thinning of ice requires decreased winter snowfall, more profound summer melting, and/or an acceleration of ice discharge. Through basal lubrication, increased surface melting may lead to an increase in ice discharge, and hence these two processes are likely to be linked.

The seismic signals from these large outlet glaciers raise the possibility that discharge processes include episodic increases in the sliding of the ice that operate in a failure mode. This type of episodic sliding or sticking over large areas to the rock and sediment that make up the glacier bed emphasizes the difficulties inherent in modeling rapid ice discharge. The factors that might control the rate of ice flow range from long-term changes in ice properties (dust content, thermal profiles, rates of accumulation of snow) to water-modulated sliding over a bed of complex composition and geometry. If episodic motion makes up a significant component of total ice flow, then ice models will require a broadened scope to deal with the processes that may be involved. Further identification of the patterns of episodic motion and the relationship between it and known forcings, such as meltwater input pulses and ocean tides, may help to constrain the problem.

Terminus of a tidewater outlet glacier in southeastern Greenland. Ice discharge from outlet glaciers may occur at rates of 10 m/day. Seismic evidence suggests that large outlet glaciers may experience similar displacements of ice over much shorter time periods.

The large mass movements required to produce the observed seismic signals should be observable with focused Global Positioning System (GPS) networks. In the case of valley glaciers, there should be changes in the appearance of the glaciers that could be mapped after the event. Ekström *et al.*'s identification of an event in the Denali Range in Alaska raises the possibility that such large mass movements occur in valley glaciers. However, in this high-relief, very active area, there may also be other sources for the observed seismic signals.

The identification of glacier-related seismic events by Ekström *et al.* (*1*) reflects a growing ability to take the pulse of the active aspects of the Earth system. Determining the role of these events in modifying the rate and response of ice flow will be of value in understanding the complex problems presented by rapid ice discharge.

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CELL SIGNALING

The BRCT Domain: Signaling with Friends?

Keith W. Caldecott

Mutations in the tumor suppressor proteins BRCA1 and BRCA2 are associated with a markedly increased risk of developing breast or ovarian cancer. Normal versions of BRCA1 and BRCA2 seem to be involved in the cellular pathways that respond to DNA damage, but their exact functions remain unclear (see news story by Couzin on page 591 of this issue). One possible clue to the activities of the BRCA proteins is the presence in BRCA1's carboxyl terminus of protein-protein interaction motifs called BRCT domains (*1*–*3*). BRCT domains are present in many other proteins besides BRCA1 and seem to facilitate physical interactions among proteins involved in the cellular response to DNA damage. Two proteomics studies published on pages 639 (*4*) and 636 (*5*) of this issue unveil more secrets about the BRCT domains of BRCA1 and other proteins. Yu *et al*. (*4*) and Manke *et al*. (*5*) report that BRCT domains are phosphopeptide binding motifs that are able to discriminate the phosphorylation status of their protein partners.

BRCT domains typically comprise 80 to 100 amino acids and may occur in tandem as in BRCA1. Structural studies highlight a relatively conserved structure of two or three α helices surrounding a central β sheet (*6*–*8*) (see the figure). It is unlikely that such a highly conserved structure arose simply to bind to other proteins, particularly because each BRCT domain has a different set of binding partners. Indeed, only a small region of the BRCT domain in the DNA repair protein XRCC1 (encompassing C2-β3-C3 in the figure) is needed for interaction with its physiological partner, DNA ligase III. This small region lacks most of the structural characteristics (including α helices) of the BRCT domains in other proteins (*9*).

BRCA1 has two tandem BRCT motifs in its carboxyl terminus. Yu *et al*. now show that these motifs bind to phosphorylated BACH1, a DNA repair helicase (*4*). BACH1 is phosphorylated at serine 990 during the G_2/M phase of the cell cycle, presumably by a cyclin-dependent kinase (CDK). This phosphorylation event appears to trigger the interaction of BACH1 with the tandem BRCT domains of BRCA1. These investigators report that this interaction is required for establishment of the G_2 cell cycle checkpoint in response to DNA damage. Their most intriguing discovery is that the BRCT domains of other proteins also target phosphorylated partners. Evidence for this includes their observation that the BRCT domains of Fcp1 (a protein phosphatase) preferentially bind to phosphorylated but not unphosphorylated RNA polymerase II. Furthermore, one of the eight BRCT domains of TopBP1 (topoisomerase II binding protein 1) binds to phosphorylated E2F1, a transcription factor involved in cell cycle control and apoptosis, but not to unphosphorylated E2F1. Yu *et al*. also examined BRCT domains in 13 other proteins from a variety of organisms that participate in the cellular response to DNA damage. They found that the BRCT domains preferentially

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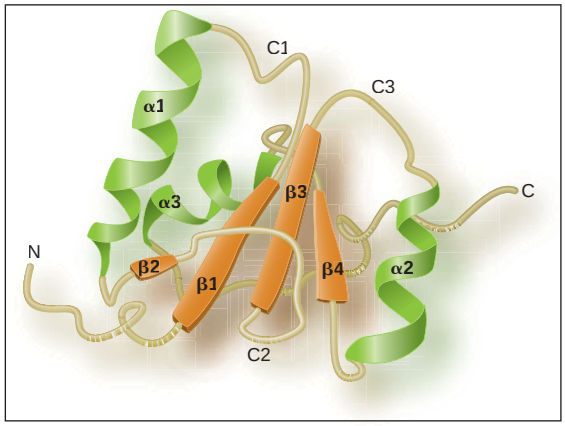
bind to a degenerate phosphoserine peptide library rather than to a control library comprising unphosphorylated peptides.

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

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