DNA Repair

Major finding: HELQ is required for replication-coupled DNA repair, germ-cell maintenance, and tumor suppression.

Mechanism: HELQ promotes homologous recombination at replication forks via interaction with RAD51 paralogues.

Impact: HELQ acts in parallel to the Fanconi anemia pathway to control interstrand crosslink repair.

THE HELICASE HELQ PROMOTES DNA REPAIR AT DAMAGED REPLICATION FORKS

Interstrand crosslinks (ICL) prevent DNA replication fork progression and are repaired via homologous recombination by replication stress response factors including components of the Fanconi anemia pathway. Studies in *Drosophila melanogaster* and *Caenorhabditis elegans* have suggested that the DNA helicase HELQ contributes to replication fork unwinding and ICL repair, but the function of HELQ in mammalian cells is unknown. Adelman and colleagues found that *Helq*-deficient mice were viable but exhibited a fertility defect characterized by testicular and ovarian atrophy and decreased stem cells. In addition, *Helq* deficiency was associated with increased frequency of tumor incidence, in particular ovarian tumors and pituitary adenomas, as well as enhanced tumor predisposition in heterozygous mice, suggesting that HELQ may function as a haploinsufficient tumor suppressor. Similar to Fanconi anemia models, *Helq* loss increased the sensitivity of hematopoietic stem and progenitor cells to ICL-inducing agents and induced chromosomal aberrations, supporting a role for HELQ in ICL repair. Consistent with this idea, HELQ interacted with replication checkpoint and DNA repair proteins involved in repair at stalled replication forks, including ataxia telangiectasia and Rad3-related (ATR), Fanconi anemia proteins, and the RAD51 paralogue complex BCDX2 (which is composed of RAD51B, RAD51C, RAD51D, and XRCC2), and triggered replication fork asymmetry and decreased replication fork extension, indicative of fork stalling and collapse. Furthermore, HELQ functioned in parallel to the Fanconi anemia pathway and was required for efficient homologous recombination; loss of *Helq* resulted in impaired DNA repair and persistence of double-strand breaks downstream of RAD51 recruitment to repair foci. These results identify HELQ as an important mediator of replication-coupled DNA repair and suggest that this function is essential for germ cell maintenance and tumor suppression in mammals. ■

Adelman CA, Lolo RL, Birkbak NJ, Murina O, Matsuzaki K, Horejsi Z, et al. HELQ promotes RAD51 paralogue-dependent repair to avert germ cell loss and tumorigenesis. Nature 2013;502:381–4.

Immunotherapy

Major finding: Pidilizumab is active and safe in DLBCL after autologous hematopoietic stem cell transplant.

Clinical relevance: PD-1 blockade may eliminate residual disease and increase survival after transplant.

Impact: Inhibition of immune checkpoints may be therapeutically effective in hematologic malignancies.

AN ANTI–PD-1 ANTIBODY IS EFFECTIVE IN DIFFUSE LARGE B-CELL LYMPHOMA

Ligand stimulation of the programmed cell death 1 (PD-1) receptor on activated immune cells inhibits antitumor T-cell immune responses, and targeted blockade of PD-1 has shown promising results in some solid tumors. In patients with hematologic malignancies such as diffuse large B-cell lymphoma (DLBCL), autologous hematopoietic stem cell transplant (AHSCT) results in remodeling of the immune system in the context of minimal residual disease, suggesting that PD-1 inhibition may be particularly effective in this setting. To test this hypothesis, Armand and colleagues evaluated the safety and activity of pidilizumab, an anti-PD1 antibody that has shown antitumor activity in preclinical models and phase I trials, in 66 patients with DLBCL who received AHSCT. Pidilizumab was well tolerated and did not induce autoimmune toxicity or treatment-related mortality. The proportion of patients who experienced a 16-month interval of progression-free survival (PFS) was 0.72, and the proportion of patients who experienced a 16-month interval of overall survival was 0.85. Among 35 patients with measurable disease after AHSCT, pidilizumab resulted in complete remission in 34%, partial remission in 17%, and stable disease in 11% of patients, corresponding to an overall response rate of 51% and a median time to response of 30 weeks. Analysis of circulating leukocyte subsets following pidilizumab treatment identified a rapid increase in the number of PD-L1–expressing $CD4^+CD25^+$ activated helper T cells, consistent with suppression of PD-1–mediated inhibition of T-cell survival. In addition, pidilizumab induced elevated numbers of circulating $CD8^+$ and $CD4^+$ memory T cells and increased expression of the interleukin-7α receptor, CD127, which promotes T-cell maturation and survival. These findings suggest that PD-1 blockade improves PFS in patients with DLBCL after AHSCT but that phase III trials are needed to validate this therapeutic approach in DLBCL and other hematologic malignancies. ■

Armand P, Nagler A, Weller EA, Devine SM, Avigan DE, Chen YB, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. J Clin Oncol 2013 Oct 14 [Epub ahead of print].

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