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Gene Section
Mini Review

CSNK1A1 (casein kinase 1, alpha 1)

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Identity

Other names: CK1; CKI-alpha; EC 2.7.11.1; HLCDGP1; PRO2975
HGNC (Hugo): CSNK1A1
Location: 5q32
Note: Member of the casein kinase family of serine/threonine protein kinases.

DNA/RNA

Description

According to Entrez-Gene, CNK1 alpha1 gene maps to NC_000005.8.

Transcription

In mammals, 7 distinct genes encoding CK1 isoforms (CK1 alpha, CK1 beta, CK1 gamma1, CK1 gamma2, CK1 gamma3, CK1 delta and CK1 epsilon) are expressed which differ mainly in length and primary structure of the C-terminal non-catalytic domain. Furthermore, CK1 alpha splice variants have been detected in many different organisms including vertebrates and mammals. Alternative splicing leads to the insertion of a long (L, 28 aa) or a short (S, 12 aa) insert into the catalytic C-terminal domain of CK1 alpha and generates different splicing products (CK1 alpha, CK1 alphaL, CK1 alphaS, CK2 alphaLS, alpha3) that differ in kinase activity, function and subcellular localization. In humans at least two isoforms of CK1 alpha have been identified encoding a 3149 bp (isoform1/NM_001025105) or 3061 bp (isoform2/NM_001892) mRNA, respectively.

Protein

Note
The hCK1 alpha isoforms are composed of 365 or 337 amino acids and have a calculated molecular weight of 41,9 or 38,9 kDa, respectively. Both isoforms contain a putative near-consensus SV40 T-antigen nuclear localization sequence.

Description

CK1 alpha is a second messenger-independent, monomeric, serine/threonine specific protein kinase that recognizes a canonical consensus sequence pS/pT-X_{1-2}-S/T or (D/E)-X_{1-2}-S/T. Additionally, a noncanonical sequence containing a SLS motif followed by a cluster of acidic residues C-terminal of the phosphoacceptor site is recognized by CK1.

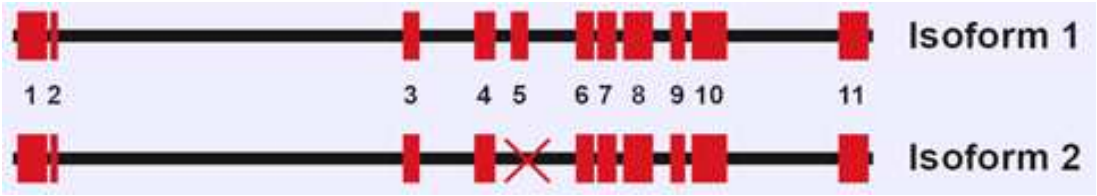

Diagram of hCK1 alpha gene. Exons for both isoforms are presented as red boxes, with exon mumbers at the bottom.

Localisation

The protein kinase CK1 alpha is ubiquitously expressed in all tissues and detected in all cellular compartments.

Function

Mammalian CK1 isoforms and their splice variants are involved in diverse cellular processes including membrane trafficking, circadian rhythm, cell cycle progression, chromosome segregation, apoptosis and cellular proliferation and differentiation.

Implicated in

Cell cycle control

Note

CK1 alpha phosphorylates the tumor suppressor p53 although it seems as if CK1 delta is the most important kinase in the regulation of p53 activity and interacts with several cellular proteins including the oncoprotein Mdm2.

Apoptosis

Note

Recently is has been shown, that CK1 is involved in negatively regulating apoptosis through phosphorylation of diverse cellular proteins including the p75 tumor necrosis factor, proteins of the death-inducing signaling complex (TRAIL induced apoptosis) or Bid (FAS-mediated apoptosis).
It is thought, that CK1 mediated phosphorylation at the level of death-inducing signaling complex (DISC) leads to resistance against caspase cleavage and thereby down regulation of TRAIL (tumor necrosis-factor-related apoptosis ligand) induced apoptosis.
Furthermore, there is evidence that CK1 alpha regulates Fas-mediated apoptosis through phosphorylation of the proapoptotic Bcl2 family member Bid, which prevents caspase 8-dependant cleavage of Bid and negatively influences Fas response.
Additionally, evidence has increased that CK1 alpha modulates RXR agonist mediated apoptosis through interaction and/or phosphorylation of RXR, which prevents cytochrome C realease from the mitochondria.

Wnt signaling

Note

The Wnt pathway is a complex signaling cascade regulating cell proliferation and differentiation. During recent years, the significance of Wnt signaling in human cancer has been elucidated. Identification of numerous pathway components and mutations in the encoding genes finally result in stabilization and accumulation of beta-Catenin and enhanced transcription of TCF/LEF- beta-Catenin target genes.
CK1 alpha is part of the beta-Catenin destruction complex where it phosphorylates beta-Catenin at Serin 45, priming the subsequent phosphorylation of beta-Catenin by GSK3 beta. These phosphorylations mark beta-Catenin for proteasomal degradation. This is one of the central regulatory events controling the Wnt signaling-pathway.
Furthermore, CK1 has been shown to additionally regulate Wnt-signaling through phosphorylation of diverse cellular proteins including LEF-1 (lymphocyte enhancer factor-1) and beta-Catenin leading to the disruption of the LEF-1/beta-Catenin transcription complex.
For additional information about Wnt-signaling in general, Wnt-signaling components and Wnt target genes, readers are referred to the Wnt-Homepage posted by the Nusse group.

Neurodegenerative disorders

Note

Deregulation of CK1 expression and activity has been linked to various diseases including neurodegenerative disorders, especially in tauophathies like Alzheimer's and Parkinson's disease.

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