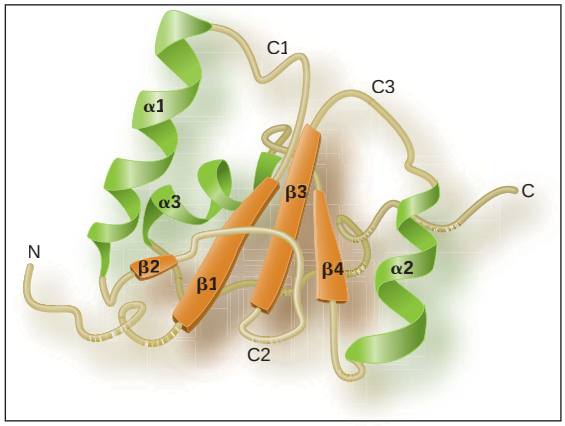
bind to a degenerate phosphoserine peptide library rather than to a control library comprising unphosphorylated peptides.

That BRCT domains are phosphopeptide binding modules also emerges from the work of Manke and co-workers (*5*). They used a similar proteomics approach to identify protein modules recognizing a library of phosphopeptides that mimic amino acid sites phosphorylated by the DNA damage response protein kinases ATM and ATR. Manke *et al*. identified tandemly repeated BRCT domains present in BRCA1 and PTIP (a putative transcriptional regulator involved in the DNA damage response) as motifs that bind to phosphorylated targets. They also discovered that some BRCT domains in other DNA damage response proteins (53BP1, Rad9, MDC1) failed to recognize the ATR/ATM-specific phosphopeptide library. Some of these BRCT domains, however, did recognize the random phosphopeptide library of Yu and colleagues. This is an important observation because it demonstrates that BRCT domains recognize phosphopeptide motifs created by different protein kinases. This scenario is attractive because it means that BRCT domains modulate protein-protein interactions controlled by a variety of protein kinases operating in different signaling cascades.



Conserved complexity. The BRCT domain in the carboxyl terminus of the DNA repair protein XRCC1 (*10*). BRCT domains of proteins are usually 80 to 100 amino acids in length and may occur in tandem as in BRCA1. Structural analyses highlight a relatively conserved structure composed of two or three α helices surrounding a central β sheet. BRCT domains bind to phosphorylated proteins involved in the cellular pathways that respond to and repair DNA damage.

As with most provocative science, the findings of Yu *et al*. and Manke *et al*. raise more questions than they answer. First, not all known interactions mediated by BRCT domains are regulated by phosphorylation. Do such BRCT domains have additional as yet unidentified protein partners that are bound in a phosphorylation-dependent manner? Second, why has a motif as distinctive as the BRCT domain evolved for phosphopeptide binding when several other structural motifs already exist for this task? What is the structural basis for phosphorylation-specific binding? One clue to these last two questions may be the observation by Manke *et al*. that a tandem pair of BRCT domains in BRCA1 or PTIP is required for binding to phosphorylated amino acid residues. Structural analyses have revealed that the characteristic conserved structure of BRCT domains enables them to dimerize, both within a single polypeptide and between different polypeptides. It is possible that these BRCT dimers facilitate phosphorylation-specific interactions. Such a scenario would ensure that dimeric or even multimeric complexes of BRCT proteins rather than single polypeptides are recruited for phosphorylation-dependent interactions. It is noteworthy that some BRCT domains are important for the aggregation of protein complexes into subnuclear foci in response to DNA damage. Could this be a consequence of phosphorylation-specific binding facilitated by multimeric BRCT domains? The two new studies reveal exciting insights about what BRCT domains do, but there is still much to learn about these ubiquitous and intriguing structures.

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GEOCHEMISTRY

The Importance of Being Alkaline

Michael John Russell

How did life begin? There are so many hypotheses that Max Delbrück made it his rule not to read the literature until someone came up with a recipe to produce things that crawled within 3 months.

"Protolife" synthesized in the lab may not have to crawl to impress the rest of us, but it should be able to reproduce and replicate. Most would also argue that early life must have been cellular. These first cells would have had to divide or bud and, at the same time, pass on a code for growth and maintenance to their offspring.

