Antonio Lee sees the most important clinical pay-offs coming from the BRCA2/Rad51 interaction.

In a recent article in Proceedings of the National Academy of Sciences, researchers in Lee’s lab identified the portions of BRCA2 protein that associate directly with Rad51. His strategy is to synthesize a small peptide that will block this interaction. Because most breast tumors, as well as other tumors, have an intact BRCA2 protein, a drug that blocks this interaction might leave the tumors more susceptible to damage from radiation or drugs causing double-stranded DNA breaks.

Even though the data for BRCA2 seems to be stronger, some would argue that it’s difficult to imagine that BRCA1 and BRCA2 are not both involved in at least some of the same pathways. Lewis Chodosh, M.D, Ph.D., at the University of Pennsylvania Medical Center in Philadelphia, is one of those.

**Finding BRCA1’s Function: A More Arduous Journey**

For BRCA1, the noisiest problem has been where the BRCA1 protein is located in the cell. While most researchers have found the protein in the nucleus of normal cells, some have found evidence of the protein in the cytoplasm of malignant cells, and one group has reported that BRCA1 is present in the cell membrane and in the secretory apparatus. However, in a paper recently submitted to Nature Genetics, Cindy Wilson, Ph.D., from the Division of Hematology Oncology at the University of California, Los Angeles, appears to have settled whatever ambiguity remains.

“It’s in the nucleus,” said Wilson. “All the antibodies that are specific show distinctive nuclear dot patterns in cells.” She compared 20 antibodies from several groups using many tests — western blotting, immunoprecipitation, immunohistochemistry, and cytchemistry on individual cells. Because BRCA1 protein is expressed at very low levels in the nucleus, very clean antibodies are required to see it.

Besides cellular location, another clue to function comes from discovering the proteins that interact with BRCA1. To date, the list has grown quite large, including several enzymes (e.g., helicase, RNA polymerase, and ubiquitin hydrolase) as well as other proteins (e.g., Rad51, p53, BARD1, and CTIP). So far, no clear consensus has emerged about which proteins are important to BRCA1’s function.

Adding to the murky picture, is the inability of researchers to produce mice lacking two copies of functional BRCA1 genes, so-called knock-out mice, which frequently provide insights into the function of the missing gene. Mouse embryos lacking BRCA1 protein do not survive.

Given these problems, a paper in the Aug. 14 Science was a first — the first direct functional evidence for BRCA1. Researchers from the Department of Radiation Oncology, University of North Carolina at Chapel Hill, showed that cells deficient in BRCA1 were unable to repair DNA that was damaged by either ionizing radiation (gamma radiation) or hydrogen peroxide. The particular kind of repair that is defective in these cells is called transcription-coupled repair (TCR) — involving machinery that tags along with RNA polymerase and repairs actively transcribing genes.

“Our results make sense with the data that show an association between BRCA1 and RNA polymerase,” said Lori Gowen, a UNC graduate student and the paper’s first author. “And it is consistent with BRCA1 being a tumor suppressor gene — mutations will accumulate if the gene is involved in repair. But it still doesn’t allow us to say whether BRCA1 is a part of the repair machinery or a transcription factor that regulates transcription of genes involved in TCR.”

And that seems to be precisely the problem — developing a good system for analyzing BRCA1, either in mice or in human cancer cells. The gene’s enormous size suggests that the BRCA1 protein is likely to have several functions, probably involving DNA repair, transcriptional regulation of genes, or others.

Ralph Scully, M.D., Ph.D., a researcher in David Livingston’s lab at the Dana-Farber Cancer Institute, Harvard Medical School, Boston, who discovered that BRCA1 associates with Rad51, believes the only way to make progress is to develop a good genetic system.

“We need a tractable genetic system to test out key hypotheses in the field. For example, we need to be able to add back normal BRCA1 to cells lacking functional BRCA1 and show that a specific defect can be reversed,” he said.

— Nancy J. Nelson
Chodosh has published a series of articles during the last three years looking at the pattern of expression of both genes during embryogenesis, in a variety of adult tissues, and in mammary glands during different developmental stages.

"Basically you can't tell them apart," remarked Chodosh. "It's remarkable. We looked at over 20 tissues, and what's extraordinary is not just that BRCA1 and BRCA2 are expressed in the same tissues, but that they're expressed at the same relative levels within the same cellular compartments and at the same developmental stages within those tissues. You just don't find that for very many genes in nature."

Because of these data, he believes that BRCA1 and BRCA2 are likely to be interconnected. His sense is that within the nucleus are dynamic macromolecular complexes that include BRCA1/2, Rad51, and other DNA damage-related proteins.

"My guess is that there are probably three, four, five or more proteins in these complexes. The particular proteins present or absent will be different, depending on the state of the cell and the state of DNA damage," he speculated.

Ralph Scully, M.D., Ph.D., a researcher in David Livingston's lab at the Dana-Farber Cancer Institute at the Harvard Medical School, agrees that BRCA1/2 functions are probably intertwined. In support of this, the Livingston group has recently shown in a paper published in September in Molecular Cell that BRCA1 and BRCA2 interact biochemically, although it is not yet clear whether this interaction is direct or indirect.

One hypothesis advanced by the group is that both genes are involved in maintaining the integrity of the DNA into breast tissue, which is uniquely vulnerable to assaults from carcinogens throughout life — during menarche, breast development, and pregnancy. One candidate is a metabolite of estrogen.

For the moment, however, until a consensus emerges, the data linking BRCA2's function to the repair of DNA breaks offers the most promise for translating knowledge of function into effective rational therapy. If progress in the BRCA2 field continues at its present pace, the answers from the clinic should be in relatively soon.

— Nancy J. Nelson

**Tea Therapy? Out of the Cup, Into the Lab**

A cup of tea provides an antioxidant boost that may protect against several types of cancers, but so far the link has been reliably shown only in tea-sipping rodents and test tubes — not in people. The antioxidants in green and black tea, called catechins, are "more potent than vitamins C and E" in their ability to scavenge potentially carcinogenic compounds called free radicals, said Catherine Rice-Evans, Ph.D., of the Antioxidant Research Centre in London.

However, Rice-Evans and other tea experts cautioned that despite promising early research, better animal models and more robust epidemiological studies are needed before tea research steams toward human trials. A decade may pass before enough clinical evidence accumulates to validate or refute tea's anticancer potential.

"The in vitro and animal data are very strong," said Jeffrey Blumberg, Ph.D., who researches tea antioxidants at Tufts University in Boston. "But clinical trials are the definitive approach."

Even without much clinical evidence, the 300 tea-swalling scientists and industry representatives who gathered at the Second International Symposium on Tea & Human Health, held in Washington in September, were steeped in news from a dozen promising studies.

Most of this research focused on the basic chemistry and biology of catechins. Among the results: Tea contains more antioxidants than do most fruits and vegetables; downing a single cup of...