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Gene Section
Review

TNIK (TRAF2 and NCK interacting kinase)

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Abstract

The serine/threonine kinase Traf2- and Nck interacting kinase (TNIK), is a member of the germinal center kinase (GCK) family that has been reported to have an important role in the regulation of Jun N-terminal kinase pathway (JNK) activation and actin cytoskeleton. It has also been demonstrated that TNIK is an important activator of Wnt pathway, where it interacts with β-catenin/TCF4 complex, phosphorylates TCF4 inducing the transcription of Wnt target genes. In several studies, the expression of TNIK has been established to be involved in different human cancers.

Keywords

TNIK, TRAF2 and NCK interacting kinase, TCF4, β-catenin, CTNNB1

Identity

Other names: TRAF2 and NCK-Interacting Protein Kinase 3 4, EC 2.7.11.1 4 52, EC 2.7.11 52, KIAA0551 4, MRT54 3

HGNC (Hugo): TNIK

Location: 3q26.2-q26.31

Local order: Starts at 171058414 and ends at 171460408 bp from pter

DNA/RNA

Description

The TNIK gene size is 397827bp encoding by 33 exons. This gene has 15 transcripts (splice variants), 312 orthologues, 35 paralogues (http://www.ensembl.org/).

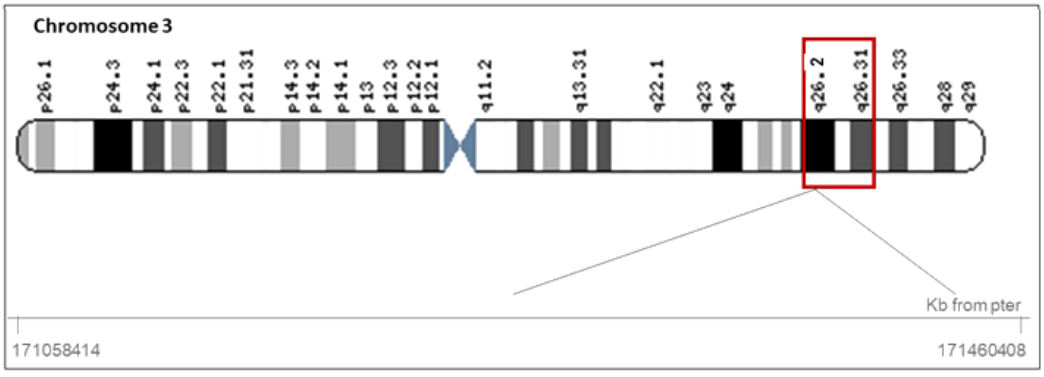

Figure 1: Location of TNIK gene on chr3.

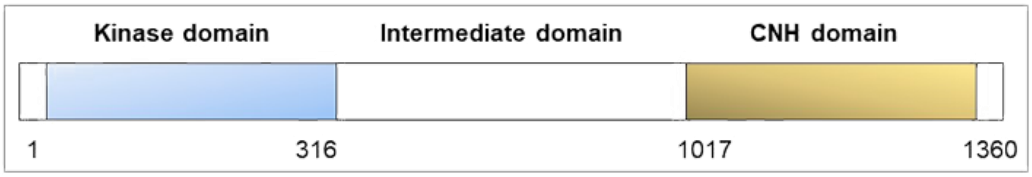

Figure 2: Schematic illustration of TNIK protein domains.

The protein encoded by this gene is a serine/threonine kinase that functions as an activator of the Wnt signaling pathway.

Transcription

15 transcripts variant have been found for this gene (http://www.ensembl.org/).
TNIK-204 ENST00000436636.7 : mRNA 9892bp, protein 1360aa
TNIK-202 ENST00000341852.10 : mRNA 4727, protein 1276aa
TNIK-201 ENST00000284483.12 : mRNA 4059, protein 1352aa
TNIK-203 ENST00000357327.9 : mRNA 3996, protein 1331aa
TNIK-210 ENST00000470834.5 : mRNA 3972, protein 1323aa
TNIK-214 ENST00000488470.5 : mRNA 3918, protein 1305aa
TNIK-206 ENST00000460047.5 : mRNA 3894, protein 1297aa
TNIK-211 ENST00000475336.5 : mrNA 3807, protein 1268aa
TNIK-209 ENST00000468757.1 : mRNA1128, protein 350aa
TNIK-208 ENST00000465393.1 : mRNA 750, protein 45aa
TNIK-207 ENST00000464785.1 : mRNA 437, no protein
TNIK-215 ENST00000496492.5 : mRNA 2736, no protein
TNIK-212 ENST00000484051.5 : mRNA 1180, no protein
TNIK-205 ENST00000459881.1 : mRNA 583, no protein
TNIK-213 ENST00000487846.1 : mRNA 573, no protein

