Hector and collaborators found a strong effect of diversity on productivity and evidence suggestive of a simultaneous effect of composition on productivity. They did not find the pattern of species dominance and competitive displacement predicted by the sampling effect model but did find evidence of overyielding. Their results suggest a rule of thumb—that each halving of diversity leads to a 10 to 20% reduction in productivity. Could an ecosystem manager avoid this reduction by choosing the right species—such as those that are most productive in monoculture? Inspection of Fig. 2 in the Hector *et al.* paper shows that, in total across all sites, there were about 23 higher diversity plots that had greater productivity than the most productive monoculture at a site. This suggests that even the best monoculture may not equal many higher diversity plots. These results further support a niche complementarity model, although the mechanisms underlying such a model are still to be identified and only long-term studies can adequately address this issue.

How much diversity might be needed to maintain high productivity within an ecosystem? The answer requires some explanation. The trans-European experiment was performed in 2 m by 2 m plots. This is an appropriate size for determining how diversity influences productivity, because the effects of diversity must come from interactions among individuals of different species. In grasslands, individual species interact within an area of about 1 m^2. To apply these results to larger scales, it is necessary to know the regional diversity needed to attain a given level of local diversity.

The species-area relationship, $S = cA^z$, states that diversity, S, scales as area, A, raised to the power z, where z ranges from 0.15 to 0.3 (*12*). Consider a local area of size A_L and a region of size A_R. For the local area to have a local diversity of S_L species, the larger region would have to have $S_R = S_L (A_R/A_L)^z$. If one were to manage 100 hectares (1 km^2) to maintain high productivity, the work of Hector and colleagues suggests that each 1 m^2 should contain about 16 species. With $z = 0.15$, a 100-hectare field would have to contain 127 species for this to occur. Comparably, in Minnesota grasslands, we have observed a close relationship between the average diversity of 0.5-m^2 plots and the diversity of the 0.5-hectare region in which they occur (see the figure). Extrapolation with this relationship predicts that a 0.5-hectare region has to contain an average of 120 species for an average 0.5-m^2 site to contain 16 species (which implies a z value of 0.21). If about 16 species must occur in a 1-m^2 neighborhood to attain high productivity, z values ranging from 0.15 to 0.21 would predict that a single hectare would have to contain about 60 to 105 plant species and 1 km^2 about 127 to 270 species for high productivity to exist. Such values are similar to the plant diversity of many natural ecosystems but greatly exceed that of many managed ecosystems. This suggests that increasing diversity in managed grasslands and forests may be cost-effective.

The first 2 years of the trans-European study have provided important insights into the effects of species diversity on ecosystems. However, many controversies, such as the effects of diversity on stability and the mechanisms whereby diversity impacts productivity, are likely to remain unresolved until more years of data are gathered.

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PERSPECTIVES: CANCER

Breast Cancer Genes and DNA Repair

Ashok R. Venkitaraman

Hopes that the cloning of two inherited breast cancer susceptibility genes—*BRCA1* and *BRCA2*—might illuminate the common mechanisms underlying this disease remain unfulfilled. About 10% of breast cancer patients have a familial form of the disease, and of these, inherited mutations in *BRCA1* or *BRCA2* are found in about half. However, somatic mutations in either gene are not a feature of the 90% of breast cancers that are sporadic (that is, not inherited) [reviewed in (*1*)]. Therefore, the biochemical connection between the BRCA1 protein and a protein kinase called ATM (mutated in ataxia telangiectasia) reported by Cortez *et al.* on page 1162 of this issue (*2*) is cause for considerable excitement because it defines the participation of BRCA1 in a cellular pathway that may be dysfunctional in a significant fraction of all breast cancers.

BRCA1 and *BRCA2* both encode large nuclear proteins (1863 and 3418 amino acids, respectively). These proteins are expressed in many tissues and are most abundant during S phase of the cell cycle [reviewed in (*3*)]. The proteins are quite distinct despite the misleading similarity in their acronyms. There is, however, much circumstantial evidence to suggest that they have common biological functions. Thus, inheritance of one defective *BRCA1* or *BRCA2* allele predisposes an individual to developing breast or ovarian cancer. Homozygosity for targeted mutations in murine Brca1 or Brca2 precipitates defective cell division, chromosomal instability, and hypersensitivity to genotoxins indicative of defects in DNA repair (*4–6*).

