# Laboratory of Chromosomal Stability

DNA damage response, DNA repair, genomic instability, cancer


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DNA damage is a frequent event in the life of a cell. Failure to repair DNA damage can lead to cell death, while inaccurate DNA repair can give rise to genomic instability, which promotes the onset of cancer in mammals. Proteins belonging to the RecQ family of DNA helicases play important roles in the maintenance of genomic stability in all kingdoms of life, which is highlighted by the finding of an association of inherited defects in three human RecQ helicases, namely BLM, WRN and RECQ4, with distinct autosomal recessive disorders characterized by genomic instability and cancer predisposition. The main goal of the research in our laboratory is to provide clear understanding of the functions of these enzymes in mammalian cells. Our current studies focus on RECQ4, which is mutated in Rothmund-Thompson syndrome, a severe disorder manifested by photosensitivity, skeletal abnormalities, aneuploidy, chromosomal rearrangements and predisposition to osteosarcomas. A number of recent studies have demonstrated that RECQ4 is essential for the initiation of DNA replication. However, RECQ4 also accumulates at DNA double-strand breaks (DSBs) and interacts with the RAD51 recombinase that mediates homology search and strand exchange during DSB repair by homologous recombination (HR). Our aim is to explore the role of RECQ4 in DNA DSB repair.

Although HR between sister chromatids provides the most accurate mechanism for repair of DSBs, it has to be tightly regulated, especially at the strand invasion step, to prevent recombination events between homologous sequences at different chromosomal loci, which can give rise to chromosomal rearrangements. A number of DNA helicases including FBH1 have been implicated in the regulation of HR, but the underlying mechanisms remain elusive. Another goal of the laboratory is to elucidate the mechanistic basis of the anti-recombinase function of FBH1.

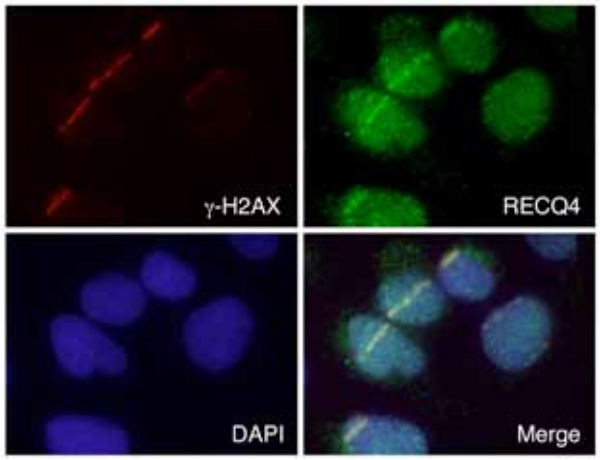


**Fig. 1.** Accumulation of the human RECQ4 protein at DNA double-strand breaks generated by laser-microirradiation.

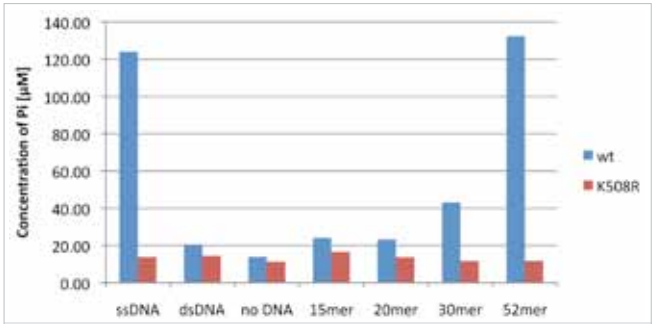


**Fig. 2.** ATPase activity of RECQ4 in the presence of different DNA cofactors.

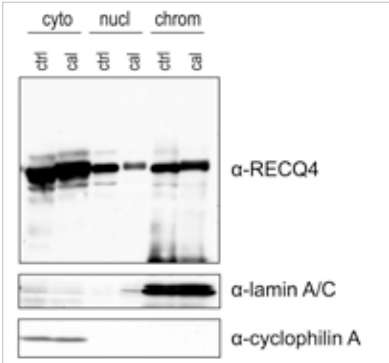


**Fig. 3.** Western blot analysis of cytoplasmic, nucleoplasmic and chromatin fractions of human U2OS cells treated or not for 20 minutes with 100 mM calyculin A (cal), a serine/threonine phosphatase inhibitor.


- GA CR, GA204/09/0565 – Role of RECQ5 DNA helicase in maintenance of genomic stability, 2009-2013, P. Janščák
- GA CR, GAP305/10/0281 – Role of the Rothmund-Thomson syndrome gene product in maintenance of genomic stability, 2010-2014, P. Janščák



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