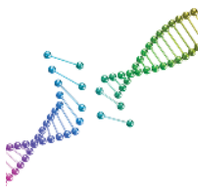
## DNA Repair

**Major finding:** PAXX is a member of the XRCC4 superfamily that regulates DNA double-strand break repair via NHEJ.

**Mechanism:** PAXX stabilizes NHEJ machinery assembly on chromatin and promotes DNA ligation via binding to Ku.

**Impact:** PAXX is a previously uncharacterized NHEJ component that is required for double-strand break repair.

### THE HUMAN PAXX PROTEIN MEDIATES NONHOMOLOGOUS END-JOINING



Effective repair of DNA double-strand breaks (DSB) is essential for maintenance of genome integrity and cell viability. DSBs can be repaired by several mechanisms, including nonhomologous end-joining (NHEJ), which requires the functions of Ku70 [also known as x-ray repair cross-complementing protein 6 (XRCC6)], Ku80 (also known as XRCC5), XRCC4, XRCC-like factor 4 (XLF, also known as NHEJ factor 1), and DNA ligase IV (LIG4). Ochi, Blackford, and colleagues identified the human protein c9orf142 as an XRCC paralog containing a conserved N-terminal motif found in proteins of the XRCC4 superfamily. Analysis of the crystal structure of this protein, termed paralog of XRCC4 and XLF (PAXX), revealed its predominant conformation as a dimer and structural properties most similar to XRCC4. PAXX interacted directly with the Ku70–Ku80 (Ku) heterodimer via its evolutionarily conserved C-terminus and localized to sites of DNA damage in response to ionizing radiation (IR). Depletion of PAXX rendered cells radiosensitive, similar to XRCC4-deficient cells, and expression of wild-type PAXX, but not a PAXX variant harboring mutations in two C-terminal residues necessary for Ku binding, restored IR resistance in PAXX-depleted cells, suggesting a role for PAXX in NHEJ. Consistent with this idea, PAXX deletion conferred hypersensitivity to IR, which was not enhanced by concomitant deletion of XRCC4 or XLF, indicative of an epistatic relationship between these proteins in NHEJ, and resulted in defective resolution of γH2AX foci and impaired DSB repair in response to IR. Mechanistically, PAXX promoted NHEJ by stabilizing the assembly of Ku and other core NHEJ proteins at sites of DSBs and stimulated LIG4-mediated DNA ligation in a Ku-dependent manner. These results establish PAXX as an XRCC4 superfamily member and previously undescribed component of NHEJ that plays a critical role in DSB repair. ■

*Ochi T, Blackford AN, Coates J, Jhujh S, Mehmood S, Tamura N, et al. PAXX, a paralog of XRCC4 and XLF, interacts with Ku to promote DNA double-strand break repair. Science 2015;347:185–8.*

## Clinical Trials

**Major finding:** Ibrutinib achieves durable remissions in *TP53*-aberrant CLL in both first- and second-line therapy.

**Approach:** A phase II trial evaluated single-agent ibrutinib in CLL with deletion of 17p13.1 or *TP53* mutations.

**Impact:** Ibrutinib should be considered for first-line treatment of patients with CLL with *TP53* aberrations.

### IBRUTINIB IS ACTIVE IN *TP53*-ABERRANT CHRONIC LYMPHOCYTIC LEUKEMIA

Patients with chronic lymphocytic leukemia (CLL) who harbor mutation and/or deletion of the *TP53* tumor suppressor gene respond poorly to chemoimmunotherapy and frequently succumb to relapse. Previous clinical studies suggested that ibrutinib, a covalent inhibitor of Bruton tyrosine kinase, induces clinical responses in patients with relapsed or refractory CLL, including patients with deletion of 17p13.1, which contains *TP53*. In order to further evaluate the efficacy of ibrutinib in *TP53*-aberrant CLL, Farooqui and colleagues enrolled 51 patients, 35 of whom had previously untreated CLL and 16 of whom had relapsed or refractory disease, in an open-label, single-arm phase II trial. Forty-seven patients harbored deletion of 17p13.1 and four patients displayed *TP53* mutation in the absence of 17p13.1 deletion. At 24 weeks, treatment with ibrutinib induced durable objective responses in 44 (92%) of the 48 evaluable patients, including 32 of 33 (97%) previously untreated patients and 12 of 15 (80%) patients with relapsed/refractory CLL. Disease progression occurred in five (10%) patients; however, 42 (82%) patients currently remain on treatment. Response to ibrutinib was rapid and increased with time, and at least a 50% reduction in tumor burden was observed in the bone marrow, spleen, and lymph nodes in the majority of patients. The estimated progression-free survival for all patients at 24 months was 82%, and overall survival at 24 months was 80%. Ibrutinib was well tolerated, and the most common grade 3 treatment-related adverse events included neutropenia, anemia, thrombocytopenia, and pneumonia. In addition, ibrutinib treatment appeared not to select for outgrowth of resistant tumor subclones with *TP53* aberrations, suggesting that the mechanism of action is p53-independent. Together, these findings reinforce the notion that ibrutinib may be useful as a first-line therapy in patients with CLL harboring *TP53* aberrations. ■

*Farooqui MZ, Valdez J, Martyr S, Aue G, Saba N, Niemann CU, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with* TP53 *aberrations: a phase 2, single-arm trial. Lancet Oncol 2014 Dec 30 [Epub ahead of print].*

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