versible interaction of two photons with high efficiency (*4*). Most physicists believed that photons would therefore not be useful for quantum computation.

In the past few years, researchers have found a different approach that uses only linear optical elements, such as beamsplitters and polarization rotators. Single photons traveling through these simple optical elements can give the desired logical output, but they do so only sometimes. One might think that this is not very useful. After all, a pocket calculator that gives the correct answer just part of the time would be a liability. However, what if our calculator also had a flashing green light to tell us when it had the right answer?

The trick is to postselect the successful operations based on the output of additional single-photon detectors after feeding in additional single photons to the optical circuit (*5*, *6*). For this to work, it is important that these detectors do not give any information about the output state of the gate, because this would destroy the quantum information. With cleverly designed optical circuitry, the photon detectors will fire only if the logic operation is successful, in which case the optical path switches to feed the output of the gate into the next stage of the computation. Knill *et al.* showed that by using quantum teleportation, the probability of success of the combined logic circuit could reach nearly 100% (*5*).

Pittman *et al.* recently reported (*7*) the successful operation of a pair of simple photonic quantum logic gates: the quantum parity check (see the figure) and the destructive CNOT gate, which flips the target qubit if and only if the control qubit is equal to **1**. The latter is particularly important because it requires quantum interference between the two photons. The authors show successful operation for **0** or **1** input states, with an average error rate of 17%. They also claim flipping of a target qubit that is in a superposition of **0** and **1**.

These results demonstrate that postselection can introduce the nonlinearity required for photon logic. However, as Pittman *et al.* point out, the gates are of limited use for quantum logic as they destroy the control qubit. The next step is to combine these gates with ancillary single photons or entangled photon pairs to form a nondestructive CNOT gate, which is a potential building block for a quantum computer.

We may soon be able to pack more information onto each photon. In addition to the spin discussed earlier, photons also possess an orbital angular momentum (OAM), which is associated with the azimuthal phase of the electric field. Unlike polarization, there are an infinite number of orthogonal OAM states for each photon, raising the possibility of encoding a superposition of more than two states on a single photon. These "quNits" could improve the efficiency of quantum-computing schemes, extend the length of quantum cryptography systems (*8*, *9*), and facilitate new networking protocols involving more than two users (*10*).

Mair *et al.* have already demonstrated entanglement between the OAM states of two photons (*11*). However, the lack of a device for sorting the OAM of a single photon has hampered multi-qubit encoding. Leach *et al.* have recently shown how this can be done using an interferometric technique (*12*). At the heart of their interferometer is another simple glass element called a Dove prism, which rotates the electric-field profile of the photon. By rotating the field profile in one arm of the interferometer by 180° relative to the path through the other arm, the authors could sort photons with even and odd values of their OAM. After cascading a number of these interferometers together, they could distinguish several OAM states.

Many formidable technological challenges remain before photonic logic is ready to use. Researchers will have to perfect nondestructive gates with much lower error rates than reported to date. They will have to integrate these gates with practical sources of single photons (*13*) with close to 100% efficiency. Photon-detector technology will also have to be improved to allow almost certain detection, as well as distinguishing the photon number. We are far from realizing such components, but recent advances give good reason for optimism.

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PERSPECTIVES: CANCER

BRCA2 Enters the Fray

John H. Wilson and Stephen J. Elledge

About half of all familial cases of breast and ovarian cancer are caused by mutations in the *BRCA1* and *BRCA2* genes. Heterozygous germline mutations in these genes confer a 30 to 70% lifetime risk of breast or ovarian cancer on affected individuals. Tumors derived from these patients invariably display inactivation of both copies (loss of heterozygosity) of either *BRCA1* or *BRCA2*. Despite numerous studies, it is still not clear what the BRCA proteins do in the cell, and their amino acid sequences hold few clues. Hints suggesting that BRCA1 and BRCA2 are involved in DNA repair have been gleaned the old-fashioned way—through cell biology, biochemistry, and inspired guesswork. On page 1837 of this issue, Yang *et al.* (*1*) place these hints on solid ground by providing structural and biochemical evidence that BRCA2 is directly involved in the repair of DNA double-strand breaks.

