DNAJA3 (DnaJ (Hsp40) homolog, subfamily A, member 3)

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Identity

Other names: FLJ45758, TID1, hTid-1
HGNC (Hugo): DNAJA3
Location: 16p13.3
Local order: According to NCBI Map Viewer, genes flanking DNAJA3 are COR07-PAM16, NMRAL1, and HMOX2.

Note
DNAJA3 was first identified by its ability to form complexes with the human papillomavirus E7 oncoprotein (Schilling et al., 1998) in a yeast-two hybrid screen. Sequence analysis revealed that DNAJA3 was the human homolog of the Drosophila tumor suppressor protein Tid56. Furthermore, DNAJA3 contained a J-domain which is characteristic of the family of DnaJ proteins which interact with and stimulate the ATPase activity of heat shock cognate 70 (hsc70) family members (Schilling et al., 1998).

DNA/RNA

Note
DNAJA3 belongs to the evolutionarily conserved DnaJ/Hsp40 family of proteins. There are 41 known DnaJ/Hsp40 proteins in the human genome (Qiu et al., 2006).

According to NCBI Gene, the DNAJA3 gene is conserved in human chimpanzee, cow, mouse, rat, chicken, zebrafish, fruit fly, mosquito, C. elegans, S. pombe, S. cerevisiae, K. lactis, E. gossypii, M. grisea, N. crassa, and rice.

Description
The DNAJA3 gene is located on chromosome 16p13.3 between markers D16S521 and D16S418. This chromosomal region carries several loci implicated in human proliferation disorders, including the tuberous sclerosis 2 gene (TSC2), polycystic kidney disease 1 gene (PKD1), and the CREB binding protein (CBP) locus (Yin and Rozakis-Adcock, 2001).
DNAJA3 is approximately 34 kb and is composed of 12 exons separated by 11 introns. Exon sizes vary from 64 to 232 nucleotides, with the exception of exon 12 corresponding to the 3’ untranslated region of DNAJA3, which extends over 1.1 kb. Introns sizes vary from 618 to 8,291 nucleotides (Yin and Rozakis-Adcock, 2001).

Sequence encoding the DNAJ domain is present in exons 2, 3, and 4, sequence encoding the Cys-rich domain is found in exons 5 an 6, and the COOH-terminal region is found in exons 7 through 11 (Yin and Rozakis-Adcock, 2001).

**Promoter elements.** DNAJA3 contains a putative transcriptional start site 21 nucleotides upstream of the initiating methionine. The presumptive promoter is characterized by the lack of TATA and CAAT motifs, and a high G+C content. The 5’ flanking region contains several consensus binding sites for transcription factors that regulate gene expression during tissue and organ development, such as myeloid zinc finger (MZF1), Ikaros 2 and homeodomain proteins, as well as factors implicated in cell growth and survival responses, including AP-1, PEA3, E2F and NF-KB.

**Splice variants.** Alternative splicing of a single heteronuclear RNA (hnRNA) species generates the three DNAJA3 isoforms. The long form DNAJA3L (hTID1L) fully incorporates all exons. The intermediate form DNAJA3I (hTID1I) is generated by splicing of exon 10 to exon 12. This results in the loss of the 34 C-terminal-most amino acids as well as the stop codon; these are replaced with six amino acids KRSTGN from exon 12. The short form DNAJA3S (hTID1S) results from an in-frame deletion of 50 amino acids that correspond precisely to exon 5 (Yin and Rozakis-Adcock, 2001).

**RNA expression.** DNAJA3 mRNA was detected in 50 different human fetal and adult tissues. However the relative abundance correlated with metabolic activity of the tissues, with the highest levels observed in liver and skeletal muscle (Kurzik-Dumke and Czaja, 2007).

Human tissues and cell lines showed differential expression of the three DNAJA3 splice variant mRNAs. Fetal brain tissue predominantly expressed DNAJA3I, while breast tissues and T-cells predominantly expressed DNAJA3L. Cell lines derived from prostate epithelia, skin and lung fibroblasts, normal astrocytes, and an osteosarcoma predominantly expressed DNAJA3L with low levels of DNAJA3L also present. DNAJA3S transcript was undetectable in all samples (Yin and Rozakis-Adcock, 2001).