On page 618 of this issue, Hanczyc *et al*. (*1*) present experimental intimations of how these two processes may have operated and been linked. They show that simple physicochemical forces can drive vesicle growth and division and that mineral particles—such as clays—can catalyze the assembly of vesicles in water. The mineral particles must have a high surface charge to be able to nucleate lipid vesicles from a solution of micelles. The same particles tend to adsorb RNA. When the vesicles are forced through narrow pores, the particles, with their load of RNA, are distributed into daughter vesicles. It has previously been shown that clays can promote the polymerization of nucleic acid monomers (*2*).

Hanczyc *et al.* show that the chemical energy needed to drive the phase change from tiny lipid micelle to vesicle derives from a change in pH from ~10 to ~8. At the same time, hydrodynamic forces are required to drive the resulting vesicle suspensions through small pores. There must also be a constant supply of negatively charged mineral particles. Did such conditions exist on early Earth?

A natural analog may have existed on the deep ocean floor, where a myriad of alkaline, hydrothermal, submarine seepages would have been sited (see the figure) (*3*). The seepages would have created porous mounds of freshly precipitated clays and other minerals, just as they do today (*4*), supplying both the hydrodynamic and chemical energies required by the model.

The seepages are caused by convection of ocean water through hot crust composed mainly of magnesium and iron silicates (*5*). Exothermic hydration of hot rock would have maintained the convecting waters at ~100°C and pH ~10 (*3*). Gradients within such a porous seepage mound, from hydrothermal fluid to ocean, would have been from pH ~10 to ~6 and from ~100°C to <20°C. There would also have been a redox gradient (*3*).

Hence, physicochemical conditions similar to those used in the experiments of Hanczyc *et al.* may have existed on early Earth. But there are some missing ingredients, which may require alternative ingredients to be considered. For example, there

The author is at the Scottish Universities Environmental Research Centre, East Kilbride, Glasgow G75 0QF, UK. E-mail: m.russell@suerc.gla.ac.uk

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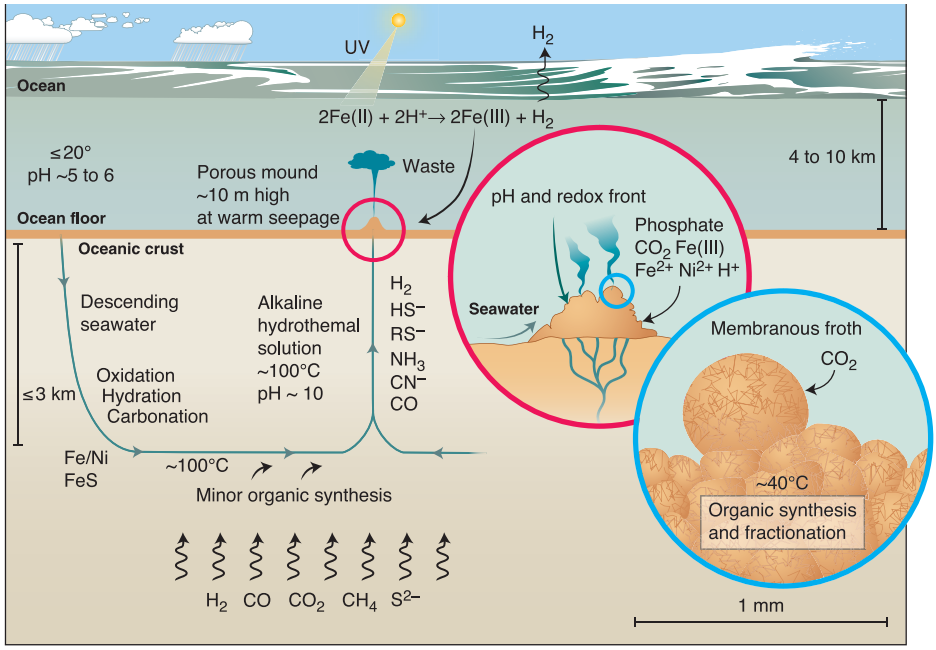

