Atlas of Genetics and Cytogenetics in Oncology and Haematology

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# Gene Section
## Review

# DKK3 (dickkopf 3 homolog (Xenopus laevis))

**Naoki Katase, Tsutomu Nohno**

Department of Molecular and Developmental Biology, Kawasaki Medical School, Kurashiki, Okayama 701-0192, Japan (NK, TN)

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## Identity

**Other names:** REIC, RIG

**HGNC (Hugo):** DKK3

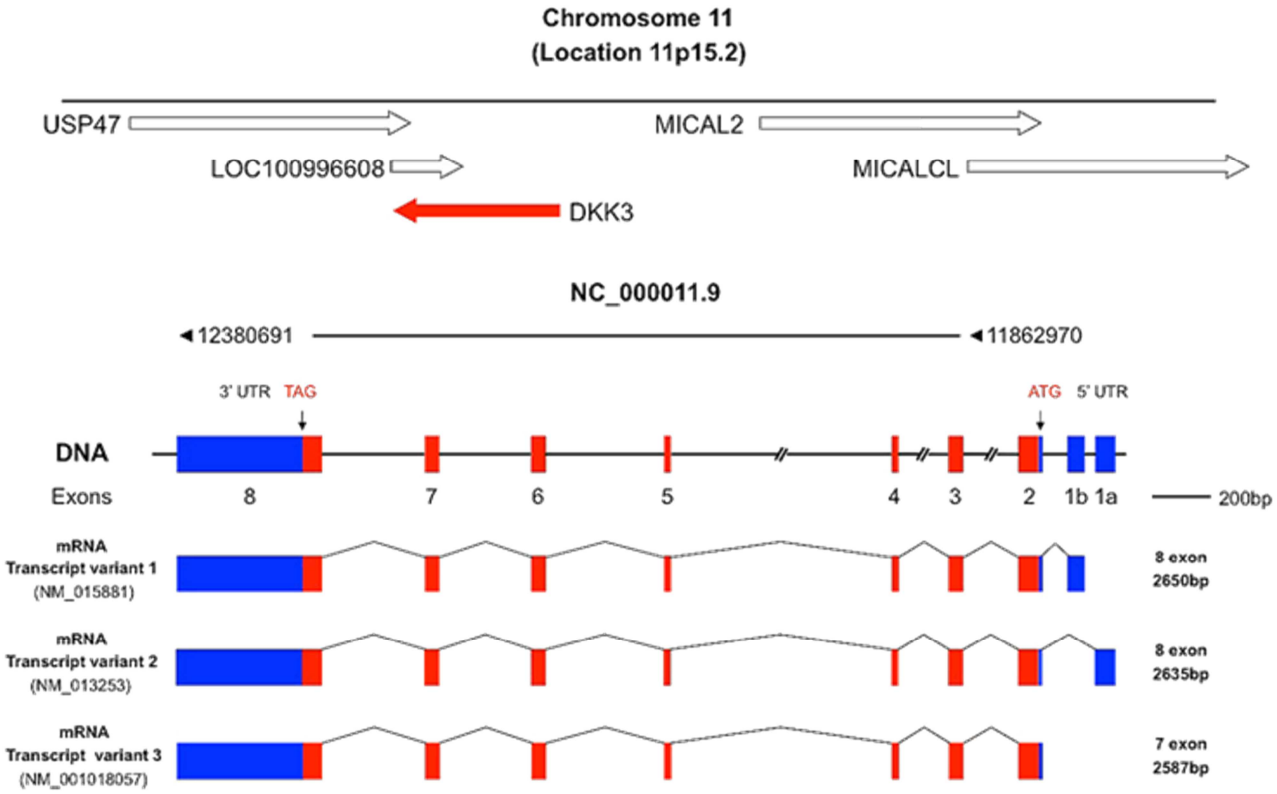
