Editorial

Molecular Cancer Research

There and Back Again: The Middle Earth of DNA Repair

Karen E. Knudsen

Future generations of cancer researchers will look upon this as a historic era, witness to an unprecedented set of discoveries that converted fundamental mechanistic observations into new therapeutic tests, clinical advances, and improved cancer care. Basic understanding of T-cell function and newly defined mechanisms to modify activity added immunotherapy to the armamentarium of treatments available to combat malignancies. Whether by adoptive cell transfer or immune checkpoint inhibitors, laboratory-based discoveries allowed for development of this new classification of cancer therapeutics. Breakthroughs using genomically informed strategies to match patients to targeted therapies were defined, inching the field closer to the aspiration of including routine molecular profiling as part of tumor boards and clinical decision making. Finally, based on decades of studying mechanisms governing DNA strand break resolution, new therapies for a subset of patients with advanced cancer were developed and approved. This is the era in which the DNA repair field flourished, met the expectation of translating basic understandings into the clinical setting, and circled back again to investigate the molecular basis of therapeutic response.

The journey started "here" in the laboratory. The concept that tumors with DNA repair defects might show synthetic lethality with PARP1 inhibitors was proposed in the early years of this century, when landmark studies revealed that cells with a BRCA1 or BRCA2 dysfunction, and therefore compromised for homologous recombination–mediated repair, are exquisitely sensitive to suppression of PARP1-dependent DNA repair pathways, and fundamental studies reporting mechanisms of PARP1 function emerged (1–3). Fast forward to the present time, the much sought-after "there" of success in the clinic was reached. The PARP1/2 inhibitor olaparib was approved for use in a subset of patients with advanced ovarian cancer with DNA repair defects, and the same compound was approved in Europe for maintenance therapy. Most recently, breakthrough status was granted by the FDA for use in BRCA1/2 or *ATM*-mutated metastatic, castrate-resistant prostate cancer, built on basic discoveries associated with this pathway (4–7) and groundbreaking clinical assessment of PARP1 inhibitor function (8). As these advances have unfolded, we now find ourselves charging forward but also "back again" to the laboratory; bold new basic science initiatives are pushing at the forefront of discerning the molecular implications of DNA repair dysfunction and mechanisms of resistance to DNA repair–associated therapies. Such "back-again" investigations have been a major focus for *Molecular Cancer Research* (MCR) and expert Senior Editors for the DNA Damage and Repair section (Drs. Robert Bristow and Toshiyasu Taniguchi), who evaluated and curated influential discoveries that advanced the field.

Defining the molecular basis of response to PARP1/2 inhibitors was a major focus of studies reported in *MCR*. Analyses of cells deficient in XRCC1 and polymerase-beta supported the theory that in addition to defects in homologous recombination, base excision repair (BER) defects can confer sensitivity to PARP1/2 inhibitors (9). The impact of this observation may be profound, as cells routinely utilize BER to resolve endogenous DNA damage. Cells altered in TGFβ function may also show differential responses to PARP1/2 inhibitors, as TGFβ induces a "BRCAness" phenotype by downregulating expression of DNA repair genes, including *BRCA1*, *ATM*, and *MSH2* (10). In addition to genetic alterations, gains were realized in understanding the contribution of PARP1 trapping on chromatin to cellular response. It was revealed that the trapping event in response to PARP1/2 inhibitors occurs due to catalytic inhibition and not allostery, thus paving the way toward not only understanding mechanisms of action but also how these attributes may or may not have an impact on clinical response (11). Leukemias with specific activated tyrosine kinases may prove particularly susceptible to PARP1 suppression, as it was discovered that enhanced downstream c-Myc activation leads to not only heightened LIG3 and PARP1 levels but subsequent repair errors as well (12). Similarly, in tumors hallmarked by amplified N-Myc (e.g., neuroblastomas), upregulation of factors involved in alternative nonhomologous end joining was observed and paralleled sensitivity to PARP1 (13). On balance, these "back-again" observations point to an emerging paradigm that, in addition to genetic alterations affecting DNA repair, dysregulation of DNA repair factor expression, may contribute significantly to the requirement for PARP1 activity in human cancers.

