Fanconi Anemia Pathway

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 79

This document contains 2 pathways and 13 reactions (see Table of Contents)
Fanconi anemia (FA) is a genetic disease of genome instability characterized by congenital skeletal defects, aplastic anemia, susceptibility to leukemias, and cellular sensitivity to DNA damaging agents. Patients with FA have been categorized into at least 15 complementation groups (FA-A, -B, -C, -D1, -D2, -E, -F, -G, -I, -J, -L, -M, -N, -O and -P). These complementation groups correspond to the genes FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCJ/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C and FANCP/SLX4. Eight of these proteins, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM, together with FAAP24, FAAP100, FAAP20, APITD1 and STRA13, form a nuclear complex termed the FA core complex. The FA core complex is an E3 ubiquitin ligase that recognizes and is activated by DNA damage in the form of interstrand crosslinks (ICLs), triggering monoubiquitination of FANCD2 and FANCI, which initiates repair of ICL-DNA.

FANCD2 and FANCI form a complex and are mutually dependent on one another for their respective monoubiquitination. After DNA damage and during S phase, FANCD2 localizes to discrete nuclear foci that colocalize with proteins involved in homologous recombination repair, such as BRCA1 and RAD51. The FA pathway is regulated by ubiquitination and phosphorylation of FANCD2 and FANCI. ATR-dependent phosphorylation of FANCI and FANCD2 promotes monoubiquitination of FANCD2, stimulating the FA pathway (Cohn and D’Andrea 2008, Wang 2007). The complex of USP1 and WDR48 (UAF1) is responsible for deubiquitination of FANCD2 and negatively regulates the FA pathway (Cohn et al. 2007).

Monoubiquitinated FANCD2 recruits DNA nucleases, including SLX4 (FANCP) and FAN1, which unhook the ICL from one of the two covalently linked DNA strands. The DNA polymerase nu (POLN) performs translesion DNA synthesis using the DNA strand with unhooked ICL as a template, thereby bypassing the unhooked ICL. The unhooked ICL is subsequently removed from the DNA via nucleotide excision repair (NER). Incision of the stalled replication fork during the unhooking step generates a double strand break (DSB). The DSB is repaired via homologous recombination repair (HRR) and involves the FA genes BRCA2 (FANCD1), PALB2 (FANCN) and BRIP1 (FANCJ) (reviewed by Deans and West 2011, Kottemann et al. 2007).
and Smogorzewska 2013). Homozygous mutations in BRCA2, PALB2 or BRIP1 result in Fanconi anemia, while heterozygous mutations in these genes predispose carriers to primarily breast and ovarian cancer. Well established functions of BRCA2, PALB2 and BRIP1 in DNA repair are BRCA1 dependent, but it is not yet clear whether there are additional roles for these proteins in the Fanconi anemia pathway that do not rely on BRCA1 (Evans and Longo 2014, Jiang and Greenberg 2015). Heterozygous BRCA1 mutations predispose carriers to breast and ovarian cancer with high penetrance. Complete loss of BRCA1 function is embryonic lethal. It has only recently been reported that a partial germline loss of BRCA1 function via mutations that diminish protein binding ability of the BRCT domain of BRCA1 result in a FA-like syndrome. BRCA1 has therefore been designated as the FANCS gene (Jiang and Greenberg 2015).

The FA pathway is involved in repairing DNA ICLs that arise by exposure to endogenous mutagens produced as by-products of normal cellular metabolism, such as aldehyde containing compounds. Disruption of the aldehyde dehydrogenase gene ALDH2 in FANCD2 deficient mice leads to severe developmental defects, early lethality and predisposition to leukemia. In addition to this, the double knockout mice are exceptionally sensitive to ethanol consumption, as ethanol metabolism results in accumulated levels of aldehydes (Langevin et al. 2011).

**Literature references**


**Editions**

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FANCM binds FAAP24

Location: Fanconi Anemia Pathway

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