**Location:** 11p15.3

**Local order:** USP47-LOC100996608-**DKK3**-MICAL2-MICALCL.

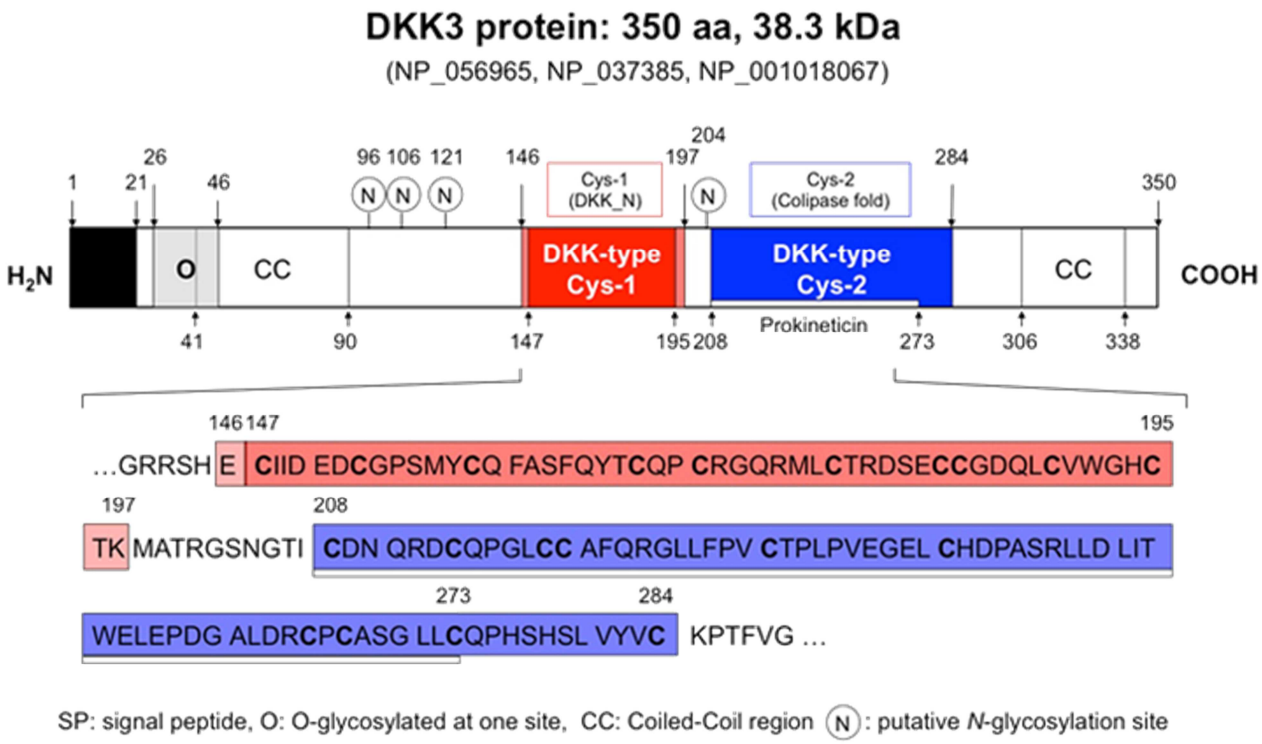
## DNA/RNA

### *Description*

DKK3 gene is 46367 bp long, containing nine exons that span over 50 kbp of genomic DNA (Kobayashi et al., 2002).




**DKK3 gene location at chromosome 11p15.2, and its annotated transcripts.** Exons are indicated as boxes, Blue boxes present untranscripted region (UTR). The start codon (ATG) in exon 2, and stop codon (TAG) in exon 8 are indicated as arrows.




