Année de publication : 2016

Zeina Kais, Beatrice Rondinelli, Amie Holmes, Colin O'Leary, David Kozono, Alan D D'Andrea, Raphael Ceccaldi (2016 Jun 7)

FANCD2 Maintains Fork Stability in BRCA1/2-Deficient Tumors and Promotes Alternative End-Joining DNA Repair.

Cell reports : 2488-99 : DOI : 10.1016/j.celrep.2016.05.031

Résumé

BRCA1/2 proteins function in homologous recombination (HR)-mediated DNA repair and cooperate with Fanconi anemia (FA) proteins to maintain genomic integrity through replication fork stabilization. Loss of BRCA1/2 proteins results in DNA repair deficiency and replicative stress, leading to genomic instability and enhanced sensitivity to DNA-damaging agents. Recent studies have shown that BRCA1/2-deficient tumors upregulate Polθ-mediated alternative end-joining (alt-EJ) repair as a survival mechanism. Whether other mechanisms maintain genomic integrity upon loss of BRCA1/2 proteins is currently unknown. Here we show that BRCA1/2-deficient tumors also upregulate FANCD2 activity. FANCD2 is required for fork protection and fork restart in BRCA1/2-deficient tumors. Moreover, FANCD2 promotes Polθ recruitment at sites of damage and alt-EJ repair. Finally, loss of FANCD2 in BRCA1/2-deficient tumors enhances cell death. These results reveal a synthetic lethal relationship between FANCD2 and BRCA1/2, and they identify FANCD2 as a central player orchestrating DNA repair pathway choice at the replication fork.

Raphael Ceccaldi, Prabha Sarangi, Alan D D'Andrea (2016 May 6)

The Fanconi anaemia pathway: new players and new functions.

Nature reviews. Molecular cell biology : 337-49 : DOI : 10.1038/nrm.2016.48

Résumé

The Fanconi anaemia pathway repairs DNA interstrand crosslinks (ICLs) in the genome. Our understanding of this complex pathway is still evolving, as new components continue to be identified and new biochemical systems are used to elucidate the molecular steps of repair. The Fanconi anaemia pathway uses components of other known DNA repair processes to achieve proper repair of ICLs. Moreover, Fanconi anaemia proteins have functions in genome maintenance beyond their canonical roles of repairing ICLs. Such functions include the stabilization of replication forks and the regulation of cytokinesis. Thus, Fanconi anaemia proteins are emerging as master regulators of genomic integrity that coordinate several repair processes. Here, we summarize our current understanding of the functions of the Fanconi anaemia pathway in ICL repair, together with an overview of its connections with other repair pathways and its emerging roles in genome maintenance.

Année de publication : 2015

Panagiotis A Konstantinopoulos, Raphael Ceccaldi, Geoffrey I Shapiro, Alan D D'Andrea (2015 Oct 15)

Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer.

Cancer discovery : 1137-54 : DOI : 10.1158/2159-8290.CD-15-0714

Résumé

Approximately 50% of epithelial ovarian cancers (EOC) exhibit defective DNA repair via homologous recombination (HR) due to genetic and epigenetic alterations of HR pathway genes. Defective HR is an important therapeutic target in EOC as exemplified by the efficacy of platinum analogues in this disease, as well as the advent of PARP inhibitors, which exhibit synthetic lethality when applied to HR-deficient cells. Here, we describe the genotypic and phenotypic characteristics of HR-deficient EOCs, discuss current and emerging approaches for targeting these tumors, and present challenges associated with these approaches, focusing on development and overcoming resistance.

Raphael Ceccaldi, Beatrice Rondinelli, Alan D D'Andrea (2015 Oct 7)

Repair Pathway Choices and Consequences at the Double-Strand Break.

Trends in cell biology : 52-64 : DOI : 10.1016/j.tcb.2015.07.009

Résumé

DNA double-strand breaks (DSBs) are cytotoxic lesions that threaten genomic integrity. Failure to repair a DSB has deleterious consequences, including genomic instability and cell death. Indeed, misrepair of DSBs can lead to inappropriate end-joining events, which commonly underlie oncogenic transformation due to chromosomal translocations. Typically, cells employ two main mechanisms to repair DSBs: homologous recombination (HR) and classical nonhomologous end joining (C-NHEJ). In addition, alternative error-prone DSB repair pathways, namely alternative end joining (alt-EJ) and single-strand annealing (SSA), have been recently shown to operate in many different conditions and to contribute to genome rearrangements and oncogenic transformation. Here, we review the mechanisms regulating DSB repair pathway choice, together with the potential interconnections between HR and the annealing-dependent error-prone DSB repair pathways.

Raphael Ceccaldi, Jessica C Liu, Ravindra Amunugama, Ildiko Hajdu, Benjamin Primack, Mark I R Petalcorin, Kevin W O'Connor, Panagiotis A Konstantinopoulos, Stephen J Elledge, Simon J Boulton, Timur Yusufzai, Alan D D'Andrea (2015 Feb 3)

Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair.

Nature : 258-62 : DOI : 10.1038/nature14184

Mécanismes alternatifs de réparation de l’ADN dans les cancers

Résumé

Large-scale genomic studies have shown that half of epithelial ovarian cancers (EOCs) have alterations in genes regulating homologous recombination (HR) repair. Loss of HR accounts for the genomic instability of EOCs and for their cellular hyper-dependence on alternative poly-ADP ribose polymerase (PARP)-mediated DNA repair mechanisms. Previous studies have implicated the DNA polymerase θ (Polθ also known as POLQ, encoded by POLQ) in a pathway required for the repair of DNA double-strand breaks, referred to as the error-prone microhomology-mediated end-joining (MMEJ) pathway. Whether Polθ interacts with canonical DNA repair pathways to prevent genomic instability remains unknown. Here we report an inverse correlation between HR activity and Polθ expression in EOCs. Knockdown of Polθ in HR-proficient cells upregulates HR activity and RAD51 nucleofilament assembly, while knockdown of Polθ in HR-deficient EOCs enhances cell death. Consistent with these results, genetic inactivation of an HR gene (Fancd2) and Polq in mice results in embryonic lethality. Moreover, Polθ contains RAD51 binding motifs and it blocks RAD51-mediated recombination. Our results reveal a synthetic lethal relationship between the HR pathway and Polθ-mediated repair in EOCs, and identify Polθ as a novel druggable target for cancer therapy.