DNAJA3 transcripts showed differential expression during development. Expression of DNAJA3 transcripts in mouse neonatal cardiomyocytes increased as development of the heart proceeded and reached a maximal level at 4 weeks of age, when cardiac myocytes have matured (Hayashi et al., 2006).

DNAJA3 expression also increased in pathological cardiac hypertrophic states (Hayashi et al., 2006).

**Pseudogene**

**Paralogs.** According to GeneCards, DNAJC16 is a paralog for DNAJA3. DNAJC16 is located on chromosome 1p36.1.

**Protein**

**Note**

The DNAJA3 gene encodes three cytosolic (Tid50, Tid48, Tid46) proteins and three mitochondrial (Tid43, Tid40, Tid38) proteins. Proteins encoded by the longer splice variant DNAJA3L have often been designated in the literature as Tid1L. Proteins encoded by the shorter splice variant DNAJA3S have often been named Tid1S. In this review, Tid1L will be designated DNAJA3L, and Tid1S will be designated DNAJA3S. Specific isoforms will be designated by size, e.g., Tid 50 will be designated as DNAJA3 (50 kD).

**Description**

DNAJA3 protein is present in two isoforms, corresponding to splice variants encoding them. The longer DNAJA3L isoform is a 480 amino acid protein with a predicted size of 52 kD. The shorter DNAJA3S isoform is a 453 amino acid protein with a predicted size of 49 kD (Lu et al., 2006; UniProt).

**Expression**

DNAJA3 protein has been detected in human breast, colon, ovarian, lung, and head and neck squamous cell carcinoma (HNSCC) tissues (Traicoff et al., 2007; Kurzik-Dumke et al., 2008; Chen et al., 2009).

**Localisation**

DNAJA3 localizes to human mitochondrial nucleoids, which are large protein complexes bound to mitochondrial DNA. Unlike other DnaJs, DNAJA3L and DNAJA3S form heterocomplexes; both unassembled and complexed DNAJA3 are observed in human cells. DNAJA3L showed a longer residency time in the cytosol prior to mitochondrial import as compared with DNAJA3S; DNAJA3L was also significantly more stable in the cytosol than DNAJA3S, which is rapidly degraded (Lu et al., 2006).

**Function**

**I. Binding partners**

Human DNAJA3 protein has been shown to interact with diverse partners, including viral proteins, heat shock proteins, and key regulators of cell signaling and growth.

**Viral proteins**

**Hepatitis B virus core protein:** DNAJA3 associated with the hepatitis B virus core protein, specifically with the carboxy-terminal region (amino acids 94-185). The N-terminal end of DNAJA3 (amino acids 1-447) was required for this interaction. Furthermore, the
DNAJA3S precursor co-sedimented with viral capsid-like particles composed of the full-length core protein (Sohn et al., 2006). Interaction between DNAJA3 and the HBV core protein was confirmed in co-immunoprecipitation experiments using transfected hepatoma cells (Sohn et al., 2006).

**Epstein-Barr virus-encoded BARF1 protein:** DNAJA3 (amino acids 149-320) associated with the Epstein-Barr virus-encoded BARF1 protein (amino acids 21-221). Interaction between DNAJA3 and BARF1 was confirmed in co-immunoprecipitation experiments using transfected HeLa cells (Wang et al., 2006).

**Herpes simplex virus type 1 UL9 protein:** DNAJA3 associated with the herpes simplex virus type 1 (HSV-1) UL9 protein. UL9 protein is an origin-binding protein. Interaction between DNAJA3 and UL9 was confirmed by in vitro co-immunoprecipitation (Eom and Lehman, 2002).