Preclinical advances have also provided the molecular foundation for novel combinations with PARP1/2 inhibitors. The concept of combining PARP1 and HDAC inhibitors was supported by observations wherein olaparib and SAHA cooperated to suppress RAD51 expression and resulted in cell death (14). Additional novel combinations were proposed for Triapine, a small-molecule inhibitor of ribonucleotide reductase, which diminished the capacity of olaparib to induce BRCA1 and RAD51 foci, mediated in part through the ability of the compound to indirectly block CtIP phosphorylation and subsequent repair mediated by homologous recombination (15). Clinical assessment now awaits.

Distinct from PARP1, new functions for DNA repair factors were discovered that advanced understanding of tumor-associated alterations in these pathways. Using elegant genetically engineered models, novel functions of the Mre11 complex were identified that are ATM independent (16). These studies showed that DNA repair functions that are independent from signaling activity are needed to suppress genome instability and lymphomagenesis in ATM-deficient cells. Synthetic lethal screens in cells with ATM loss of function identified ATR as a rational target, based

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on a shift in reliance to ATR function (17). Cell-autonomous pathways were also considered with regard to continuous DNA repair signaling; it was discovered that prolonged engagement of the DNA repair checkpoint facilitates enrichment of mutant p53 (18). Epigenetic alterations resulting from metabolic reprogramming in cancer cells were observed to promote DNA repair and thereby enhance cell survival, adding strength to the concept that cross-talk between DNA repair and metabolic pathways may affect cancer phenotypes. The role of miRNAs was assessed; using unbiased screening in glioblastoma cells identified four miRNAs that promote radioresistance and connect regulation to TGFβ (19). Conversely, miR-155 was shown to induce genomic instability by reducing expression of polymerase-delta and thereby facilitating error-prone DNA repair (20). New kinase targets were also investigated. MPS1 was nominated as a putative target to suppress DNA repair, based on new findings showing that MPS1 suppression alters expression of *PRKDC*/DNAPK, resulting in both compromised DNA repair and radiosensitization (21). The present emphasis on functional assessment of clinically observed DNA repair alterations will no doubt allow refinement of therapeutic strategies and development of biomarkers to predict response.

Multiple forms of stress were identified as upstream effectors of DNA repair, leading to new understanding of microenvironmental and cell-autonomous factors alike that modify the repair process. The ability of the proinflammatory factor angiopoietin-like protein 2 (ANGPTL2) to induce tumor formation and progression was shown to be linked to oxidative stress and reduced MSH2 expression, providing fresh insight into the mechanisms underlying UV-induced carcinogenesis (22). Further implicating the contribution of the microenvironment, chronic hypoxia was shown to result in decreased expression of BER factors in colorectal cancers, resulting in altered DNA repair capacity (23). Furthermore, UV-A radiation was shown to induce oxidative stress, and resultant extensive oxidation of nucleotide excision repair proteins increased susceptibility to UV-B–mediated DNA damage (24), thus bringing new and unexpected understanding to the mechanisms of UV-induced DNA damage.

In summary, we are witnessing a remarkable era; when basic science discoveries exploring mechanisms of DNA repair responsiveness were translated into the clinic, successes were realized, and clinical observations circled back again into the laboratory to tackle new questions about molecular modifiers of response and resistance. As scientists at the forefront of discovery, we are surrounded by riddles such as these, much like The *Hobbit* is the book by Tolkien, "*There and Back Again*" is the story The Hobbit's character (Baggins) writes within The Hobbit. "*Go back? . . . No good at all! Go sideways? Impossible! Go forward? Only thing to do! On we go.*" Tolkien could have been writing about this time, in this era of ever-expanding knowledge, tackling the riddles that are before us with sword in hand, hearts all of a pitter and a patter.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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