Protein

Description

The serine/threonine kinase Traf2- and Nck interacting kinase (TNIK), is a member of the germinal center kinase (GCK) family, that it was isolated by yeast two-hybrid screening for proteins that interact with TRAF2 and NCK (Fu CA et al.,1999).
It was demonstrated that TNIK regulates Jun N-terminal kinase pathway (JNK), the actin cytoskeleton, it is an important activator of Wnt signaling and it is involved in in the survival of many human cancer cells (Lee Y. et al., 2017).
The gene TNIK encodes a 1360 aa protein with several spliced isoforms. This protein has an N-terminal kinase domain, an intermediate domain and an C-terminal germinal center kinase homology (GCKH) region, later called Citron homology (CNH) domain (Fu CA et al.,1999; Taira K. et al., 2004) It was observed that it shared about 90% amino acid identity with other two previously cloned GCK family member, NIK and MAPK4, in both its kinase and CNH domains. However, this homology goes down to about 50% in the intermediate region suggesting potentially different signaling role for these GCK proteins (Su YC. et al.,1997; Taira K. et al., 2004).

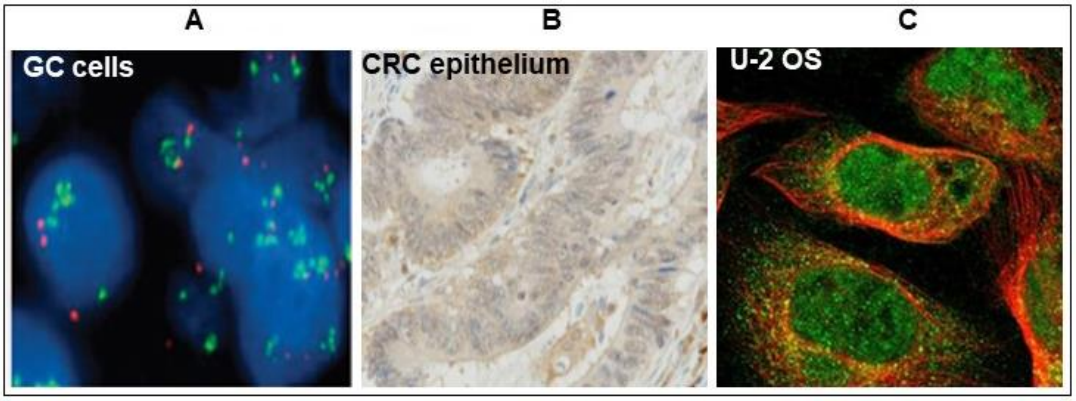

Figure 3: Representative images of: A) TNIK FISH on gastric cancer cells sample; B) TNIK immunostaining on CRC epithelium sample; C) TNIK Immunofluorescent staining of human cell line U-2 OS (Yu DH et al., 2014; Takahashi H et al.,2015; https://www.proteinatlas.org/)

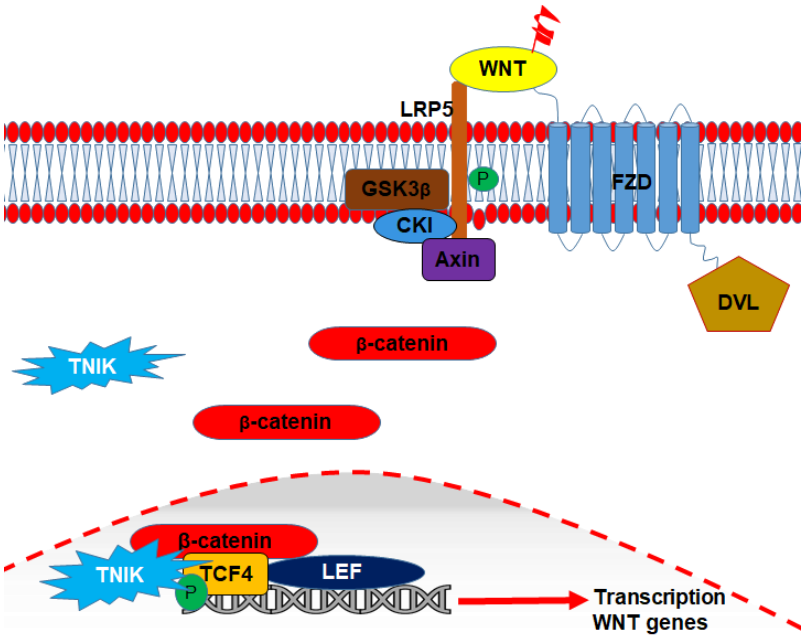

Figure 4: Schematic illustration of Wnt signaling activation. Binding of Wnt proteins to FZD leads to activation of CTNNB1 (β-catenin) in the cytoplasm. Subsequently, TNIK binds to active β-catenin and this complex is recruited to the nucleus, where TNIK directly phosphorylates TCF4 inducing the transcription of Wnt target genes.