All the DKK3 gene transcripts encode a 350 aa, 38.3 kDa glycoprotein (NM_015881→NP_056965, NM_013253→NP_037385, and NM_001018057→NP_001018067, respectively). DKK3 protein contains N-terminal signal peptide, two cysteine rich domains (i.e. DKK-type Cys-1 and DKK-type Cys-2). DKK-type Cys-1 is located within the DKK_N (Dickkopf N-terminal cysteine rich region, pfam04706) region. DKK-type Cys-2 include prokineticin region (pfam06607, white dashed lines). Two coiled-coil regions are present in N-terminal side and C-terminal side. Putative N-glycosylation sites are indicated.

There are two exons in exon 1, which are alternatively used in two different transcripts. Totally, three transcript variants are known.

### Transcription

DKK3 gene is transcribed into three different isoforms (NM_015881, 2650 bp, NM_013253, 2635 bp, and NM_001018057, 2587 bp). Two of them result from alternative use of first exon (i.e. exon 1a and exon 1b, although they are both non-coding). One more variant lacks exon 1. All the variants share exons 2 to 8, and code for a 350 aa functioning protein.

### Pseudogene

None sited.

## Protein

### Description

DKK3 protein possesses several defined regions, which may confer multiple functions to the protein. Amino acid (aa) 1-21 is a signal peptide (SP) that characterizes this protein as a secreted protein. Four putative N-glycosylated sites and O-glycosylated at one site region (aa 26-46) suggest that the protein may undergo posttranslational modification before its secretion.

Two cysteine-rich domains are conserved over species. N-terminal one is DKK_N (formerly called Cys-1) and C-terminal one is called Colipase fold (formerly called Cys-2). Both two domains contain 10 cysteine residues and are separated by a 12 aa linker region. Colipase fold features lipid hydrolysis and may contribute to lipid binding (interact with cell surface LRP5/LRP6, for instance). Colipase fold is solved to form interactive surface with finger-like structure. The presence of coiled-coil domain suggests possible protein-protein interaction. All these structural features facilitate Wnt/DKK interactions (as will be apparent below). Moreover, DKK3 possesses potential proteolytic cleavage sites by furin-type proteases, suggesting that the protein is subject to posttranslational processing.

### Expression

Human DKK3 DNA/RNA expression is widely observed in human normal tissues. Northern blotting analyses reveal that DKK3 mRNA is expressed in brain, heart, lung, liver, pancreas, spleen, kidney, small intestine, colon, skeletal muscle and placenta. Amongst them, DKK3 expression is particularly high in heart and brain.

Reflecting the alias of this gene, RIG (Regulated in glioma) or REIC (Reduced expression in cancer), DKK3 mRNA and protein expression is deregulated in a wide range of tumors, including glioma, gastric carcinoma, colorectal carcinoma, hepatocellular carcinoma, pancreatic cancer, leukemia, renal cell carcinoma, bladder carcinoma, prostate cancer, testicular carcinoma, ovarian carcinoma, cervical cancer, breast cancers, non-small cell lung cancer,

