Human cancer cells have several malignant phenotypic features that distinguish them from normal cells. One such feature, namely, their chromosome instability, often results from germline or somatic mutations in DNA repair genes. To date, six major mechanisms of DNA repair have been identified (Table 2). Researchers have identified druggable targets for each of these pathways, as well as biomarkers that reveal the integrity of these pathways. For instance, Polβ protein expression levels predict the integrity of the base excision repair pathway, while PARP1 is integral to the pathway’s function and serves as a promising therapeutic target.

Human cancer cells are often defective in one DNA repair pathway. Determining which repair pathway is affected may help clinicians identify the best course of therapy (i.e., precision medicine). For instance, BRCA1 mutation predicts sensitivity to PARP inhibition in breast cancer, ERCC2 mutation predicts cisplatin sensitivity in bladder cancer, and MGMT silencing predicts temozolomide sensitivity in glioblastoma.

During the last two decades, the study of rare inherited human DNA repair disorders, such as Fanconi anemia (FA), ataxia telangiectasia, and Bloom’s syndrome, has provided new insights into the critical DNA repair pathways in human cancers. In particular, the FA pathway illustrates how DNA repair pathways can be deregulated and serves as a model for using pathway biomarkers to guide therapeutic management in clinical practice.

Fanconi anemia is a rare autosomal recessive disease with a prevalence of 1 per 100,000 births. The disorder is characterized by bone marrow failure leading to aplastic anemia, developmental defects, and cancer susceptibility. Aplastic anemia typically develops by age 5 years, and 50% of patients who survive the anemia develop acute myeloblastic leukemia by age 40. Patients with FA are also susceptible to head and neck, gastrointestinal, and gynecologic cancers and squamous cell carcinoma.

FA cells demonstrate the characteristic cellular phenotype of hypersensitivity to interstrand DNA crosslinking agents such as cisplatin, melphalan, and mitomycin C (MMC). Treatment with such agents, which results in G2/M arrest and increased chromosome breakage in cultured FA cells, is the definitive diagnostic test for this disorder.

The FA pathway involves at least 18 genes, including BRCA1 (FA gene S) and BRCA2 (FA gene D1). The FA and BRCA1/2 proteins appear to work in concert to control the monoubiquitinated state (i.e., the addition of one ubiquitin, a 76 amino acid tag, to the internal lysine residue of a protein) of this common FA/BRCA pathway. Fanconi anemia complementation group D2 (FANC D2) monoubiquitination is a biomarker of FA pathway activation that is easily detected by Western blotting. Additional biomarkers of DNA repair pathways have potential clinical utility in predicting the efficacy of new classes of anticancer drugs, such as poly(ADP-ribose) polymerase inhibitors and checkpoint inhibitors.

Acquired mutations in the genes of the FA/BRCA pathway account for the chromosome instability of many human cancers, including ovarian, breast, and prostate cancer. One active area of research involves predicting cisplatin sensitivity of sporadic cancers in non-FA adults. Ovarian cancers to develop cisplatin resistance after showing an initial response to cisplatin.

Ovarian cancer can be described as a disease of DNA repair, although the mechanisms of impaired DNA repair are diverse. Rapid screening of ovarian tumor samples using FANCD2 reveals that 20% of ovarian tumors have a defect in the FA/BRCA pathway. Approximately 50% of serous ovarian cancers harbor mutations associated with homologous recombination (HR) repair deficiency. HR-proficient ovarian tumors display alternate mechanism of genomic instability, including nucleotide excision repair (NER) mutations and miRNA suppression of DNA repair. Approximately 7% of high-grade serous ovarian tumors harbor somatic mutations in NER genes.

Sensitivity to platinum and PARP inhibitors (PARPis) commonly coexist in ovarian cancer due to the high prevalence of FA/BRCA pathway mutations that confer sensitivity to both drugs. In contrast, NER mutation represents
a novel mechanism of cisplatin sensitivity in ovarian cancer that, in contrast to HR deficiency, leads to discordance in sensitivity to platinum-based chemotherapy and PARPi. Two NER mutations in particular, ERCC6-Q524* and ERCC4-A583T, demonstrate high platinum sensitivity in vitro. Therefore, platinum sensitivity should not be regarded as an accurate biomarker of PARPi sensitivity, especially for NER-mutated tumors lacking HR defects.

Cancer cells with one defective DNA repair pathway tend to become hyperdependent on a second pathway. “Synthetic lethality” describes the process of inhibiting the second pathway to eradicate the cancer cell. The DNA polymerase θ protein (POLQ), a novel polymerase that mediates double-strand break repair, is strongly upregulated in HR-deficient ovarian tumors. The POLQ protein participates in an error-prone alternative end-joining pathway (Alt-EJ), and it is an essential protein in HR-deficient ovarian tumors. Knockdown of POLQ, or small molecule inhibitors of the POLQ enzyme, may result in synthetic lethality in these tumors.

PARP1 is required for POLQ recruitment to sites of DNA repair, making PARP1 an essential modulator of DNA damage repair. The PARP/POLQ pathway is a previously-unrecognized and critical target of PARP1 inhibitors in BRCA1/2 mutant tumors. POLQ inhibitors, like PARP inhibitors, may be useful in the treatment of HR-deficient tumors. Moreover, a POLQ inhibitor may be useful for PARPi-resistant cancers. POLQ overexpression and its resulting genomic mutational signature (e.g., INDELs, LOH) may be useful biomarkers for PARP inhibitor or POLQ inhibitor activity. In addition, POLQ overexpression may correlate with high HRD score.

Profiling the activity of the DNA repair pathways in human cancers may improve and extend the use of new anticancer drugs in the oncology clinic. On December 19, 2014, the FDA announced the approval of a PARP inhibitor, olaparib, for the treatment of advanced ovarian cancer associated with germline mutations in BRCA1 and BRCA2. Several questions related to the optimal use of this therapeutic class remain: Are BRCA1/2 mutations necessary and sufficient for PARPi response? How do tumors become resistant to PARPi? What are the critical target pathways of the PARPi?

**Future Directions**

Recent advances in the understanding of the underlying DNA repair mechanisms driving tumor growth and development may translate to novel therapies for ovarian cancer. In 2015, Stand Up To Cancer (SU2C), Ovarian Cancer Research Fund (OCRF), Ovarian Cancer National Alliance (OCNA), National Ovarian Cancer Coalition (NOCC), and American Association for Cancer Research (AACR) announced the formation of the Ovarian Cancer Dream Team. Led by Dr. Alan D’Andrea of the Dana-Farber Cancer Institute in Boston and Dr. Elizabeth Swisher of the University of Washington in Seattle, the SU2C-OCRF-OCNA-NOCC Ovarian Cancer Dream Team is dedicated to developing new treatment options for patients with ovarian cancer through collaborative research and expanded clinical trials.

**Financial Disclosures**

Dr. D’Andrea discloses no financial relationships relevant to the content of this presentation.

**Acknowledgements**

This summary was created from the proceedings of the 2015 Chabner Colloquium: Collaboration in Clinical Trials, which was held on Monday, October 26, 2015, in Boston, MA. The Society for Translational Oncology received educational grants in support of this activity from AbbVie Inc., Chugai Academy for Advanced Oncology (CHAAO), Epizyme, Inc., Incyte Corporation, Lilly USA, LLC, Merrimack Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, Otsuka America Pharmaceutical, Inc., and Pfizer Inc.

**References**