The DNA in the nuclei of our cells gets tattered every day from forces within, such as free radical damage, and also from without, such as the sun’s UV rays. The result is an estimated 20,000 DNA lesions per cell each day.

Ryan B. Jensen, PhD

The body’s DNA repair system is superb at fixing these, but no system is perfect. If defective DNA is left unmended, it can cause cellular mutations that lead to cancer.

Ryan B. Jensen, PhD, Assistant Professor of Therapeutic Radiology and Pathology, is unraveling the connections between DNA repair, breast cancer, and ovarian cancer.

His lab is looking for the instigating molecular events that trigger mutations by tracing their origins to the BRCA2 (Breast Cancer Susceptibility) gene. It is well established that women who inherit a mutation in BRCA2 are at high risk of developing breast and ovarian cancer. Without the BRCA2 mutation, for instance, women have a 12 percent chance of getting breast cancer; with the mutation, the risk jumps to 90 percent over a patient’s lifetime.

What’s unclear is why BRCA2 mutations strike the breast and ovaries.

“It’s a big mystery. My lab is doing basic research to understand the biology of what BRCA2 does, and what happens when it can’t do its job. BRCA2 is a DNA repair protein that responds to DNA double-strand breaks. These physical breaks in the DNA helix are healed by BRCA2 through a complex process called homologous recombination. But if the breaks aren’t repaired properly, you get mutations in the genes that drive the cancer process.”

One reason for the mystery is that scientists didn’t understand BRCA2 biochemistry. To study it would require, for starters, purifying the protein coded for by the BRCA2 gene. But the BRCA2 protein is large, unstable, and fragile, all obstacles to purifying it. Dr. Jensen and his colleagues worked on the problem for several years, and in 2010 became the first to succeed at purifying the entire BRCA2 protein.

Using the same process, they are now purifying mutant forms of BRCA2 taken from patients. That allowed the researchers to study the proteins without all the interfering noise within cells. They put the purified proteins—normal and mutant—into test tubes or in vitro assays, mixed them with broken pieces of DNA, and watched how they handled repair or failed to. The goal is to pinpoint how and why something goes wrong when BRCA2 is mutated, and why this defect leads cells down the path towards tumorigenesis in the breast or ovaries.

In addition to the biochemical research, Dr. Jensen’s lab is studying BRCA2 genetics. Using breast and ovarian cells isolated from human patients, they can then treat the cells in tissue culture with various chemotherapy drugs, and study the cellular response of the BRCA2 gene.

Most of the drugs cause DNA damage. Dr. Jensen wants to know where it goes from BRCA2 is depleted from a breast or ovarian cell. “Does it instantly become genomically unstable? Does it shut down? Does it die? Does it become a tumor cell?”

“A failure in DNA repair,” explained Dr. Jensen, “is probably the driving force behind all mutations that arise in cancer. DNA damage is an ever-present danger, and if these DNA repair genes are not working properly, you’re getting more genomic instability and mutations. DNA repair genes are in charge of this process. If we can understand that process, we can develop new therapeutic avenues for treating cancer.”

If we know that, a patient could come in and get the sequencing done, and then get the drugs that are most effective.”

The Interconnected Mysteries Of DNA Repair And Breast Cancer

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