The initial link between the *BRCA* genes and DNA repair derives from the key observation that BRCA1 displays a characteristic nuclear dot pattern during S phase of the cell cycle after immunostaining (*2*). This pattern is similar to that observed for human RAD51, a homolog of the bacterial recombination protein RecA. RAD51 is a bona fide participant in the homologous repair of DNA double-strand breaks, a process that uses the sister chromatid as a template for repair. During S phase, BRCA1, BRCA2, and RAD51 become colocalized in nuclear dots, which then disperse after arrest of DNA synthesis. In response to ionizing radiation or cross-linked DNA, these S-phase nuclear dots disperse and reform smaller foci that contain proliferating cell nuclear antigen and are presumptive sites of DNA repair (*3*, *4*). Furthermore, coimmunoprecipitation experiments indicate that BRCA1, BRCA2, and RAD51 are physically associated (*4*–*6*). Finally, cells containing mutations in either *BRCA1* or *BRCA2* are

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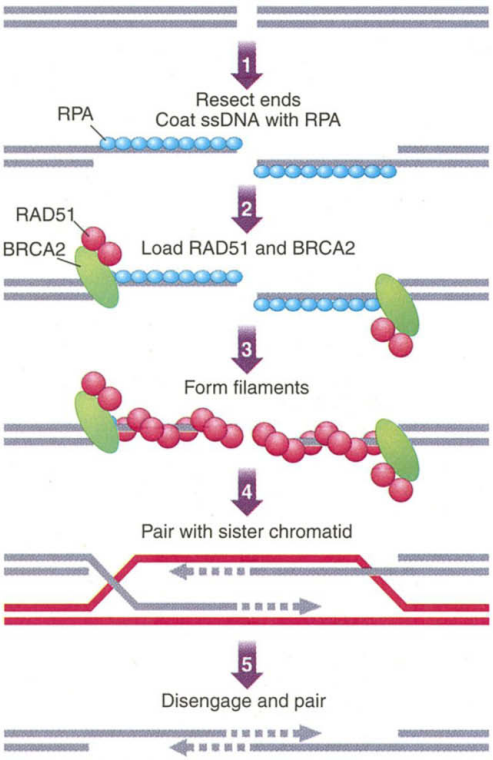
exquisitely sensitive to DNA cross-links, showing severely impaired homologous repair of DNA double-strand breaks (*7*, *8*). Together, these studies indicate that BRCA1 and BRCA2, along with RAD51, are crucial components of homology-dependent DNA repair in cells. This connection is reinforced by the finding that mice lacking either BRCA1, BRCA2, or RAD51 show proliferation defects and die in utero.

Recent studies have revealed that BRCA1 and BRCA2 participate in a nexus of interactions with the products of other cancer-associated genes, including those responsible for ataxia telangiectasia, Fanconi anemia, and Nijmegen breakage syndrome (*9*, *10*). Collectively, these proteins protect the genome from the consequences of ionizing radiation and DNA cross-linking by halting the cell cycle and promoting damage repair. In this effort, BRCA1 appears to operate as a midlevel executive, transducing DNA-damage signals from the ATM and ATR checkpoint kinases to effector proteins such as the Fanconi D2 protein and possibly CHK1.

Although a set of amino acid repeats in the center of BRCA2 (the BRC motifs) mediate a direct interaction with RAD51 (*11*, *12*), it has not been clear whether BRCA2 works in concert with RAD51 or is just another component of the DNA repair regulatory pathway. Yang *et al.* (*1*) now provide compelling evidence for direct involvement of BRCA2 in DNA repair. They analyzed the structure of the 800-residue carboxyl-terminal domain of human, mouse and rat BRCA2 (BRCA2-CTD), which lies beyond the BRC motifs and is the most evolutionarily conserved region of this protein. Crystal structures of BRCA2-CTD bound to another protein DSS1 (required for crystallization) at a resolution of 3.1 Å reveal that this region has five domains, four with features suggestive of a direct role for BRCA2 in DNA repair.