Expression

TNIK is ubiquitously expressed in human. It is expressed with high level in brain, small intestine, duodenum, testis, heart, normal and cancer epithelia colon tissues.
Its expression it also observed in endometrium, lung, lymph node, kidney, spleen, thyroid, urinary bladder, gall bladder, prostate, endometrium, adrenal, bone marrow (https://www.ncbi.nlm.nih.gov/)

Localisation

TNIK is mainly localized in the nucleoplasm and cytosol (https://www.uniprot.org/)

Function

TNIK was discovered by Fu CA et al. in 1999, with a yeast-two-hybrid screen for interaction partners of the adapter proteins TRAF2 and NCK.
Like several other GCK family members, TNIK regulates activation of JNK pathway which is induced through the CNH domain by a yet undefined mechanism (Fu CA et al., 1999).
TNIK overexpression also modulates the actin cytoskeleton; through its kinase domain, inducing disruption of F-actin structure and inhibiting cell spreading (Taira K et al., 2004).
TNIK protein is known to be implicated in Wnt pathway activation. Mahmoudi T. et al. in 2009, have identified TNIK as a co-activator protein that interact both TCF4/β-catenin complex in the proliferative cripts of mouse small intestine. Through in vitro assays they showed that TNIK directly bind both TCF4 and β-catenin and phosphorylates TCF4 leading to transcriptional activation of Wnt target genes.
This protein is also involved in the dendrite development. NEDD4, the TNIK, and RAP2A form a complex that controls NEDD4-mediated ubiquitination of RAP2A.
Ubiquitination by NEDD4 inhibits RAP2A function, which reduces the activity of Rap2 effector kinases of the TNIK family and promotes dendrite growth (Kawabe H. et al., 2010).

Homology

TNIK is conserved in human, mouse, chicken, C. Elegans

Mutations

Germinal

Recently, Anazi S. et al. in 2016 have identified in 2 unrelated consanguineous Saudi families affected with autosomal recessive mental retardation-54 (MRT54) the same homozygous truncating mutation in the TNIK gene that results in complete loss of the protein, indicating that the mutation resulted in a null allele.

Somatic

Some somatic mutations have been identified and described by COSMIC (Catalogue of Somatic Mutation In Cancer) and they are listed mostly as substitution; their role in disease has not yet been fully elucidated.

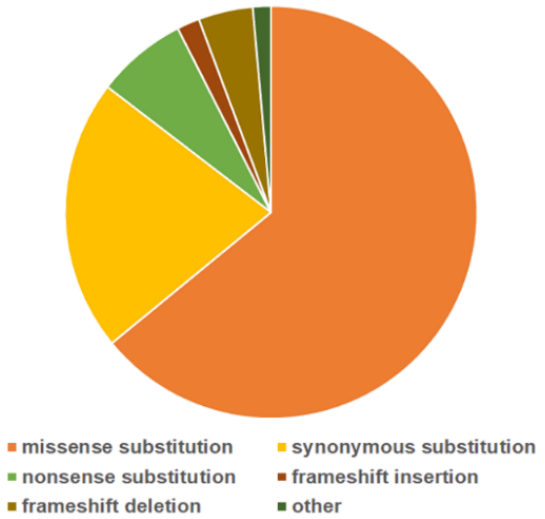

Figure 5: Overview of the major types of mutations occurring in TNIK

Implicated in

Mental retardation, autosomal recessive 54; MRT54

Mental retardation autosomal recessive 54 (MRT54) is a disorder characterized by significantly below average general intellectual functioning. MRT54 is caused by homozygous mutation in the TNIK gene. Anazi S. et al. in 2016 identified a homozygous c.538C-T transition (c.538C-T, NM_001161563) in the TNIK gene, resulting in an arg180-to-ter (R180X) substitution. This mutation causes the formation of a truncated protein resulting in a null allele.

Glioma

Glioma is the most common primary cancers of the central nervous system. NEDD4 is reported to bind rather than ubiquitinate TNIK in regulating the ubiquitination of GTP-RAP2A in neuron development. Wang L.et al in 2017, showed that NEDD4 plays a pivotal role in promoting the migration and invasion of glioma cell lines U251 and U87 by the inhibition of the RAP2A/TNIK complex activity.

Colorectal cancer

TNIK protein is essential for the Wnt signaling activation and it was demonstrated that colorectal cancer cells were highly dependent on TNIK for their growth (Shitashige M. et al., 2010). Masuda M et al. in 2016, showed that NCB-0846 small molecule, with high inhibitory activity against TNIK, blocked Wnt signaling and presented anti tumor and anti-CSC effect on CRC cells.