**Human T cell leukemia virus type 1 (HTLV-1) Tax protein:** DNAJA3 associated with HTLV-1 Tax. The interaction occurred through a central cysteine-rich zinc finger-like region of DNAJA3 (amino acids 236 to 300). Interaction between DNAJA3 and Tax was confirmed by co-immunoprecipitation experiments using transfected human embryonic kidney cells (HEK) (Cheng et al., 2001). Furthermore, the DNAJA3 and Tax interaction occurred through a complex comprised of DNAJA3, Tax, and heat shock protein 70 (Hsp70), in which the cysteine-rich region of DNAJA3 interacted with Tax, while the J domain of DNAJA3 interacted with Hsp70 (Cheng et al., 2001).

**Human papilloma virus-16 (HPV-16) E7 oncoprotein:** DNAJA3 was initially characterized through its interaction with the HPV-16 E7 oncoprotein. DNAJA3 amino acids 1 to 235 and 297 to 342 independently interacted with HPV-16 E7. Interaction between DNAJA3 and HPV-16 E7 was confirmed by in vitro binding assays and co-immunoprecipitation experiments using transfected human osteosarcoma (U2OS) cells (Schilling et al., 1998).

**Heat shock proteins**

**Hsp70 and Hsc70:** endogenous DNAJA3 (specifically the cytosolic form) immunoprecipitated with the heat shock proteins Hsp70 and Hsc70 in normal colon epithelium and colon cancer cell lines (Kurzik-Dumke and Czaja, 2007). Endogenous DNAJA3 also interacted with Hsp70/Hsc70 in HEp2 cells, and this interaction was reduced in cells treated with interferon-gamma (Sarkar et al., 2001). The J domain of DNAJA3 was shown to be required for interaction with Hsp70 in HEK cells (Cheng et al., 2001). Proteins encoded by the long and short splice forms of DNAJA3, DNAJA3L and DNAJA3S, respectively, showed differential interactions with heat shock proteins. Unassembled DNAJA3L (the long splice variant) was shown to interact with Hsc70 specifically in the cytosol (Lu et al., 2006). The unique carboxyl terminus of DNAJA3L was required for this interaction (Lu et al., 2006). Both DNAJA3S and DNAJA3L could interact with Hsp70 (Kim et al., 2004). Endogenous DNAJA3L and DNAJA3S coimmunoprecipitated with mitochondrial Hsp70, but not Hsc70, in U2OS osteosarcoma cells (Syken et al., 1999).

**Tumor suppressor proteins**

**Adenomatous polyposis coli (APC):** endogenous cytosolic DNAJA3 proteins interacted with APC in normal colon epithelium and colorectal cancer cell lines (HT-29, Caco-2, and HRT-18). The N-terminal Armadillo domain of APC was sufficient for binding to DNAJA3. The DNAJA3 and APC interaction comprised part of a larger multi-component complex that also contained Hsp70, Hsc70, Actin, Dvl, and Axin. This complex functions independently of the known roles of APC in beta-catenin degradation and proliferation mediated by Wg/Wnt signaling (Kurzik-Dumke and Czaja, 2007). Endogenous DNAJA3 proteins were shown to interact with the caspase-cleaved N-terminus of APC in HCT116 cells (Qian et al., 2010). The caspase-cleaved APC protein has an important physiological role in mediating apoptosis (Qian et al., 2010).

**Patched:** endogenous human Patched interacted with the cytosolic forms of the DNAJA3 proteins in human colon epithelium and colon tumor cells (Kurzik-Dumke and Czaja, 2007). The tumor-associated polymorphism in Patched (PtcH FVB allele) was associated with poorer binding to DNAJA3 (Wakabayashi et al., 2007).

**INT6:** endogenous human DNAJA3 interacted with INT6 (the p48 subunit of the eIF3 translation initiation factor) in log phase, but not confluent, Jurkat T-cells (Traicoff et al., 2007).

**Von Hippel-Lindau protein (VHL):** endogenous pVHL co-immunoprecipitated with DNAJA3L protein in HEK293 cells (Bae et al., 2005).

**p53:** DNAJA3 directly interacts with p53 through the DNAJA3 N-terminal domain. Either the N- or C-terminal domains of p53 was sufficient for the interaction (Trinh et al., 2010).

