MECHANISMS OF DNA REPAIR

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SUMMARY & MISSION STATEMENT

The research in our laboratory is centered on defining the molecular mechanisms underlying DNA-repair processes in human cells. A long-term goal of our work is to exploit this knowledge for the development of new therapeutic strategies for the treatment of cancer, which are based on targeting specific DNA-repair pathways with small molecule inhibitors.

OVERVIEW

DNA damage is a frequent event in the life of a cell. One of the intrinsic causes of DNA damage is DNA-replication stress, a condition characterized by a global slowdown of the progression of replications forks, which arises upon activation of oncogenes and represents a major source of genomic instability in early stages of tumorigenesis. We are interested in understanding how replication stress gives rise to DNA damage and how cells deal with this pathological condition to preserve genomic stability. Our recent studies provided insights into the molecular mechanism underlying the activation of ATR kinase, a master regulator of the cellular response to replication stress, whose inhibitors can selectively kill p53-negative cancer cells and are currently in phase II clinical trials. Moreover, we have characterized the molecular events involved in the initiation of mitotic prophase-specific DNA-repair synthesis that serves to complete DNA replication of difficult-to-replicate loci such as common fragile sites under conditions of replication stress to prevent chromosome missegregation and accumulation of DNA damage in G1 daughter cells. Ongoing and future studies will address the role of transcription-replication interference in oncogene-induced replication stress and the molecular processes involved in the resolution of conflicts between transcription and replication machineries during S-phase.

SELECTED CANCER RELATED PUBLICATIONS

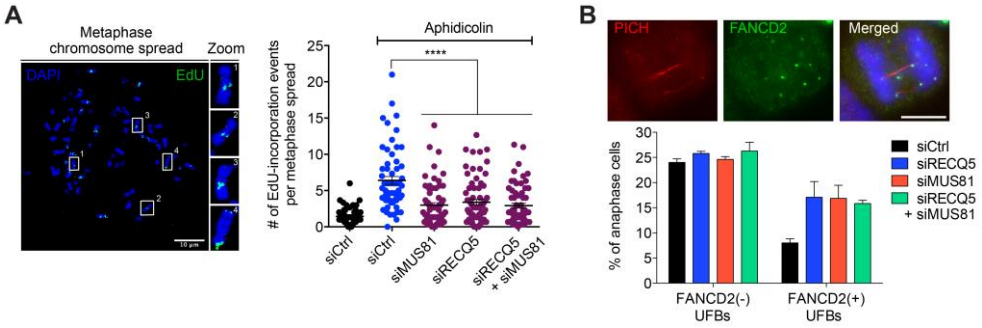
RECQ5 Helicase Cooperates with MUS81 Endonuclease in Processing Stalled Replication Forks at Common Fragile Sites during Mitosis. Di Marco S, Hasanova Z, Kanagaraj R, Chappidi N, Altmannova V, Menon S, Sedlackova H, Langhoff J, Surendranath K, Hühn D, Bhowmick R, Marini V, Ferrari S, Hickson ID, Krejci L, Janscak P. **Mol Cell.** 2017 Jun 1;66(5):658-671

Replication fork reversal triggers fork degradation in BRCA2-defective cells. Mijic S, Zellweger R, Chappidi N, Berti M, Jacobs K, Mutreja K, Ursich S, Ray Chaudhuri A, Nussenzweig A, Janscak P, Lopes M. **Nat Commun.** 2017 Oct 16;8(1):859

RECQ5 helicase promotes resolution of conflicts between replication and transcription in human cells. Urban V, Dobrovolna J, Hühn D, Fryzelkova J, Bartek J, Janscak P. **J Cell Biol.** 2016 Aug 15;214(4):401-415

The Mismatch-Binding Factor MutSβ Can Mediate ATR Activation in Response to DNA Double-Strand Breaks. Burdova K, Mihaljevic B, Sturzenegger A, Chappidi N, Janscak P. **Mol Cell.** 2015 Aug 20;59(4):603-614

Human RECQ5 helicase promotes repair of DNA double-strand breaks by synthesis-dependent strand annealing. Paliwal S, Kanagaraj R, Sturzenegger A, Burdova K, Janscak P. **Nucleic Acids Res.** 2014 Feb;42(4):2380-2390



RECQ5 DNA helicase promotes MUS81-dependent DNA-repair synthesis at common fragile sites in early mitosis to prevent chromosome mis-segregation and accumulation of DNA damage in newly born G1 cells. (A) Examples and quantification of aphidicolin-induced EdU foci (cyan) on metaphase chromosomes (DAPI, blue) of U2OS cells transfected with indicated siRNAs. (B) Examples and quantification FANCD2-positive (cyan) ultrafine DNA bridges (USB, red) induced by aphidicolin in cells transfected with indicated siRNAs.