FANCC (Fanconi anaemia complementation group C)

Hemantika Dasgupta, Chinmay Kumar Panda

Chittaranjan National Cancer Institute, 37, S P Mukherjee Road, Kolkata 700026, India (HD, CKP)

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Identity

Other names: FAC, FACC, FA3
HGNC (Hugo): FANCC
Location: 9q22.32
Local order: Next to PTCH and XPAC !!

Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description
14 exons; spans 80 kb.

Transcription
mRNA of 2.3, 3.2, and 4.6 kb (alternative splicing in 5', variable 3' untranslated region, exon 13 skipping).

Protein

Description
558 amino acids; 63 kDa.

Expression
Wide, in particular in the bones; high expression in proliferating cells, low in differentiated cells.

Localisation
Cytoplasmic (mostly) and nuclear.

Function
- FANCA and FANCG form a complex in the cytoplasm, through a N-term FANCA (involving the nuclear localization signal) - FANCG interaction; FANCC join the complex; phosphorylation of FANCA would induce its translocation into the nucleus. This FA complex translocates into the nucleus, where FANCE and FANCF are present; FANCE and FANCF join the complex. The FA complex subsequently interacts with FANCD2 by monoubiquitination of FANCD2 during S phase or following DNA damage. Activated (ubiquinated) FANCD2, downstream in the FA pathway, will then interact with other proteins involved in DNA repair, possibly BRCA1; after DNA repair, FANCD2 return to the non-ubiquinated form.
- FANCC may have multifunctional roles, in addition to its involvement in the FA pathway. FANCC binds to cdc2 (mitotic cyclin-dependent kinase), STAT1, GRP94 (a chaperon protein), NADPH, and a number of other proteins; involved in DNA repair and in suppressing interferon gamma induced cellular apoptosis.

There are 15 FA genes that make up the FA pathway. Among these FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCM and FANCL form the core complex.

During G1 phase of cell cycle these proteins are localized in the cytoplasm. During S phase or during DNA damage FANCA and FANCG at first form a complex in the cytoplasm followed by its interaction with FANCC.

Then the complex translocates to the nucleus. In the nucleus other FA proteins like FANCE, F, B, M and L interact with the complex. They cooperatively bind to
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form the core complex. FANCL has E3 ubiquitin ligase activity.
The core complex then activates FANCD2 and FANCI by monoubiquitination.
The activated FANCD2-FANCI complex then interact with other FA genes like FANCP/SXL4, FANCD1/BRCAL2, FANCL/BRIP1 and FANCP/PALB2 for efficient DNA repair.
FANCC helps in accumulation of FANCE and it has role in foci formation of MRE11/RAD50/NBS1 complex in response to intrastrand crosslink inducers.
FANCC binds to cdc2 (mitotic cyclin-dependent kinase), it is necessary for DNA damage-induced G2/M checkpoint in vitro and in vivo.
In response to oxidative DNA damage, FANCC prevents premature senescence in hematopoietic stem cells.
It interacts with cytochrome p-450 reductase and NADPH during increased production of reactive oxygen species (ROS).
In hematopoietic stem cells it regulates apoptosis, self renewal capacity and cell cycle control. It inhibits activity of dsRNA dependent protein kinase mediated death signaling pathway by interacting with Hsp70.
FANCC and p53 cooperatively work in apoptosis. It has role in suppressing interferon gamma induced cellular apoptosis.
In normal oral epithelium, a gradual increase of FANCC protein expression from basal to parabasal layer to spinous layer suggesting its role in cellular proliferation and differentiation.
FANCC is important for proper functioning of monocytes/macrophages. It suppresses TNFa production in mononuclear phagocytes by suppressing TLR8 activity.
FANCC interacts with STAT1, GRP94 (a chaperon protein). It has role in telomere attrition and telomere recombination.

Homology
No known homology.

Mutations

Germinal
Most mutations are found in exon1, intron 4, and exon 14.

Implicated in

Fanconi anaemia (FA)

Note
FACC is implicated in the FA complementation group C; it represents about 15% of FA cases.

Disease
Fanconi anaemia is a chromosome instability syndrome/cancer prone disease (at risk of leukaemia).

Prognosis
- Fanconi anaemia's prognosis is poor; mean survival is 16 years: patients die of bone marrow failure (infections, haemorrhages), leukaemia, or androgen therapy related liver tumours.
- It has recently been shown that significant phenotypic differences were found between the various complementation groups. FA group C patients had less somatic abnormalities. However, there is a certain clinical heterogeneity.

Cytogenetics
Spontaneous,chromatid/chromosome breaks; increased rate of breaks compared to control, when induced by breaking agent.

Hybrid/Mutated gene
Mutations in exon 4, 13 leading to deletion of exon 9 were reported in Brazilian Fanconi Anemia patients.

Oncogenesis
Fanconi anemia patients are prone to develop head and neck, esophageal, gastrointestinal, vulvar and anal cancers.
Frequent deletion and promoter methylation are observed in FANCC gene in oral cancer, breast cancer, acute leukemia and pancreatic cancer.

Diabetes and obesity

Note
FANCC prevents diabetes and obesity.

To be noted
Note
Apart from its function in DNA damage repair, FANCC plays important role in apoptosis, cell cycle, differentiation and innate immunity.

References

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