**Receptors**

**Interferon-gamma receptor (IFN-gammaR) subunit IFN-gammaR2:** DNAJA3 interacted with IFN-gammaR2 in transfected COS cells. Furthermore, DNAJA3 bound more efficiently to an IFN-gammaR2 chimera with an active kinase domain than to a similar construct with an inactive kinase domain (Sarkar et al., 2001).

**ErbB-2 (HER2/neu):** endogenous ErbB-2 and DNAJA3 co-immunoprecipitated in SK-BR-3 breast cancer cells (Kim et al., 2004). The cytoplasmic domains of ErbB-2 and DNAJA3 were sufficient for this interaction (Kim et al., 2004).

ErbB-2 co-immunoprecipitated with DNAJA3 and the carboxyl terminus of heat shock cognate 70 interacting protein (CHIP). This complex was demonstrated in tissue extracts from breast tumor specimens as well as in transfected cell lines (Jan et al., 2011).
Trk receptor tyrosine kinases: the carboxyl-terminal end of DNAJA3 (residues 224-429) bound to Trk at its activation loop in a phosphotyrosine-dependent manner (Liu et al., 2005).

Muscle-specific kinase (MuSK) component of the agrin receptor: DNAJA3S, but not DNAJA3L, associated with the cytoplasmic portion of MuSK in mouse skeletal muscle cells (Linnoina et al., 2008).

Signaling proteins

NF-kappaB: DNAJA3 strongly associated with the cytoplasmic protein complex of NF-kappaB-IkappaB through direct interaction with IkappaBalpha/IkappaBbeta and the IKKalpha/beta subunits of the IkappaB kinase complex. The endogenous interaction was observed in Jurkat, SAOS-2, and HEK293 cells (Cheng et al., 2005).

JAK/STAT: Jak2 interacted with DNAJA3S as well as DNAJA3L as shown by immunoprecipitation from transfected COS-1 cells expressing these proteins. Endogenous DNAJA3 and Jak2 were shown to interact in HEp2 cells (Sarkar et al., 2001). The carboxyl terminus of endogenous DNAJA3L, but not DNAJA3S, co-immunoprecipitated with STAT1 and with STAT3 in U2OS cells (Lu et al., 2006). DNAJA3L remained associated with activated phosphorylated STAT1 upon treatment with interferon-gamma (Lu et al., 2006).

The DNAJ domain of DNAJA3 interacted with the transactivation domain of Stat5b in hematopoietic cell lines (Dhenin-Duthille et al., 2011).

p120 GTPase-activating protein (GAP): both the cytoplasmic precursor and mitochondrial mature forms of murine DNAJA3 associated with GAP in vivo in rodent cells. GAP selectively bound to the unphosphorylated form of murine DNAJA3 (Trentin et al., 2001).

DNA replication proteins

DNA polymerase gamma (Polga) alpha subunit: endogenous DNAJA3 interacted with the alpha subunit of Polga in HEK293 cells. Polga is the only mitochondrial DNA polymerase responsible for all mitochondrial DNA synthetic reactions (Hayashi et al., 2006).

II. Signaling pathways and cellular effects

DNAJA3 modulates diverse signaling pathways and cellular effects that are vital for cell growth and differentiation.

Neural pathways

Neuromuscular synaptogenesis: DNAJA3 is an essential component of the agrin signaling pathway that is crucial for synaptic development. Motoneuron-derived agrin clusters nicotinic acetylcholine receptors (AChRs) in mammalian cells. DNAJA3 binds to the cytoplasmic domain of muscle-specific kinase (MuSK), a component of the agrin receptor and colocalizes with AChRs at developing, adult, and denervated motor endplates. DNAJA3 transduces signals from MuSK activation to AChR clustering, culminating in cross-linking to the subsynaptic cytoskeleton, as demonstrated by knockdown and overexpression experiments.

