**The Right Time and Place**

Spatial analysis, such as that used in epidemiology, is vulnerable to many errors, including that caused by spatial dependence or autocorrelation. For transmission of many infections, individuals need to be neighboring, and because the environment and behavior of nearby surroundings tend to be more similar than distant ones, neighbors will tend to be statistically dependent. This phenomenon causes complications for accurate epidemiological modelling. However, pathogens can also be mapped in time, as well as place, and evolutionary biologists have developed phylogeographic methods to aid this sort of historical sleuthing. Given current concerns about the unexpected emergence of pathogens such as West Nile virus (WNV) in the United States, Pybus et al. have merged these concepts to develop an alternative, less error-prone approach. Taking data for WNV, they show how the diffusion coefficient and variation in the spatial spread of a pathogen can be estimated from genome data alone. This approach revealed that instead of a steady front of east-to-west dissemination of WNV, it progressed in fact by rare long-range movements, probably triggered by bird migrations or anthropogenic transport of mosquitoes. These rare events leave a detectable phylogenetic footprint. Ignorance of this hitherto hidden heterogeneity has led in turn to considerable overestimation of the pathogen’s basic reproductive number, $R_0$, a key parameter for estimating the epidemic potential of a pathogen. — CA


**Biomedicine**

**The Good and the Bad in ALS**

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron death. Development of effective therapies will require an understanding of the molecular and cellular mechanisms that go awry in the disease—insights that often come from genetic approaches. Mutational analyses of rare hereditary forms of ALS have already implicated >12 culprit genes. Although several of these genes converge on common pathways, the overall view of pathogenesis remains incomplete.

Recent studies have uncovered two new genetic mutations that have an impact on ALS; interestingly, in one case the mutations appear to have a salutary effect on the course of the disease. Through exome sequencing of two large ALS families, Wu et al. discovered disease-associated mutations in the *PFN1* gene, which encodes the actin-binding protein profilin-1. In cultured cells, mutant profilin-1 formed insoluble aggregates and inhibited axonal outgrowth. Starting with a zebrafish model of ALS, Van Hoecke et al. discovered a disease-modifying gene called *EPHA4*, which encodes a receptor tyrosine kinase that interacts with ephrins, proteins involved in axonal repulsion. Inhibition of EphA4 signaling had beneficial effects in fish and rodent models of ALS. Importantly, two ALS patients who carried inactivating mutations in *EPHA4* showed uncharacteristically long survival. — PAK


**Cell Signaling**

**Flip-Flop Messenger**

CD38 is a transmembrane protein present on lymphocytes that appears to function in signal transduction. It has multiple enzymatic activities, two of which cause the generation of molecules that function to regulate the release of calcium from intracellular stores [cyclic ADP-ribose and nicotinic acid adenine dinucleotide polyphosphates (NAD(P)H)]. CD38 can activate the protein CD40, which is expressed on lymphocytes and is involved in immune regulation. CD38 activation increases the production of several cytokines, including IL-6, which stimulates CD40 expression. CD38 is also involved in the regulation of cell adhesion and trafficking, and its activity is modulated by various factors such as soluble CD38 ligands and antibodies. Understanding the mechanisms by which CD38 modulates these processes can provide insights into the regulation of immune responses and potentially offer new therapeutic targets for autoimmune and inflammatory diseases. — RZ

phosphate (NAADP). Enigmatically however, the catalytic domain of CD38 has been localized to the outside of the cell. Zhao et al. used antibodies specific to the N- and C-termini of CD38 to look more closely at its orientation. They found that in multiple cell lines and in primary human peripheral blood mononuclear cells, a few percent of the cells expressed CD38 with the catalytic C-terminal portion of the protein on the inside, with some cells expressing the protein in both orientations. The authors propose that regulated expression of CD38 in its different orientations might provide a mechanism for control of its effects on intracellular signaling. — LBR


CHEMISTRY

Fast Protein-Binding Nanoparticles

One possible use of synthetic polymeric nanoparticles is to target and bind protein in vivo. As such, these nanoparticles have potential for medical applications, but often their performance is lower in vivo than in vitro because of slow binding kinetics and nonspecific protein binding. Hoshino et al. borrowed the concept of “induced fit” for enzymatic binding to substrates to improve the binding kinetics of a polymeric nanoparticle. They used a poly-N-isopropylacrylamide (PNIPam) backbone, which has a temperature-driven phase transition from a flexible random coil to a rigid conformation. The protein target, concanavalin A, binds the sugar mannose. To prepare synthetic polymeric nanoparticles that recognized the target protein through multipoint interactions, the authors synthesized PINPam nanoparticles copolymerized with p-acrylaminodiphenyl- β-mannopyranoside. Nanoparticles in the flexible conformation have faster binding kinetics than those in the rigid conformation, but the fastest kinetics was observed at the transition temperature between the swollen and collapsed phases. — PDS


OCEAN SCIENCE

Heavyweight Measurements

One of the potentially most serious consequences of global warming is the rise of sea level that will occur as the polar ice sheets shrink. Part of that sea-level rise will be due to ocean warming, because warmer water occupies a larger volume than an equivalent amount of colder water; the other part will be due to more water in the sea; i.e., to a larger mass of water. Good measurements of ocean temperatures are available, but how does one go about measuring the mass of the ocean? There may be an easy way, according to Hughes and colleagues from the UK National Oceanography Centre and the School of Civil Engineering and Geosciences of Newcastle University.

It turns out that there are places on the ocean floor where the pressure of the overlying water does not change much in response to the wide array of causes (such as ocean dynamics, tidal forcing, and changes in atmospheric pressure, among others) that can make it vary independently of ocean volume changes. In such a spot, one could theoretically install a single ocean-bottom pressure (OBP) sensor and measure how whole-ocean mass was changing. The authors used models to identify a suitable spot and OBP measurements from the Pacific Ocean to illustrate the technique’s potential. If their idea is correct, and if OBP sensors with low enough measurement drift can be developed, there may be a sweet spot for monitoring ocean mass changes. — HJS


ENVIRONMENTAL SCIENCE

Dissolving CO₂ in Brine

Carbon dioxide capture and long-term storage are seen as one way to mitigate and defer global warming. One idea for capturing and storing CO₂ is injecting it into the highly saline groundwaters that are common on many continents. These brines are often relics of earlier hydrologic systems and have persisted for millions to tens of millions of years (or longer) because their high salinity makes them denser than shallow freshwater systems. Using thermodynamic modelling of the system CO₂-H₂O-NaCl-CaCO₃, Steele-MacInnis et al. explore what will happen to CO₂ when injected as a supercritical fluid into deep saline formations, with a goal of estimating the available storage volume. Initially, injected CO₂ will displace the brine, but over time, it will dissolve in the brine. Their thermodynamic analysis shows that this dissolution will yield the most favorable storage conditions and will markedly reduce storage volume requirements. It will also increase the density of the brine, stabilizing it further. — BH

The Right Time and Place
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