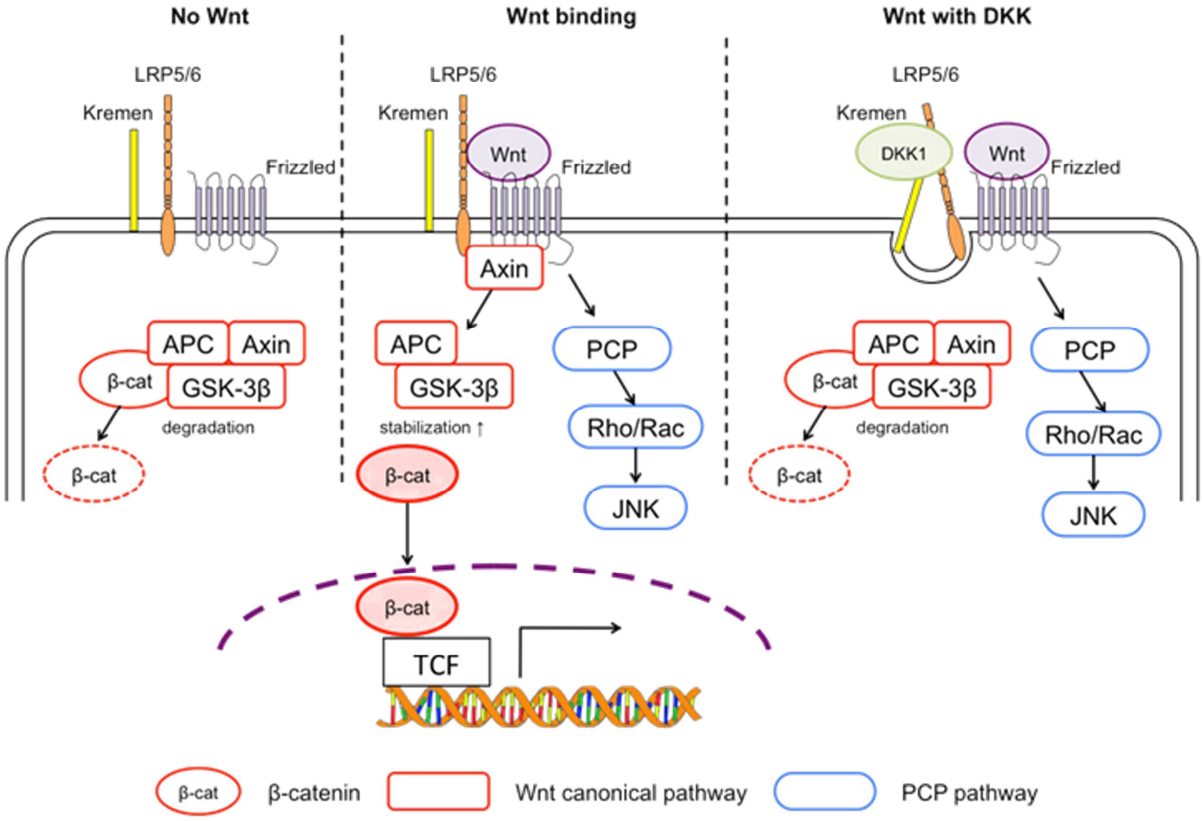
mesothelioma and skin cancers. This downregulation in mRNA expression is caused by promoter hypermethylation.
Thus, DKK3 is thought to be a potential tumor suppressor, and is focussed as a therapeutic target. However, in DKK3 protein expression level, some reports show that DKK3 protein expression is up-regulated, suggesting cancer specific expression pattern and potential alternative role in cancer invasion.

## Localisation

DKK3 protein is an extracellular secreted protein. Its intracellular localization is observed in cytoplasm, organelle and endoplasmic reticulum.

## Function

DKK is firstly identified in Xenopus embryogenesis (Glinka et al., 1998), and named after its role as head inducer, Dickkopf (dick=thick, kopf=head). DKK binds to the Wnt co-receptor, lipoprotein receptor-related protein5/6 class (LRP5/6), and exert antagonistic function for Wnt induced beta-catenin stabilization (Fedi et al., 1999; He et al., 2004). DKKs play an important role in vertebrate antero-posterior axial patterning, limb formation, eye formation and bone formation (Niehrs, 2006).
The Wnt signaling inhibitory ability differs between the DKK members; DKK1 and DKK4 can inhibit Wnt/beta-catenin pathway, and DKK2 can both inhibit and activate beta-catenin signaling (Wu et al., 2000), and co-receptor class of Kremen protein facilitates DKK1, 2, and 4 binding to block Wnt signaling (Bafico et al., 2001).
However, DKK3 neither bind to LRP5/6 nor does Kremen (Mao et al., 2003; Brott et al., 2001).
The receptor for DKK3 is yet to be investigated and its Wnt/beta-catenin inhibitory function is still elusive (Veeck et al., 2012).
However, Wnt modulating function of DKK3 are reported in several kinds of malignancies including glioma (Mizobuchi et al., 2008), breast cancer (Wang et al., 2008), prostate cancer (Abarzua et al., 2005 and Kawano et al., 2006) and lung cancer (Yue et al., 2008).
And because of its obvious tumor suppressor function, DKK3 is regarded as tumor suppressor.
Recently, intracellular function of DKK3 was noted. Cytoplasmic DKK3 may bind to beta TrCP, and facilitate beta-catenin degradation (Lee et al., 2009).




