ing G_1 and G_2, and on DNA polymerase ε during S phase. A model presents itself: Rad9 binds to FHA2 to mediate the Rad53 response during G_1 or G_2 while another protein, perhaps polymerase ε, binds to FHA1 to mediate the Rad53 response during S phase (see the figure). If this is the case, then the sensitivity of the FHA1 deletion mutant and resistance of the FHA2 deletion mutant to UV light may be explained by the fact that cells in S phase are more sensitive to UV light. This analysis is complicated by the fact that the FHA1 deletion mutant also reduces the catalytic activity of Rad53 (*12*). Point mutations in the FHA1 domain (that do not affect catalytic activity) will determine whether FHA1 specifically confers sensitivity to UV light.

The gene *cds1* encodes a homolog of Rad53 in fission yeast (*13*), but its function is not entirely parallel. Cds1 has only a single FHA domain, and mutants lacking cds1 function have only some of the phenotypes of *rad53* mutants in budding yeast. Like *rad53* mutants, cells without *cds1* function lose viability when exposed to either replication blocks or DNA damage; unlike *rad53* mutants, however, they arrest the cell cycle in either case (*14*). Thus, Cds1 does not share Rad53's checkpoint function. Even so, both proteins clearly respond to DNA damage in a cell cycle–specific fashion. Cds1 activity is increased by DNA damage, but only during S phase (*14*). Rad53 requires Rad9 to function during G_1 and G_2, but not during S phase. The FHA domain in Cds1 may be analogous to the FHA1 domain of Rad53 in conferring S phase–specific regulation on these kinases. The second function of Rad53, to mediate arrest in response to DNA damage, is provided by the fission yeast protein kinase Chk1 (*15*). The fission yeast homolog of Rad9, Crb2, binds Chk1 (*6*). Although Crb2 is phosphorylated in response to DNA damage, it is not yet known whether phosphorylation of Crb2 or its association with Chk1 is necessary for Crb2 function in fission yeast. Chk1 does not have an obvious FHA domain, suggesting that the Crb2-Chk1 interaction may be mediated by another mechanism.

Rad9 joins a growing list of proteins implicated in the cell cycle checkpoint pathway that are phosphorylated in response to DNA damage. Which kinases are responsible for these events? Certainly a number of protein kinases function along the checkpoint pathways, but we are still a long way from understanding how they are regulated by DNA damage or replication blocks and what their in vivo substrates actually are. The protein kinases thus far implicated in regulating the damage response in *S. cerevisiae*—Mec1, Tel1, and Rad53—are thought to function downstream of Rad9. The results of Sun *et al.*, however, inform us that Rad9 phosphorylation may in fact be dependent on these kinases (*2*), implying that they act upstream of Rad9. Either way, an additional as yet unidentified kinase could be involved, and the pathways are more complicated than we have thought.

How best to dissect this complex pathway of interacting proteins, kinases, and substrates? Forge ahead with open minds. A combination of genetics, cell biology, and biochemistry has gotten us into this tangle. Let us hope that these approaches can eventually lead us out.

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NOTA BENE: IMMUNOLOGY

Monie a Mickle Maks a Muckle

For the first time, we have a set of benchmark figures for the prokaryotes in the planet's active biosphere. In a paper in the *Proceedings of the National Academy of Science*, Whitman *et al.* calculate the number and location of the world's prokaryotes and the amount of carbon sequestered in their biomass (*1*). The figures are large, staggeringly so, and these new data have implications for the understanding of global geochemical cycles and the control of genetic diversity. Seldom has the old Scots saying (which means many small things combined can make a big thing) seemed so appropriate.

The numbers were calculated by scaling up from existing measurements in representative habitats, making a daunting task quite manageable. Three habitats dominate—seawater, soil, and subsurface sediment.

For marine environments, the several published estimates of cell densities in different localities are in reasonable agreement, allowing for a fairly secure computation of 1×10^{29} cells, one-third of which are in the upper ocean and two-thirds in deep water. Counts for freshwater and in polar ice are several orders of magnitude smaller.

In soil there are estimated to be around 2.5×10^{29} prokaryotes. Surprisingly, most soils, including grassland, cultivated, and desert soils, have similar concentrations of prokaryotes, an exception being forest soils, which are considerably less populous.

A decade ago, soil and seawater data would have been considered sufficient to assess prokaryote abundance. But the recent descriptions (*2*) of bountiful life in the subsurface sediment (below 8 m) lead Whitman *et al.* to estimate that these populations may dwarf all others: There may be in excess of 4×10^{30} subsurface prokaryotes, accounting for more than 90% of the global population. Other notable but numerically minor populations occur in animals (for example, around 10^{14} per human), on leaves (1×10^{11} per square meter), and in the air itself.

These figures were used to calculate that the amount of carbon allocated to prokaryotes is about 5×10^{17} g (assuming that carbon is half of the dry weight of cells). This is half the amount found in plants, whereas for nitrogen and phosphorous the prokaryotic pool may actually rival that of plants (because a large proportion of plant material is extracellular). These huge numbers are significant in the global carbon, nitrogen, and phosphorus cycles.

Although subsurface prokaryotes dominate numerically, their metabolism is constrained because of limited access to nutrients. Their total productivity is merely equivalent to that of the rapidly growing population associated with domestic animals. Far and away the greatest productivity occurs in marine environments, with upward of 10^{30} generations per annum. This frantic replication provides enormous scope for mutation and speciation. The factors that constrain these processes are yet unknown—just one more set of questions to add to the list on prokaryotes. **–RICHARD GALLAGHER**

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