Medical & Healthcare, Drug discovery

Elucidation of the mechanism of pathway choice for the repair of DNA double strand break

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Abstract

The daily bombardment of chemicals, radical oxygen and radiation can damage the DNA molecules. If left unrepaired, the damage could lead to genomic instability. Thankfully, evolution has created in the cell innate repair mechanisms to fix any damaged DNA. For example, BRCA1, a protein that is well-known for its mutation in hereditary breast cancer, is an important part of the repairing double-strand DNA breaks. We have uncovered new mechanisms in which cells protect these broken DNA ends to make sure that they are repaired correctly.

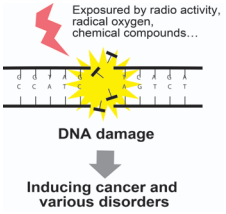
Background & Results

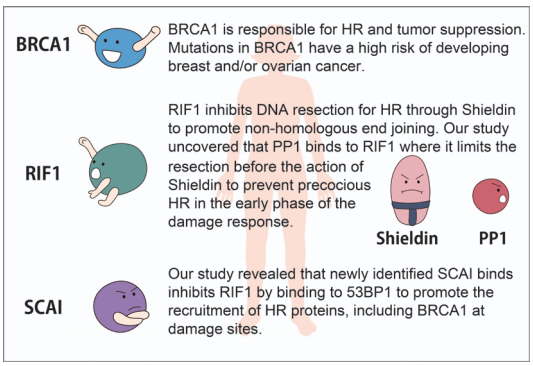
The two mechanisms in the cell are non-homologous end joining (NHEJ) and homologous recombination (HR) for repairing DNA double-strand break. While NHEJ and HR both function to repair damaged DNA, they respond to different situations; types of damage, presence or absence of homologous template or cell cycle stages, etc. What has continued to elude us is how the cell knows which system to call.

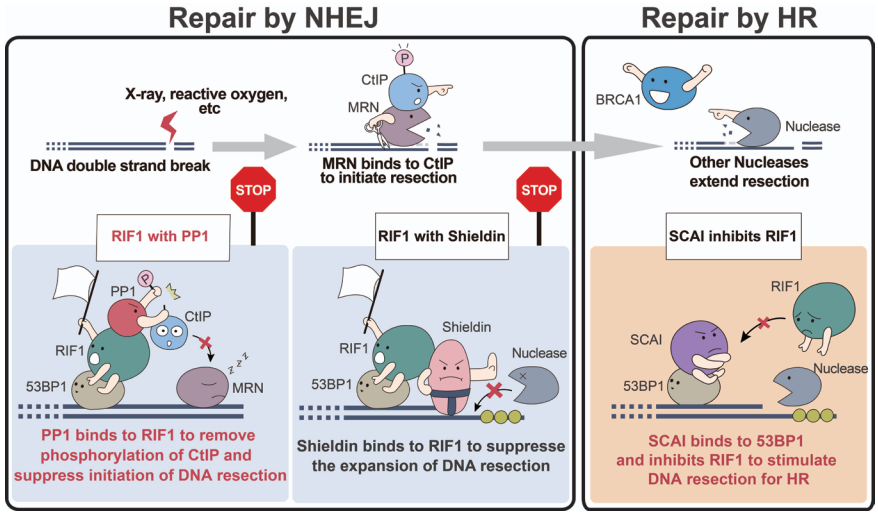
The decision on which of these two pathways is carefully regulated by the cell in several different ways. One method involves a protein called RIF1 binding to broken DNA ends through 53BP1, where it prevents a nuclease from further resection of the break site to repair by HR. A protein called Shieldin can bind to this single-stranded DNA tail through RIF1 to prevent further resection, but we suspected that other factors may also play a role in this process. Using proteomic approach, we found that PP1 binds specifically to RIF1 at the broken DNA ends, and that the physical interaction between these two proteins is necessary to block the nuclease from binding at the break sites. Importantly, the interaction between PP1 and RIF1 helps to keep double-strand DNA breaks from developing a single-stranded "tail," which is what Shieldin binds to. This means that PP1 acts earlier in the process than Shieldin. We also uncovered that, following this stage, newly identified SCAI, binds to 53BP1 to promote the recruitment of HR proteins including BRCA1 at damage sites. Interestingly, RIF1 initially accumulated at sites of DNA damage but was gradually replaced by SCAI. We concluded that RIF1 and SCAI competed to bind to 53BP1 and this temporal transition from RIF1 to SCAI after damage determined the choice of DNA repair pathway.

Significance of the research and Future perspective

Our findings reveal a novel mechanism of the pathway choice for a double-strand DNA break repair. Given that problems with double-strand break repair are a crucial feature of many cancers, understanding more about how the cell decides which pathway to use to fix these damaged sites could provide important insight into cancer development. The results from our study could therefore help develop new options for treating hereditary breast and ovarian cancer in the future.







Patent

Treatise
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