Three of the five BRCA2-CTD domains are structurally homologous, each containing an oligonucleotide/oligosaccharide binding (OB) fold. The OB fold is present in most single-stranded DNA binding proteins (SSBs). The crystal structure of BRCA2-CTD bound to single-stranded DNA reveals that its OB folds interact with DNA in the same way as the OB folds of replication protein A (RPA), the most abundant eukaryotic SSB. The three OB folds of BRCA2-CTD are packed so that their individual binding grooves are aligned. A fourth domain—the so-called tower domain—is inserted into one OB fold, away from its DNA binding surface. The tower domain consists of a pair of long α helices that support a three-helix bundle. This bundle closely resembles the DNA binding domains of bacterial site-specific recombinases and eukaryotic Myb and homeodomain proteins, all of which bind to the major groove present in double-stranded DNA. Although Yang *et al.* did not detect direct binding of BRCA2-CTD to double-stranded DNA, the tower domain is critical for BRCA2's tumor suppressor activity, because four of the seven most common missense mutations in BRCA2-CTD affect this domain.



Faster with BRCA2. A possible model of how BRCA2 enhances homologous recombination during repair of DNA double-strand breaks. RAD51 and BRCA2 bind to single-stranded DNA that is coated with the protein RPA. BRCA2 could affect the rate of RAD51 loading or the organization of RAD51 filaments. Alternatively, it could enhance the ability of this complex to locate and invade the homologous target DNA on the sister chromatid. Precisely where in steps 2, 3, or 4 BRCA2 acts remains to be determined.

Yang *et al.* follow up on these structural clues by testing the influence of BRCA2-CTD (in a complex with DSS1) on homologous recombination in a standard in vitro assay. During repair of double-strand breaks, RAD51 normally coats the single-stranded portions of recombination substrates to initiate transfer to a homologous duplex, the first step in recombination (see the figure). RAD51 relies on help from RPA to eliminate secondary structure in the single strands so that it can bind efficiently. Yet RPA binds to single strands so tightly that it interferes with the binding of RAD51. This molecular conflict is resolved by other recombination proteins—such as RAD52 or the RAD54-RAD57 complex—that mediate the orderly replacement of RPA by RAD51 (*13*). Like these better defined mediators of homologous recombination, BRCA2-CTD stimulates strand transfer in the presence of RAD51 and RPA.

The Yang *et al.* study demonstrates the power of structural analyses to illuminate the function of proteins, and marks an important milestone in BRCA2 research. Like all watershed discoveries, the new findings beg additional questions. How does BRCA2-CTD stimulate strand transfer mechanistically? Do the RAD51 binding domains in BRCA2 (the BRC repeats, which are absent from BRCA2-CTD) enhance or inhibit its effects on strand transfer? If BRCA2 is so important for DNA repair, then why are there no *BRCA2* homologs in yeast, flies, or worms? How are upstream regulatory signals integrated into the behavior of BRCA2 and RAD51? And does DSS1 simply stabilize a particular conformation of BRCA2, or does it play some larger role in the DNA repair mechanism?

Although profound, the insights into BRCA2 provided by Yang and colleagues do not solve the classic mystery of why *BRCA2* mutations lead to tumors in such a well-defined subset of human tissues. Are breast and ovary exposed to higher rates of DNA damage? Do other tissues have a better back-up DNA repair system and, if so, what might that be? Are these tissues less efficient at eliminating *BRCA*-deficient cells, enabling survival mutations to arise and tumors to form (*14*)? Finally, how can we take advantage of this deficiency in homologous recombination to specifically kill *BRCA2*-mutant cells in cancer patients? As recombination seems to be essential for cell survival, probably because of its requirement for restarting stalled replication forks, might a further incapacitation of recombination in BRCA2-deficient tumor cells cause their death? Stay tuned for more insights, coming soon to an x-ray beam near you.

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