DKK family is known as a negative regulator of Wnt signaling. There are three pathways in Wnt signaling, Wnt/beta-catenin pathway, planar cell polarity pathway and Wnt/$Ca^{2+}$ cascade. Wnt/beta-catenin pathway is called canonical pathway and latter two are called non-canonical pathway. In Wnt/beta-catenin pathway, cytoplasmic beta-catenin is ubiquitinated and degraded without Wnt ligand binding. When Wnt ligands bind to the receptor complex, Frizzled and Lrp5/6, cytoplasmic beta-catenin is stabilized and translocated into the nucleus, inducing TCF/LEF mediated transcription. DKK family members antagonize this pathway by binding Lrp5/6 and Kremen. Among DKK family member, DKK1, 2 and 4 can bind to LRP5/6, but DKK3 cannot. DKK2 can also activate beta-catenin accumulation. Binding of DKKs with LRP5/6 and Kremen complex resulted in endocytosis of Kremen.

In cancers, DKK3 mRNA expression is down-regulated by promoter methylation (see below), but there is a discrepancy between mRNA expression and protein expression in tissue samples, which may reflect tumor heterogeneity.

### Homology

DKK3 homolog is conserved over species, in vertebrates including zebrafish, murine, rat, chicken, dog, cow, Rhesus monkey and chimpanzee and invertebrate, such as Dictyostelium, cnidarian, tunicate and ascidian.
In vertebrates, DKK proteins consist from 4 members (i.e. DKK1, 2, 3 and 4). Although all these proteins possess two cysteine-rich domains, the homology among DKK1, 2 and 4 is 41-50%, whereas that between DKK3 and other members it is 37-40%.

## Mutations

**Note**
Neither germinal nor somatic mutation is reported. 5 single nucleotide polymorphisms (SNP) are known (rs3206824, rs11022095, rs1472189, rs7396187, and rs2291599). Please refer to the link below.

## Implicated in

### Brain tumors (neuroblastoma, glioma and ganglioneuroma)

**Note**
DKK3 protein expression is down-regulated in brain tumors.
In neuroblastoma, DKK3 mRNA expression is low. DKK3 functions as tumor suppressor, and its expression is negatively regulated via miR92, which is up-regulated by MYCN (De Brouwer et al., 2012; Haug et al., 2011).
In ganglioneuroma, DKK3 expression is high (Koppen et al., 2008).
In glioma and malignant glioma, DNA hypermethylation in DKK3 and consequent reduced expression of DKK3 protein are observed.
Forced expression of DKK3 in glioma cell lines induces JUN phosphorylation-mediated apoptosis (Götze et al., 2010; Mizobuchi et al., 2008).

**Prognosis**
Low DKK3 expression in neuroblastoma correlates with poor prognosis.

**Oncogenesis**
DKK3 methylation status may indicate neuroblastic tumor maturation.

### Head and neck and oral cancers

**Note**
Some reports indicate that loss of DKK3 function may be involved in oral, and head and neck squamous cell carcinomas (SCC). Frequent LOH in DKK3 locus (11p15.2) is reported (Katase et al., 2008).
DKK3 mRNA expression is decreased in oral SCC tissue sample and cell lines (Pannone et al., 2010).
However, protein expression status is different. DKK3 protein is dominantly expressed in oral SCC tissue sample and cell line (Katase et al., 2012).
Moreover, DKK3 knockdown in oral SCC derived cells resulted in reduced cell migration and invasion (Katase et al., 2013).
DKK3 expression increases from epithelial dysplasia, carcinoma in situ to invasive cancer, and is though to be independent with Wnt/beta-catenin pathway (Fujii et al., 2011).

