. 2008 Oct 3;322:92-6), high-resolution structures of the stressosome components were fitted into an electron microscopy structure to determine a pseudoatomic resolution structure of the stressosome from Bacillus subtilis. The complex has an icosahedral virus capsid-like core with 20 protruding turrets. Sequences comprising the turrets are variable, perhaps allowing them to sense different signals. The conserved domains of the core may integrate these signals to give a single signaling outcome.

Developing new drugs for treatment of infections with drug-resistant bacteria is an expensive and arduous process. New drugs may be effective for a lesser period of time than that taken to develop the drugs. Hence, delaying the onset of resistance by administering drugs in combination is a currently favored strategy. However, a recent, counterintuitive discovery (Proc. Natl. Acad. Sci. U.S.A. 105, 13977, 2008) showed that synergistically acting drug pairs, such as doxycycline and erythromycin, may actually accelerate the evolution of resistance. In fact, antagonistic drug pairs are more effective at forestalling resistance emergence because as one drug becomes ineffective, its suppressive effect on the other diminishes and unmasks the potency of the second drug. The precise outcome would depend on drug ratios, doses, pharmacokinetics, and modes of action.

Clinical trials in India, particularly those involving new antibiotic molecules, have been much maligned. To bring transparency to the process of conducting and reporting the results of these trials, the Clinical Trials Registry, India, was formally launched on the 20th of July, 2007 (NMJI, May-June 2008,21: 105 -106). This is a free online registry of clinical trials, at www.ctri.in, hosted at the National Institute of Medical Statistics, Indian Council of Medical Research, New Delhi. From January 2010 onwards, biomedical journals in India will consider publication of a trial only if it has been registered prospectively if started in or after 2008. Trials undertaken before June 2008 will need to be registered retrospectively.