Similar abnormalities occur in human or murine cells after disruption of the *ATM* gene, which provokes a disease characterized by cerebellar dysfunction, chromosomal instability, and predisposition to cancer (*7*). ATM belongs to a family of protein kinases homologous to the catalytic subunit of phosphoinositide 3-kinase. This family includes the related ATR (AT- and Rad3-related) protein kinase in vertebrates and MEC1 and Rad3 in yeast. These kinases are essential—and quite proximal—components in the pathways that signal cell cycle checkpoint arrest after DNA damage or incomplete DNA replication.

The observations of Cortez and coworkers now place BRCA1 downstream of ATM in these pathways. They show that ATM resides in a nuclear complex that contains BRCA1, and that it phosphorylates BRCA1 after exposure of cells to γ radia-

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tion. Phosphorylation occurs in a cluster of serine-glutamine amino acid residues located toward the carboxyl terminus of BRCA1, in a region (amino acids 1280 to 1524) that also contains the recently identified cyclin-CDK2 phosphorylation site (*8*). A number of serine residues in BRCA1 become phosphorylated in vivo, both constitutively and after γ radiation. Two of these—Ser^{1423} and Ser^{1524}—are particularly important. A mutant protein in which both residues are replaced with alanine fails to rescue the radiation sensitivity of a BRCA1-deficient cell line. Thus, phosphorylation of BRCA1 by ATM may be important for protecting the cell against DNA damage.

BRCA1 phosphorylation is diminished, but not entirely absent, in ATM-deficient cells. Furthermore, phosphorylation of BRCA1 after DNA damage induced by agents other than γ radiation (such as ultraviolet light or hydroxyurea) appears to be independent of ATM activity (*9*). Collectively, these findings speak to a specific role for ATM in signaling the cellular response to DNA lesions (such as double-strand breaks) induced by γ radiation. In other situations, BRCA1 phosphorylation may be carried out by alternative pathways. A precedent for this comes from studies of the phosphorylation of the p53 tumor suppressor protein, an important component of the cellular response to DNA damage. In response to different stimuli, p53 can be phosphorylated by ATM or by the ATM homolog, ATR (*10*). Similarly, it is possible that ATR could phosphorylate BRCA1 when ATM does not.

Consistent with the particular importance of ATR and its yeast homologs in monitoring genome integrity during S phase, such an alternative phosphorylation pathway is germane to the idea that BRCA1 and BRCA2 participate in DNA repair through homologous recombination (see the figure) (*3*). Recombination mechanisms are essential not only for the repair of DNA damage during S phase, but also for normal DNA replication (*11*). The evidence linking BRCA1 and BRCA2 to recombination mechanisms has thus far been indirect. Both molecules are reported (*6, 12*) to associate with mRad51, the mammalian homolog of *Escherichia coli* RecA, which is essential for double-strand break repair through recombination. Furthermore, chromosomal aberrations reflecting defects in mitotic recombination occur in murine Brca1-deficient (*7*) and Brca2-deficient cells (*5*). Direct evidence substantiating a role for BRCA1 in recombination is now provided by new data that demonstrate a considerable reduction in the frequency of recombination between homologous DNA substrates integrated into the genome of Brca1-deficient cells (*13*). A model is now emerging in which phosphorylation of BRCA1 by ATM (and perhaps ATR) is an essential prelude to the recombination repair of DNA lesions that occur or persist during DNA replication (see the figure).

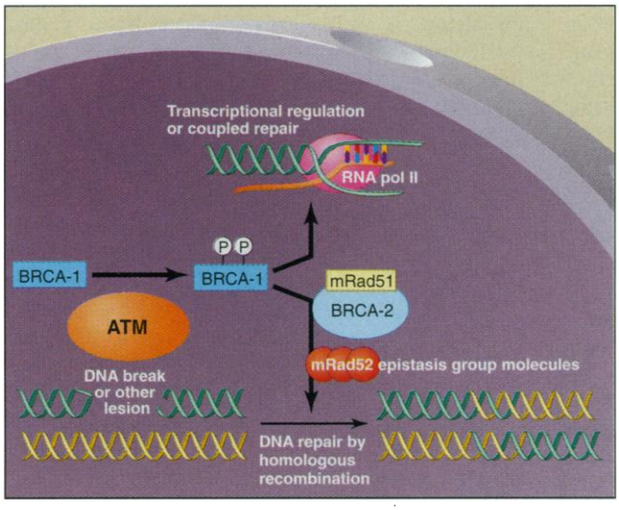
However, it is important to appreciate the multiplicity of additional—or alternative—functions proposed for BRCA1, many of which were discussed at a recent workshop (Second International Workshop on the Function of BRCA1 and BRCA2, 9–10 September 1999, Cambridge, UK). Some of the proposed functions, such as BRCA1's participation in cell cycle checkpoints during G_2/M phase (*7*), are in accord with processes regulated by ATM and its relatives. The proposed involvement of BRCA1 in transcription, supported by manifold data (*14*), could also be regulated by phosphorylation. BRCA1 copurifies with the RNA polymerase II holoenzyme. Certain BRCA1 domains activate transcription when fused to heterologous DNA binding proteins, and may induce genes such as *GADD45* that mediate apoptosis. Disruption of murine Brca1 cripples the repair of oxidative base damage on the transcribed DNA strand, consistent with Brca1's proposed involvement in transcription-coupled repair.