**Prognosis**
LOH in DKK3 locus inversely correlates with lymph nodal metastasis and overall survival. DKK3 protein expression correlates with shorter disease free survival, metastasis free survival.

**Oncogenesis**
DKK3 is suggested to be involved in SCC carcinogenesis in head and neck, and oral region. However, its detailed function is yet to be investigated.

### Esophageal cancer

**Note**
DKK3 DNA is hypermethylated in esophageal cancer patient samples and cell lines (Liu et al., 2011; Maehata et al., 2008). However, one report indicates that DKK3 protein is overexpressed (Zhang et al., 2010).

**Prognosis**
Methylation of DKK3 predicts risk of recurrence. DKK3 protein expression correlates with invasive depth, lymph nodal metastasis and advanced TNM stage.

**Oncogenesis**
DKK3 methylation may be involved in esophageal cancer development.

### Gastric cancer

**Note**
In gastric adenocarcinoma cell lines, DKK3 mRNA expression is down-regulated (Yu et al., 2009; Maehata et al., 2008; Sato et al., 2007). However, in tissue samples, DKK3 protein expression was observed. DKK3 protein expression is also observed in tumor endothelium adjacent to cancer tissue (Mühlmann et al., 2010).
In mice gastric scirrhous carcinoma model, intraperitoneal administration of adenovirus vector carrying DKK3 significantly decreases tumor dissemination and increased recruitment of killer T cells (Than et al., 2011).

**Prognosis**
Methylation of DKK3 is a prognostic predictor for shorter survival. DKK3 protein expression in cancer

cells is associated with pT-stage and UICC stage. DKK3 protein expression correlates with favorable prognosis.

**Oncogenesis**

Reduced DKK3 mRNA expression by CpG methylation is thought to be involved in gastric cancer development, and might be a potential clinical target.

## Colorectal cancer

**Note**

In colorectal adenocarcinoma cell lines, DKK3 expression is down-regulated both in mRNA and protein level. Forced overexpression of DKK3 mRNA results in G0/G1 cell cycle arrest, induction of apoptosis and reduced cell proliferation. Increased cytoplasmic beta-catenin is also noted (Yang et al., 2012).

In clinical tissue samples, DKK3 protein expression is decreased compared to corresponding normal tissues, and DKK3 expression correlates with invasion depth, TNM stage and dedifferentiation (Wang et al., 2012).

DKK3 protein expression in tumor vessels is noted. Immunohistochemical analysis revealed that vessels in/adjacent to the cancer tissue shows DKK3 protein expression, whereas normal vessels do not. This implies pro-angiogenic function of DKK3 protein (Zitt et al., 2008; Untergasser et al., 2008).

**Oncogenesis**

DKK3 might be involved in carcinogenesis of colorectal cancer via Wnt/beta-catenin pathway.

## Liver tumors, hepatocellular carcinoma and hepatoblastoma

**Note**

In hepatocellular carcinoma (HCC) and cirrhosis-related HCC tissue samples, DKK3 mRNA expression is low because of promoter hypermethylation (Yang et al., 2010; Ding et al., 2009).

However, in HCC and hepatoblastomas tissue sample, DKK3 protein expression is up-regulated (Pei et al., 2009).

**Prognosis**

Hypermethylation of DKK3 may correlate to shorter progression free survival in cirrhosis-related HCC. Hypermethylation is more frequent in high-grade tumor.

**Oncogenesis**

DKK3 may be involved in tumorigenesis of HCC and associated with dedifferentiated nature.