Gastric cancer

Microarray analysis in Chinese gastric cancer patients reported that TNIK gene is amplified in 7% of samples analyzed. Moreover, it was showed that both silencing and TNIK inhibitor increased cell death and reduced cell growth in TNIK amplified gastric cancer cell line, but not in TNIK not amplified cell line. Difference of CRC, in gastric cancer the role of TNIK protein is independent of Wnt pathway. (Yu DH et. al., 2014)

Pancreatic cancer

In pancreatic cancer patients has been shown the clinical and prognostic value of TNIK. It was observed that mRNA and protein levels of TNIK in pancreatic cancer were both significantly higher than those in corresponding paratumor tissues. In addition, they revealed that patients with high expression of TNIK had a shorter overall survival (OS) and disease-free survival (DFS) than those with low expression (Zhang Y. et al., 2016).

Prostate cancer

Prostate cancer is the fifth leading cause of cancer-related deaths in men worldwide. It was demonstrated a nuclear expression of TNIK in prostate cancer primary cells and its correlation with ERG expression. Interestingly, inhibition of expression and activity of TNIK in ERG positive prostate cancer cells reduced colony formation and cell viability suggesting TNIK as a novel therapeutic target to the treatment of ERG positive prostate cancer. (Lee RS et al., 2019)

Lung adenocarcinoma

It is known that TINK regulates both the Wnt and Smad pathways, which are both important for epithelial-to-mesenchymal transition (EMT) on cancer cells (Mahmoudi T. et al., 2009; Kaneko S. et al., 2011). Jiyeon Kim J. et al. in 2014, showed that KY-05009 molecule, a potent inhibitor of TNIK activity reduces TGFB1 (TGF-β1=-Mediated Epithelial-to-Mesenchymal Transition in Human Lung Adenocarcinoma A549 cell line. They observed that KY-05009 inhibitor had a double effects on A549 cells: it is able to inhibits TGF-β1-mediated Wnt signaling through inhibition of the kinase activity of TNIK, which phosphorylates TCF4 and it inhibits TGF-β1-induced phosphorylation and nuclear translocation of SMAD2 and the expression of SNAI2 (Snail) and TWIST1 cofactors involved in the TGF-β1-induced EMT.

Breast cancer

Breast cancer is the most common cancer in the woman malignant with a high percentage of chemoresistance. It was observed that RNA interference assays on breast cancer cell lines led to inhibition of cell growth (Jiao X et al., 2013).
Li Z. et al. in 2018 through RNA-seq data showed that TNIK is positive regulated by transcriptional coactivator WBP2 in triple negative breast cancer cells (TNBC). They demonstrated that WBP2 primes

cells to response to Wnt ligands by up-regulation of TNIK and GPS1 in triple negative TNBC cells. WBP2 integrates JNK with Wnt signaling improving the growth of TNBC cells.

Multiple Myeloma

Multiple myeloma (MM) is a plasma cell malignancy characterized by an accumulation of monoclonal plasma cells in the bone marrow. It was demonstrated that silencing and pharmacological inhibition of endogenous TNIK protein suppressed the proliferation of MM cells and induced caspase-dependent apoptosis (Chon HJ. Et al., 2016). Moreover, inhibition of Wnt signaling by TNIK inhibitors can suppress the IL6 -induced proliferation of MM cells suggesting TNIK protein as a target to develop new therapeutic strategies against MM (Lee Y. et al., 2017).

Chronic myelogenous leukemia

Schürch C. et al. in 2012, identified CD27 signal transduction as a new link between the immune system and Wnt signaling/leukemia development in CML.

It was demonstrated that the TNF receptor family member CD27 is present on leukemia stem cells and its bond with CD70 ligand increased expression of Wnt target genes in LSCs by enhancing nuclear localization of active β-catenin and TRAF2-and NCK-interacting kinase (TNIK). As a consequence of this, they revealed an increased proliferation and differentiation of LCS. Moreover, blocking CD70 by monoclonal antibody (mAb) treatment reduced disease progression and prolonged survival of CML mice.

Polycystic ovarian syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy, affecting about 10% of the reproductive-age female population. Wang XX et al. in 2014, saw that PCOS ovarian tissues showed a specific methylation and expression pattern of the TNIK gene.

They also reported that the TNIK transcript was up-regulated in PCOS ovarian tissues, compared with normal ovarian tissues, and that methylation of cg10180092 site play a key role in the regulation of TNIK transcription (Li D. et al., 2015).

It is necessary other studies to better understood the epigenetic mechanism involved in the initiation and progression of TNIK-related PCOS.

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