How BRCA1 may affect such apparently disparate processes can only be guessed at. A single function in transcriptional regulation could underpin multiple effects (see the figure). Alternatively, distinct functions may be performed through cooperation with different protein partners. Regardless, Cortez and colleagues show that a large fraction of cellular BRCA1 undergoes phosphorylation, at least after γ radiation, suggesting that this is a crucial step in several different pathways.

As yet, it is unclear how the function of BRCA1 relates to that of BRCA2. The similarities in the phenotypes induced by disruption of these molecules, as well as their reported colocalization (*15*) along with mRad51 to the nucleus of somatic cells and synaptonemal complexes in meiotic cells, certainly suggest that they perform common functions. Nevertheless, there are important differences. In particular, BRCA2 binds with relatively high stoichiometry to mRad51 through the conserved BRC repeat region in exon 11 as well as through a carboxyl-terminal motif (*6, 12*), possibly speaking to a more direct role in recombination repair. On the other hand, halting cells with damaged DNA at a cell cycle checkpoint seems less affected by disruption of Brca2 than by disruption of Brca1. The new evidence placing BRCA1 downstream of ATM (and, by implication, ATR) suggests that BRCA1 may link the DNA repair functions of BRCA2 to the pathways that signal DNA damage or incomplete DNA replication.

Heterozygous mutations in ATM may predispose to breast cancer (*16*), although contrary evidence also exists (*17*). ATM heterozygosity affects between 0.5% and 1% of individuals, creating a large population who are potentially at risk. On this basis, up to 4% of sporadic breast cancers in women younger than 40 years of age may occur in ATM heterozygotes (*18*). Thus, the links between ATM, BRCA1, and (by inference) BRCA2 established by Cortez *et al.* define a cellular pathway that could be dysfunctional in a significant fraction of breast cancer patients. This fraction may increase still further if mutations affecting other components in the pathway (see the figure) also contribute to breast cancer. Further epidemiological studies will be needed to clarify this important issue.

Many important biological questions also remain. Not least among them is the paradox that although ATM, BRCA1, and BRCA2 are ubiquitously expressed and important in processes apparently fundamental to all cells, their disruption leads to an excess of cancer predisposition in particular tissues such as breast epithelium. The resolution of this paradox will surely be central to a better understanding of the genesis of breast cancer.



Repairing damaged DNA. BRCA1 is phosphorylated by the ATM protein kinase in response to DNA damage induced by γ radiation. Phosphorylated BRCA1 activates DNA repair through homologous recombination, in cooperation with BRCA2, mRad51, and other molecules related to members of the yeast RAD52 epistasis group. Phosphorylated BRCA1 may also regulate transcription and transcription-coupled DNA repair.