## Pancreatic cancer

**Note**

DKK3 expression is low in pancreatic cancer cell lines (MIA PaCa-2 and AsPC-1), due to DNA methylation. DKK3 expression in transfection of expressing plasmids decreased cell proliferation and beta-catenin expression (Gu et al., 2011).

However, another report indicates that DKK3 expression is overexpressed in PANC-1 cell line (derived from human pancreatic ductal carcinoma), and that its down-regulation results in reduction in cellular proliferation (Zenzmaier et al., 2012).

DKK3 protein expression in tissue samples revealed that DKK3 protein expression is observed both in cancer cells and tumor endothelium (Fong et al., 2009).

**Prognosis**

DKK3 expressing endothelium is sensitive to anticancer drug. Low DKK3 protein expression in tumor endothelium correlates with worse clinical outcome.

**Oncogenesis**

DKK3 may be involved in carcinogenesis in pancreatic carcinoma via Wnt/beta-catenin signaling.

## Hematopoietic neoplasm and leukemias

**Note**

The possible function of DKK3 as immune modulator and involvement in hematopoietic neoplasms are reported. As for chronic lymphatic leukemia (CLL), CLL-derived cell line demonstrated DKK3 methylation ranging 23-37%. DKK3 methylation is also observed in CLL patients, ranging 18.7-61% (Moskalev et al., 2012).

A small population of acute myeloid leukemia (AML) patient shows DKK3 methylation (Griffiths et al., 2010; Valencia et al., 2009).

DKK3 methylation is also reported in acute lymphatic leukemia (ALL) derived cell lines and patients (Roman-Gomez et al., 2004).

Recombinant DKK3 may alter CD14+ monocyte into novel phenotype, which demonstrates dendritic cell like appearance and IL-4, GM-CSF. Administration of recombinant DKK3 results in tumor regression with CD11c+, CD8+ T-cell infiltration (Watanabe et al., 2009).

**Prognosis**

DKK3 methylation is a prognostic predictor of disease free survival in ALL.

## Cervical cancer

**Note**

In cervical squamous cell carcinoma (SCC) tissue samples and cell lines, DNA methylation of DKK3 is reported (Kang et al., 2012). Overexpression in cervical SCC cell line results in reduction of cellular beta-catenin level (Lee et al., 2009).

DKK3 methylation is reported also in cervical adenocarcinoma (van der Meide et al., 2011).

**Prognosis**

DKK3 DNA methylation status may correlate with larger tumor size and shorter disease free survival.

**Oncogenesis**

DKK3 methylation and aberrant Wnt/beta-catenin signaling may be involved in cervical SCC.

## Ovarian and endometrial cancers

**Note**

DKK3 mRNA expression is decreased in ovarian cancer tissue (You et al., 2011), and serum DKK3 protein level is low in ovarian cancer patients compared to non-cancerous subject (Jiang et al., 2010).

In endometrial cancer tissue samples, DKK3 mRNA expression is down-regulated, and overexpression in endometrial cancer cell lines results in reduced cell proliferation and beta-catenin mediated TCF activity (Dellinger et al., 2012).

**Prognosis**

Low serum DKK3 level correlate with high frequency of lymph nodal metastasis. Low DKK3 mRNA level correlates with high stage and high incidence of lymph nodal metastasis.

**Oncogenesis**

DKK3 may be involved in carcinogenesis of ovarian and endometrial cancer.

## Breast cancer

**Note**

DNA hypermethylation of DKK3 is reported both in breast cancer tissue samples and cell lines (Veeck et al., 2008; Veeck et al., 2009; Fujikane et al., 2010).

Forced expression in cancer cell lines results in induction of JNK-mediated apoptosis and reduction of anticancer drug resistance (Kawasaki et al., 2009).

Another report demonstrated that knockdown of DKK3 by shRNA transfection revealed the possible function of DKK3 as modulator of Wnt/beta-catenin signaling modulator in breast cancer (Wang et al., 2008).

