XRCC5 (X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining))

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Identity

Other names: KARP-1, KARP1, KU80, KUB2, Ku86, NFIV
HGNC (Hugo): XRCC5
Location: 2q35

DNA/RNA

Description
The Ku80 gene is composed of 21 exons. It belongs together with KU70 to the family of caretaker genes.

Protein

Description
Two isoforms of Ku80 encoded by the same genes, namely Ku80 and Karp-1 are expressed and function in primate cells.
Karp-1 has some biochemical properties, which resemble those of Ku80, and the function of Karp-1 could partially replace that of Ku80 in DSB repair (Koibe et al., 2011). However the role in the cells of this isoform is still unclear.
The Ku80 protein is 732 amino acid long and its molecular weight is 83 kDa. It is composed of 3 domains: an amino (N) terminal alphabeta domain, a central beta-barrel domain and a helical-C terminal arm. The 19 kDa C-terminal region of Ku80 is implicated in the recruitment of DNA-PKcs by Ku to sites of damage (Rivera-Calzada et al., 2007). Moreover it belongs to the "Care Taker gene", detecting double strands breaks.

Expression
Ku80 expression has been demonstrated in various cell types and its localization changes during the cell-cycle progression or with a pathological state.
Ku80 in addition to its well known regulatory functions in DNA repair, revealed to behave as a somatostatin receptor in gastric carcinoma cell (Le Romancer, 1994).

Localisation
Ku was originally reported to be a nuclear protein, consistent with its function as a subunit of DNA-PK involved in DNA double strand breaks repair. However several studies have revealed the cytoplasmic or cell surface localization of ku proteins in various cell types (Prabhakar et al., 1990).
In highly infiltrative and metastatic tumors of the colon, breast and bladder, the impaired DNA-repair activity is due to the loss of Ku80 and to the Ku70 shifting from the nucleus to the cytoplasm (Pucci et al., 2001). This mechanism can be controlled by various external growth-regulating stimuli.
In normal cell Ku80 activation and translocation into nucleus could be regulated or stimulated by the induction of nuclear Clusterin (nClu)-Ku70 interactions (Pucci et al., 2009a; Pucci et al., 2009b; Mazzarelli et al., 2009).
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**Function**

Ku80 is one component of a protein complex, the Ku70/80 heterodimer that can bind tightly to free DNA ends and activate the DNA-PKcs. The principal role of Ku proteins is to take care of the homeostasis of the genome being involved in telomere maintenance, regulation of apoptosis induction, specific gene transcription, DNA replication and cell-cycle regulation. The function of this caretaker gene is to suppress chromosomal aberrations translocation and aneuploidy. It has been demonstrated that Ku80 may act as a caretaker gene that maintains the integrity of the genome by a mechanism involving the suppression of chromosomal rearrangements (Difilippantonio et al., 2000).

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**Implicated in**

**Cancer insurgence and progression**

**Note**

The changes in Ku70 and Ku80 expression and localization are related to tumor progression. In normal cell they usually are placed in the nucleus, where they cooperate to repair double strands breaks that could occur during DNA replication. In breast, bladder, and colon cancers (Pucci et al., 2004a; Pucci et al., 2009c) DNA repair is inhibited in high infiltrative carcinomas through the loss of Ku80 and the Ku70 cell compartment shifting from nucleus to the cytoplasm.
Ku70 shifts from the nucleus to the cytoplasm and binds, together with sCLU, Bax inhibiting its homodimerization and translocation to the mitochondria preventing apoptosis induction.

Somatostatin treatment to a colon carcinoma cell line (Caco-2) strongly modulates the activation of Ku70/80 heterodimer and the level of Ku80 in the nucleus by increasing its specific mRNA level (Pucci et al., 2004b). Ku80 could be a signal transducer and activator factor behaving as the intermediate of the SST transduction pathway by the internalization and the migration from the cell membrane to the nucleus.

References


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