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PERSPECTIVES: CELL BIOLOGY

Cell Migration—Movin' On

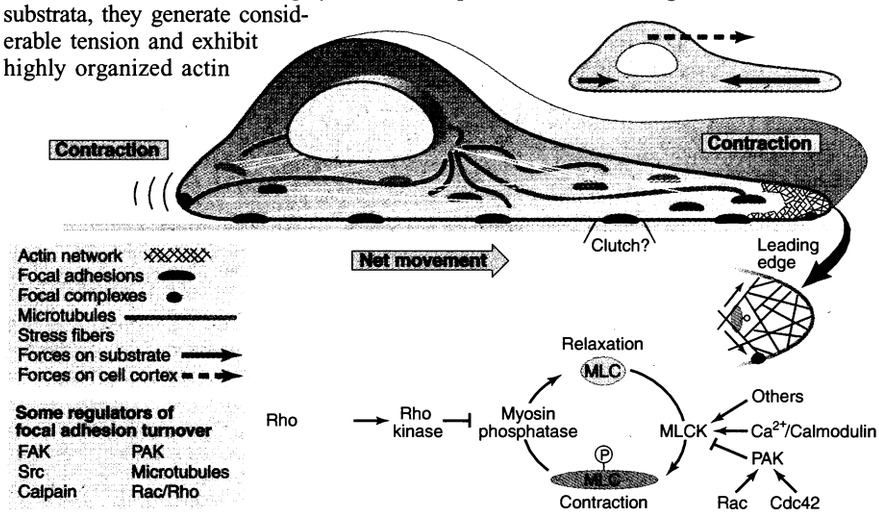
Alan Rick Horwitz and J. Thomas Parsons

Cell migration is crucial for embryonic development, the inflammatory immune response, wound repair, and tumor formation and metastasis (*1*). It begins with an initial protrusion or extension of the plasma membrane at the front (leading edge) of the cell (see the figure). The protrusions are driven by the polymerization of a network of cytoskeletal actin filaments and are stabilized through the formation of adhesive complexes. These adhesive complexes are regions of the plasma membrane where integrin receptors, actin filaments, and associated proteins cluster together. As the cells migrate, the small nascent adhesive complexes (focal complexes) at the front of the cell grow and strengthen into larger, more organized adhesive complexes (focal adhesions) that serve as points of traction over which the body of the cell moves. Finally, release of adhesions at the rear results in a net displacement of the cell. The mechanisms that regulate the formation of focal complexes at the cell's leading edge and the release of focal adhesions at the cell's rear remain unclear. Now, on page 1172 of this issue, Smilenov *et al.* (*2*) demonstrate that focal adhesions are highly motile in stationary fibroblasts yet stationary in migrating fibroblasts, suggesting the existence of a molecular clutch that couples traction and contractile forces. Other recent findings highlight the importance of tension, the actin and myosin filament network, the Rho/Rac family of signaling molecules, and microtubules in cell migration. Coordinating all of these complex processes is the challenge facing cells that are on the move.

Most adherent cells, although spread, are under tension. The mediators of tension are the integrin family of transmembrane adhesion receptors that link components of the extracellular matrix on the outside of the cell with the cell's cytoplasmic actin cytoskeleton (*1, 3*). It is tension that causes cells to round up when integrin-directed adhesions are perturbed. In fibroblasts, at least, the degree of tension determines the strength of the adhesions and the organization of the actin cytoskeleton. For example, when cells adhere to firm, highly adhesive substrata, they generate considerable tension and exhibit highly organized actin bundles and adhesion complexes. When placed on a more pliable substrate, cells exhibit less organized actin and smaller, weaker focal adhesions. The response of the integrin receptors to the rigidity of the substrate is illustrated in experiments in which fibronectin-coated beads are placed on cells and held in position with a laser beam (laser tweezer) (*4*). The cells sense the strength of constraint imposed by holding the bead in place. They respond with a local, proportional strengthening of cytoskeletal attachments, as revealed by the increased force required to mechanically displace the bead from its cytoskeletal connections.

The distribution of forces over the surface of cells can be visualized by growing them on collagen-coated sheets in which fluorescently tagged beads are embedded (*5*). The contractile forces within the cell cause the substrate to move. Thus, the forces in migrating cells can be visualized by the movement of the fluorescent beads. These studies reveal a radial distribution of force from the cell perimeter toward a region near the cell nucleus (see the figure). In migrating cells, forces near the leading edge are strong and transient, whereas forces at the rear are weaker and more stable. These observations are consistent with cell movement being driven, at least in part, by contractile forces generated from behind the leading edge.

Smilenov and colleagues (*2*) labeled focal adhesions with a green fluorescent protein marker fused to the transmembrane and cytoplasmic domains of an integrin receptor. Because these marker proteins home to focal adhesions, the investigators were able to



Can you feel the force? Cell migration is regulated by a combination of different processes: forces generated by contraction of actin and myosin, G protein signaling, microtubule dynamics, and the turnover of focal adhesions. Migration is initiated by polymerization of an actin network at the cell's leading edge and is maintained by contraction of myosin. The formation of new focal complexes is controlled by the Rac signaling molecule, and their growth is determined by a Rho-dependent process. Contractile forces behind the leading edge drive movement of the cell body. The turnover of adhesive complexes is regulated by the combined activity of microtubules and regulators that reside in these complexes. The forces on the substratum and cell body are shown by solid and dotted arrows, respectively. In motile cells, traction on the substrate results in net forward movement.

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