Knockdown of DNAJA3 in skeletal muscle fibers resulted in dispersed synaptic AChR clusters and impaired neuromuscular transmission. Knockdown of DNAJA3 in myotubes resulted in inhibition of AChR clustering, inhibition of agrin-induced activation of the Rac and Rho small GTPases and tyrosine phosphorylation of AChR, and decreased Dok-7-induced clustering of AChRs. In contrast, overexpression of the N-terminal half of DNAJA3 led to the MUSK-independent phosphorylation and clustering of AChRs (Linnoina et al., 2008; Song and Balice-Gordon, 2008).

Neurite outgrowth: DNAJA3 regulated nerve growth factor (NGF)-induced neurite outgrowth in PC12-derived nnr5 cells. DNAJA3 bound to Trk at the activation loop and DNAJA3 was tyrosine phosphorylated by Trk in yeast cells, transfected cells, and in neurotrophin-stimulated primary rat hippocampal neurons. Overexpression of DNAJA3 led to NGF-induced neurite outgrowth in TrkA-expressing nnr5 cells. In contrast, knockdown of DNAJA3 resulted in reduced NGF-induced neurite growth in nnr5-TrkA cells (Liu et al., 2005).

Viral pathways

Hepatitis B virus replication: expression of DNAJA3 suppressed replication of HBV in human hepatoma cells, while knockdown of DNAJA3 led to increased HBV replication. The mechanism for inhibited replication was through accelerated degradation and destabilization of the viral core and HBx proteins (Sohn et al., 2006).

Herpes simplex virus type 1 replication: the HSV-1 UL9 protein is an origin-binding protein that is essential for viral DNA replication. DNAJA3 modulates DNA replication by enhancing the binding of UL9 protein to an HSV-1 origin and facilitating formation of the multimer from the dimeric UL9 protein, perhaps through a chaperone function. However, DNAJA3 had no effect on the DNA-dependent ATPase or helicase activities associated with the UL9 protein (Eom and Lehman, 2002).

Epstein-Barr virus secretion: the EBV BARF1 gene encodes a secretory protein with transforming and mitogenic activities. Coexpression experiments with BARF1 and DNAJA3 showed that DNAJA3 could promote secretion of BARF1, perhaps through chaperone functions (Wang et al., 2006).

Motility and metastasis

DNAJA3 was shown to negatively regulate the motility and metastasis of breast cancer cells through attenuation of nuclear factor kappab activity on the promoter of the IL8 gene (Kim et al., 2005). Reductions of DNAJA3 levels in MDA-MB231 breast cancer cells increased their migration as a result of increased interleukin-8 (IL-8) secretion without affecting survival or growth rate. Furthermore,
DNAJA3 was shown to negatively modulate de novo synthesis of IL-8 through regulating NFkappaB activity. Additionally, DNAJA3 knockdown enhanced the metastasis of breast cancer cells in animals (Kim et al., 2005). Other studies also indicate a potential role for DNAJA3 in inhibiting transformation and metastasis. Stable DNAJA3 knockdown cells exhibited an enhanced ability for anchorage-independent growth, as measured by an increase in soft-agar colony formation (Edwards and Münger, 2004). In contrast, ectopic expression of DNAJA3 in HNSCC cells was shown to significantly inhibit cell proliferation, migration, invasion, anchorage-independent growth, and xenotransplantation tumorigenicity (Chen et al., 2009). Expression of DNAJA3 inhibited the transformation phenotype of two human lung adenocarcinoma cell lines (Cheng et al., 2001).

Apoptosis

DNAJA3 encodes two mitochondrial matrix localized splice variants: DNAJA3 (43 kD) and DNAJA3 (40 kD). DNAJA3 (43 kD) and DNAJA3 (40 kD) do not themselves induce apoptosis; instead they have opposing effects on apoptosis induced by exogenous stimuli. Expression of DNAJA3 (43 kD) increases apoptosis induced by both the DNA-damaging agent mitomycin c and tumor necrosis factor-alpha. This activity is J domain-dependent, since a J domain mutant of DNAJA3 (43 kD) suppressed apoptosis. Conversely, expression of DNAJA3 (40 kD) suppressed apoptosis, while expression of a J domain mutant of DNAJA3 (40 kD) increased apoptosis (Syken et al., 1999).

