

Theme of the Quarter: DNA Damage Response

The Jackson Laboratory Clinical Knowledgebase (CKB) team is thrilled to announce an exciting update to CKB CORE™. We are launching a new initiative called the Theme of the Quarter (TOQ) series. This initiative will provide refined content focusing on 50 highly relevant cancer genes, while continuing to offer CKB CORE™ users with **free** access. Each quarter, a new theme will be featured and a subset of the 50 genes will be exchanged, ultimately increasing the extent of freely available content provided throughout the year. In addition to the quarterly theme, a newsletter will be distributed discussing the newly accessible genes and their connection to precision oncology. This quarter we are highlighting **DNA damage response (DDR)** pathway genes. Of the 50 available genes in CKB CORE™ this quarter, you will find 18 which specifically relate to DNA repair.

It is well known that one of the key requirements for organismal survival is maintaining genome integrity. Fortunately, our cells are able to ensure this through the coordination of various pathways within the **DNA Damage Response** signaling network. DNA damage can occur in both proliferating and quiescent cells and may be a result of intrinsic and/or extrinsic factors. In brief, DNA damage is detected by DNA sensors, and upon this detection, cell cycle arrest is induced via cell cycle checkpoints, followed by activation of DNA repair mechanisms. The repair mechanism(s) activated is dependent upon the type of DNA lesion. The two major types include double strand breaks (DSBs) and single strand breaks (SSBs). The repair of SSBs rely on base excision repair while DSBs rely on homologous recombination and non-homologous end-joining. Lesions due to a base mismatch utilize the mismatch repair mechanism, and bulky lesions, induced by reactive oxygen species, are repaired via nucleotide excision repair (Fig. 1). In the event that the DNA damage is too extensive, the cell undergoes apoptosis.

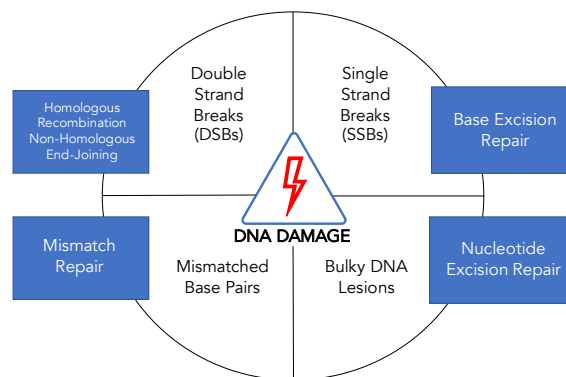


Figure 1. A schematic of the different types of DNA damage and the associated DNA repair mechanisms.

In cancer, some pathways within the DDR signaling network might be deregulated, often a result of an alteration within one or more of the DDR genes. Loss of the functional protein may render the cancer cell more susceptible to mutagenesis, thereby potentially driving cancer progression. Cancer treatment often includes agents that induce DNA damage such as chemotherapy and radiotherapy. However, resistance to these therapies may occur as a result of intact DNA repair mechanisms¹. A sound approach to overcome this resistance is the use of targeted therapies that inhibit complementary repair mechanisms. The less chance for DNA repair to occur, the greater the possibility of inducing apoptosis and achieving a therapeutic benefit.

One such class of drugs used to inhibit DNA repair is PARP inhibitors, which target cells deficient in homologous recombination. Repair pathways often overlap, and PARP is one such enzyme that facilitates the repair process of SSBs. By inhibiting PARP, SSBs escape repair and accumulate and then result in DSBs. If a cell harbors defects in proteins that play a role in homologous recombination repair (HRR), the cell may be unable to repair the DNA and apoptosis is initiated. This mechanism of inhibiting PARP is referred to as synthetic lethality².

There are currently four PARP inhibitors that are FDA-approved, including Zejula (niraparib) for ovarian cancer patients, Talzenna (talazoparib) for breast cancer patients, and Rubraca (rucaparib) and Lynparza (olaparib) for patients with breast cancer, ovarian cancer, or prostate cancer. All four PARP inhibitors are approved in the specified tumor types for patients with deleterious or suspected deleterious BRCA1/2 mutations. In addition, Lynparza (olaparib), along with a companion diagnostic assay, was recently approved in May 2020 for metastatic

castration-resistant prostate cancer patients with deleterious or suspected deleterious mutations in HRR genes. There are 14 HRR genes included in the companion diagnostic assay and 12 of those 14 genes as well as their related content are available in CKB CORE™ (Fig. 2). While ATR, a checkpoint kinase, plays a role in homologous recombination repair, it has also been shown to play a role in the nucleotide excision repair pathway⁴. Currently, there are PARP inhibitor clinical trials recruiting patients with ATR inactivating mutations (Fig. 2). Along with HRR genes, two mismatch repair genes, MLH1 and MSH6 are also accessible in CKB CORE™ (Fig. 2). Preclinical and clinical evidence has shown tumors deficient in mismatch repair are responsive to immune checkpoint inhibitors³.

DNA Repair Genes Available in CKB CORE™




Double Strand Breaks (DSBs)				Mismatched Base Pairs		Bulky DNA Lesions	
							
CKB CORE™ Genes Involved in Homology-Directed DSB Repair				CKB CORE™ Genes Involved in Mismatch Repair		CKB CORE™ Genes Involved in Bulky Lesion Repair	
ATM	CDK12	FANCL	RAD51C	MLH1	MSH6	ATR	
BARD1	CHEK1	PALB2	RAD51D	Potential Treatment Approaches			
BRIP1	CHEK2	RAD51B	RAD54L				
ARID1A	ATR	ATRX	FANCA				
				Olaparib (Prostate Cancer)	Immune Checkpoint Inhibitors	ATR and/or PARP Inhibitors	
				FDA Approved	Clinical Trials		

Figure 2. The DNA repair genes available in CKB CORE™ grouped by their associated DNA repair mechanism. Cell colors correspond to the potential treatment approaches.

Summary

With the 18 DNA repair genes available in CKB CORE™, users have access to nearly 2,500 gene variants for interpretation, and several lines of preclinical and clinical efficacy evidence to help guide treatment decisions. We hope this updated version of CKB CORE™ continues to serve as a valuable resource for your variant interpretation needs, and if you have any questions or comments, please feel free to contact us at ckbsupport@jax.org.

Resources

<https://www.fda.gov/drugs>

References

1. Li, L, Guan, Y, et al. DNA Repair Pathways in Cancer Therapy and Resistance. *Frontiers in Pharmacology*. 2021;11:629266
2. Topatana, W, Juengpanich, S, et al. Advances in synthetic lethality for cancer therapy: cellular mechanism and clinical translation. *J Hematol Oncol*. 2020; 13(1):118
3. Le, DT, Uram, JN, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015; 372(26):2509-2520
4. Wu, X, Shell, SM, et al. ATR-dependent checkpoint modulates XPA nuclear import in response to UV irradiation. *Oncogene*. 2007; 26(5):757-764

Test your DNA Repair skills!

To reveal a **secret answer**, repair the CKB CORE™ DNA Repair Genes from Figure 2 by combining their broken pieces below and filling in the missing letters. CHEK2 has been repaired to get you started. Created by Amanda Dupuy, PhD