**Prognosis**

DKK3 DNA methylation status may be a prognostic factor for disease free survival and overall survival.

**Oncogenesis**

DKK3 may be involved in carcinogenesis of breast cancer, and may modulate Wnt/beta-catenin signaling.

## Renal and bladder cancers

**Note**

In renal cell carcinoma (RCC), DKK3 mRNA expression is down-regulated because of promoter CpG island methylation.

Stable transfection of DKK3 in RCC cell lines does not affect in Wnt/beta-catenin pathway, but induce apoptosis via JNK pathway (Ueno et al., 2011). Methylation of DKK3 is also observed in renal clear cell carcinoma (RCCC) (Kurose et al., 2004).

SNP in DKK3 gene is reported in RCC (Hirata et al., 2009).

DKK3 methylation is observed in bladder cancer, and forced expression in bladder cancer cell lines induces JNK mediated apoptosis (Urakami et al., 2006; Hirata et al., 2012; Jin et al., 2012).

**Prognosis**

rs1472189 SNP correlates with distant metastasis.

**Oncogenesis**

DKK3 methylation may be involved in carcinogenesis in RCC and bladder carcinoma.

## Prostate and testicular cancers

**Note**

In prostate cancer, mRNA and protein expression are down-regulated. DKK3 protein expression in prostate cancer decreases gradually in prostate carcinogenesis (Kawano et al., 2006; Zenzmaier et al., 2008).

High DKK3 protein level is reported in seminal plasma of prostate cancer patients (Zenzmaier et al., 2011).

Overexpression in prostate cancer cell line induces JNK-mediated apoptosis (Abarzua et al., 2005) and decreases lymph nodal metastasis in prostate cancer mice model (Edamura et al., 2007; Chen et al., 2009).

In testicular cancer, DKK3 expression is down-regulated, and forced expression in cancer cell lines induce JNK-mediated apoptosis (Tanimoto et al., 2007).

**Prognosis**

DKK3 protein expression loss may correlate to tumor grade. Overexpression of DKK3 in prostate cancer model may ameliorate tumor progression.

**Oncogenesis**

DKK3 methylation may be involved in carcinogenesis in prostate and testicular cancers.

## Lung cancer and mesothelioma

**Note**

Reduced DKK3 mRNA level is firstly reported in human non-small cell lung cancer (NSCLC) tissue sample (Nozaki et al., 2001). Decreased expression of DKK3 mRNA is due to DNA methylation, and DKK3 may regulate cancer cell growth via Wnt/beta-catenin pathway (Yue et al., 2008). DKK3 methylation is observed also in precarcinomatous lesion, atypical adenomatous hyperplasia (Licchesi et al., 2008).

In mesothelioma cell line, DKK3 expression is down-regulated, and overexpression of DKK3 induces JNK-mediated apoptosis (Kashiwakura et al., 2008).

**Oncogenesis**

DKK3 may be involved in NSCLC via Wnt/beta-catenin signaling regulation.

## Skin cancer and malignant melanoma

**Note**

DKK3 protein expression is down-regulated in skin cancers (Du et al., 2011). In malignant melanoma tissue sample and cell lines, DKK3 mRNA expression is strongly reduced. Stable expression of DKK3 in malignant melanoma reduces cellular migration (Kuphal et al., 2006).

**Oncogenesis**

DKK3 may function as a tumor suppressor in skin tumors and malignant melanoma.

### Osteosarcoma

**Note**

Osteosarcoma-derived cell line, Saos2 shows decreased expression of DKK3, which may modulate Wnt/beta-catenin signaling (Hoang et al., 2004).

**Oncogenesis**

DKK3 may be involved in osteosarcoma carcinogenesis.

### Alzheimer's disease

**Note**

DKK3 level in the cerebrospinal fluid in Alzheimer's disease patients is higher than plasma DKK3 level (Zenzmaier et al., 2009).

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