Cells lacking expression of DNAJA3 proteins were protected from cell death in response to multiple stimuli, including cisplatin, tumor necrosis factor alpha/cycloheximide and mitomycin C (Edwards and Münger, 2004). DNAJA3 regulates activation-induced cell death (AICD) in the Th2 subset of helper T cells. AICD is an apoptotic process induced by stimulation through the T-cell receptor and Th2 cells are significantly less prone to AICD than Th1 cells are. The antiapoptotic variant, Tid-1S was shown to be selectively induced in murine Th2 cells following activation. Expression of a dominant-negative mutant of hTid-1S in a Th2 cell line strikingly enhanced activation of caspase 3 in response to CD3 stimulation, and caused the cells to become sensitive to AICD. Therefore, the accumulation of Tid-1S in Th2 cells following activation may contribute to the induction of apoptosis resistance during the activation of Th2 cells (Syken et al., 2003).

DNAJA3 mediates apoptosis through the nuclear factor kappaB (NF-kappaB) pathway. DNAJA3 repressed the activity of NF-kappaB through physical and functional interactions with the IKK complex and IkappaB. Overexpression of DNAJA3 led to inhibition of cell proliferation and induction of apoptosis of human osteosarcoma cells and human melanoma cells regardless of the p53 expression status. In contrast, cells transduced with a DNAJA3 mutant that has an N-terminal J domain deletion and that lost suppressive activity on IKK, continued to proliferate (Cheng et al., 2005).

DNAJA3 mediates apoptosis through the Bcl-2 pathway. DNAJA3 induced apoptosis in SF767 glioma cells that contained a tumor-associated mutation at the DNAJA3 locus. Apoptosis resulted from caspase activation and cytochrome c release from mitochondria. However, Bcl-XL protected cells from hTid-1S-induced cell death and cytochrome c release. However, hTid1S caused S and G2/M arrest in cells with wild type Tid1. Interestingly, hTid1L had no effect on growth of glioma cells (Trentin et al., 2004). Immature dnaja3(-/-) DN4 thymocytes exhibited significantly reduced expression of the antiapoptotic bcl-2 gene (Lo et al., 2005).

Expression of constitutively active AKT (pAKT) counteracted and inhibited DNAJA3-induced apoptosis in HNSCC cells (Chen et al., 2009).

DNAJA3 mediates apoptosis through APC. DNAJA3 (40 kD) isoform inhibited apoptosis through antagonizing the apoptotic function of the N-terminal region of the APC protein (Qian et al., 2010).

DNAJA3 mediates apoptosis through p53. Overexpression of DNAJA3 enhanced p53-dependent apoptosis, and restored pro-apoptotic activity of mutant p53 in colon, breast, and glioma cell lines (Ahn et al., 2010). The mechanism is through direct interaction of the DNAJ domain of DNAJA3 and p53 (Trinh et al., 2010). In contrast, depletion of DNAJA3 resulted in the inhibition of hypoxia or genotoxic stress-induced p53 mitochondrial localization and apoptosis (Trinh et al., 2010).

Mitochondrial functions

Although DNAJA3 has many cellular functions, DNAJA3 often localizes to the mitochondria and also has important functions in the mitochondria.

Epidermal growth factor (EGF) response: GAP and DNAJA3 were shown to colocalize at perinuclear mitochondrial membranes in response to EGF stimulation (Trentin et al., 2001).

p53 localization and apoptotic function: depletion of DNAJA3 prevented p53 accumulation at the mitochondria and resulted in resistance to apoptosis under hypoxic or genotoxic stresses (Trinh et al., 2010). DNAJA3 formed a complex with p53 under hypoxic conditions that directed p53 translocation to the mitochondria and the subsequent initiation of apoptosis (Ahn et al., 2010). Loss of DNAJA3 expression abrogated p53 translocation to the mitochondria and inhibited apoptosis (Ahn et al., 2010). Conversely, overexpression of DNAJA3 promoted p53 mitochondrial localization and apoptosis (Ahn et al., 2010).