The submarine setting for the emergence of life. The initially alkaline conditions required by both Hanczyc *et al.* (*1*) and Huber *et al.* (*7*) in their respective demonstrations of the emergence of RNA-bearing vesicles and a possible primordial peptide cycle are met on the 4.3-billion-year-old ocean floor. This vertical section through atmosphere, ocean, and oceanic crust illustrates how alkaline hydrothermal solution of constant temperature (~100°C) and pH (~10) is convectively pumped through a confining porous mound of freshly precipitated clays, hydroxides such as $Mg(OH)_2$, and iron-nickel sulfides into a cool and acidulous ocean—a kind of natural hydroponic feed to the first cells.

is no evidence that lipids would be produced in sufficient quantities, either in hydrothermal interactions or from extraterrestrial sources, to allow vesicle formation.

Instead of lipids, the easily synthesized amino acids, joined together as polypeptides, could have formed the first organic membranes. Huber and Wächtershäuser have shown that amino acids can be converted into peptides under alkaline conditions (*6*). Huber *et al.* (*7*) have established a peptide cycle using chemicals similar to those that exist at porous hydrothermal mounds (see the figure). For example, they use $Mg(OH)_2$ to stabilize pH at ~9.8. In nature, this is the mineral brucite, which is formed during the convective hydration of rocks expected to have existed on the early ocean floor (*3*), and also occurs at alkaline submarine mounds predicted as the hatchery of emergent life (*3*, *5*).

These studies suggest that submarine alkaline seepages provide a more congenial site for life to emerge than the acidic, high-temperature, and violent "CO-laden volcanic exhalations" favored in Wächtershäuser's theory of surface metabolism (*8*). Alkaline fluids have other advantages: They favor both phosphate and amine chemistry, encourage acid-base catalysis, and provide a sink for protons, which drives the protonmotive force across membranes that is required for all cells.

In particular, RNA would have required what is known as a polymerase—that is, a polypeptide that can catalyze the joining of ribonucleotides to form RNA—for its construction. But this polymerase could only be constructed with reference to a preexisting RNA polymer. How can this "chicken or egg" conundrum be resolved?

Most promising in this regard is the suggestion that the basis for the genetic code rests on a natural affinity between an RNA codon and a particular amino acid side chain (*9*, *10*). RNA composed of polyadenine, when bound to a solid phase, does select for its coded diamino acid, lysine (*11*). And because its positively charged side chains can bind to the phosphates of RNA monomers, polylysine has many of the characteristics expected of a primitive polymerase (*9*). That RNA must be adsorbed on a solid to be able to select its appropriate amino acids is consistent with the model of Hanczyc *et al.* (*1*).

A hydrothermal mound offers a natural reactor for such interactions. Thus, the "bottom-up" geochemical approach and the "top-down" biochemical approach to the origin of life appear to be converging. With each approach informing the other, the experimental quest for the recipe for "protolife" can begin in earnest.

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ATMOSPHERIC SCIENCE

An Environmental Experiment with H_2?

Michael J. Prather

Clean, hydrogen-fueled transportation—as envisioned in a recent U.S. presidential initiative (*1*)—has great appeal. When H_2 is "burned" in a fuel cell, directly producing electricity to power a vehicle, the exhaust contains none of the odd-nitrogen compounds (NO_x) associated with combustion. NO_x is the key factor in photochemical smog formation (*2*). Furthermore, if the H_2 is generated from nonfossil energy, it could eliminate the CO_2 emissions from the transport sector. H_2 thus seems to be capable of solving major environmental problems.

However, the chemicals that we dispose of in the atmosphere often return as unexpected environmental problems—witness the transport sector and local air pollution, halocarbon production and global ozone depletion, and fossil fuel use and global climate change. The seriousness of these problems was not discovered until after the technologies had been introduced, partly explaining the contentiousness of the public debate over remedying them. Given the growing interest in an H_2 economy, now is the time for assessing its environmental consequences. Three recent publications

The author is in the Department of Earth System Science, University of California, Irvine, CA 92697, USA. E-mail: mprather@uci.edu