Cell Cycle 12:23, 3585–3585; December 1, 2013; © 2013 Landes Bioscience

PTEN sumo-wrestles human RAD52 to mystery land

Comment on: Choi BH, et al. Cell Cycle 2013; 12:3442–7; PMID:24047694; http://dx.doi.org/10.4161/cc.26465

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The PTEN gene was initially known as a gatekeeper tumor suppressor that inhibits the growth signaling mediated by phosphatidylinositol-3,4,5-trisphosphate. It is now recognized that PTEN also acts as a caretaker to maintain genomic stability. The precise mechanisms by which PTEN regulates genomic stability remain elusive, but several possibilities exist. It localizes to chromosome centromeres and regulates RAD51 recruitment to DNA damage sites.[1] A fraction of nuclear PTEN is sumoylated at lysine-254. This modification is attenuated following DNA damage.[2] Mutation of lysine-254 results in the inability of PTEN to localize to the nucleus and facilitate homologous recombination (HR). These findings suggest that PTEN sumoylation and its participation in HR contribute to the PTEN's responsibility as a caretaker.

The article by Choi et al. adds new mechanistic understanding of PTEN's role in HR.[3] It was shown that phosphorylation of PTEN at S366/T370 promotes the chromatin translocation; PTEN co-precipitates human RAD52 protein and is required for hydrogen peroxide-induced RAD52 sumoylation.[3] It is well established that budding yeast Rad52 plays critical role in promoting Rad51-dependent HR and, likewise, sumoylation of yeast Rad52 is critical for HR. Thus, it is plausible that the function of PTEN in HR and genomic stability may be mediated by its RAD52 sumoylating ability. This hypothesis is consistent with the delayed disappearance of RAD51 nuclear foci associated with DNA breaks in PTEN-deficient cells.[2]

In eukaryotes, HR plays a major role in ensuring faithful DNA replication and double-strand break repair. *S. cerevisiae* Rad52 is essential for efficient Rad51 assembly at DNA breaks, but functional diversities exist within RAD52 homologs, and the function of mammalian RAD52 is elusive. While human RAD52 does redistribute inside the nucleus in response to genotoxic and replication stress, it is surprising that RAD52 deficiency has little consequence in HR efficiency and cell sensitivity to genotoxic agents. One explanation is that the mammalian BRCA2 and associated proteins may have taken over the major responsibility of yeast Rad52 in assisting Rad51.[4] Human RAD52 may have evolved to serve as a backup for BRCA2 or is responsible for only a subset of RAD51-dependent recombination.[5] This is consistent with the observed synthetic lethality between RAD52 defect and the deficiencies of BRCA1, BRCA2, and PalB2.[4]

There is also a divergence of RAD52 sumoylation between human and *S. cerevisae.* The interaction between human RAD52 and SUMO-1 (also called UBL1) was initially reported in 1996,[6] and the covalent conjugation of human RAD52 by SUMO-1 was briefly described in 2006.[7] While sumoylation of yeast Rad52 directly impacts DNA repair,[7] sumoylation of the human counterpart has little impact on its biochemical activities and occurs at a poorly conserved C-terminal region.[8] However, sumoylation of human RAD52 affects its nuclear localization,[8] which conceivably would affect the availability of nuclear RAD52 that is responsible for a subset of RAD51-dependent recombination.

Despite the divergence of human RAD52 from the central role of yeast Rad52 in HR, the report by Choi et al.[3] possesses significant implications and questions. First, HR deficiency is known to confer sensitivity to DNA cross-linking agents and PARP inhibitors. First, if the PTEN-mediated sumoylation of human RAD52 is critical for nuclear localization, leading to RAD51-dependent HR, then it stands to a reason that PTEN-deficient cells should be synergistically sensitive to both PARP inhibitors and DNA cross-linking reagents. Second, if PTEN-mediated sumoylation of RAD52 is critical to back up the deficiencies of BRCA1, BRCA2, and PalB2, inhibition of RAD52 sumoylation should confer a synthetic lethality to cancer cells with these deficiencies. RAD52 sumoylation can thus be explored as a therapeutic target for cancers with the same deficiencies. Third, upon genotoxic treatment, there is an increase of RAD52 sumoylation,[3] which is required for RAD52 nuclear retention.[8] Under these genotoxic conditions, PTEN was found to be de-sumoylated and relocated from nucleus to cytoplasm,[2] which presumably causes PTEN to lose binding with Rad52.[3] Whether de-sumoylation of PTEN and the sumoylation of RAD52 are a pair of coupled events in response to genotoxic stress remains enigmatic.

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