Viral protein localization: in the absence of Tax, expression of the DNAJA3/Hsp70 molecular complex was targeted to perinuclear mitochondrial clusters. In
the presence of Tax, DNAJA3 and its associated Hsp70 are sequestered within a cytoplasmic "hot spot" structure, a subcellular distribution that is characteristic of Tax in HEK cells (Cheng et al., 2001).

**APC interaction:** the amino terminus of APC interacted with DNAJA3 at the mitochondria in vivo in colorectal cancer cell lines (Qian et al., 2010).

**Chaperone function:** DNAJA3 isoforms were also shown to exhibit a conserved mitochondrial DnaJ-like function substituting for the yeast mitochondrial DnaJ-like protein Mdj1p (Lu et al., 2006).

**Mitochondrial biogenesis:** DNAJA3 was shown to be crucial for mitochondrial biogenesis partly through chaperone activity on DNA polymerase gamma (Hayashi et al., 2006). Mice deficient in Dnaja3 developed dilated cardiomyopathy (DCM) and died before 10 weeks of age (Hayashi et al., 2006). Progressive respiratory chain deficiency and decreased copy number of mitochondrial DNA were observed in cardiomyocytes lacking Dnaja3 (Hayashi et al., 2006).

**Tumor suppressor pathways**

**APC:** DNAJA3 directly bound to the APC tumor suppressor protein and promoted a physiological function for APC that was independent of APC's involvement in beta-catenin degradation or regulation of the actin cytoskeleton (Kurzik-Dumke and Czaja, 2007).

**pVHL:** TID1L directly interacted with von Hippel-Lindau protein and enhanced the interaction between HIF-1 alpha and pVHL. This resulted in destabilization of HIF-1 alpha protein, decreased vascular endothelial growth factor expression, and inhibition of angiogenesis (Bae et al., 2005).

**Interferon-gamma:** DNAJA3L and DNAJA3S interacted with the interferon-gamma receptor chain IFN-gammaR2 and modulated IFN-gamma-mediated transcriptional activity. Furthermore, IFN-gamma treatment reduced the interaction between Hsp70/Hsc70 and DNAJA3 (Sarkar et al., 2001).

**Oncogenic pathways**

**Erb-B2/HER2:** DNAJA3 physically interacted with the signaling domain of ErbB-2 and ErbB-2 were shown to colocalize in mammary carcinoma cells (SK-BR-3). Overexpression of DNAJA3 induced growth arrest and apoptosis in ErbB-2-overexpressing breast cancer cells; the DNAJ and C-terminal domains of DNAJA3 were critical for mediating apoptosis. Downregulation of ERK1/ERK2 and BMK1 MAPK pathways also contributed to apoptosis. DNAJA3S negatively regulated ErbB-2 signaling pathways by enhancing the degradation of ErbB-2. Finally, increased cellular DNAJA3 inhibited the growth of ErbB-2-dependent tumors in mice (Kim et al., 2004). Mammary tumor tissue from breast cancer patients and transgenic mice carrying the rat HER-2/neu oncogene suggest that DNAJA3 suppresses ErbB-2 in breast cancers (Kurzik-Dumke et al., 2010).

**NF-kappaB:** expression of DNAJA3 was upregulated upon cellular senescence in rat and mouse embryo fibroblasts, as well as in premature senescence of REFS2 cells triggered by activated ras. Conversely, spontaneous immortalization of rat embryo fibroblasts was suppressed upon ectopic expression of DNAJA3. Suppression of endogenous DNAJA3 activity alleviated the suppression of tumor necrosis factor alpha-induced NF-kappaB activity by DNAJA3. These results suggest that DNAJA3 contributes to senescence by repressing NF-kappa B signaling (Tarunina et al., 2004).

DNAJA3 repressed NF-kappaB activity induced by Tax, tumor necrosis factor alpha (TNFalpha), and Bcl10. DNAJA3 specifically suppressed serine phosphorylation of IkappaBalpha by activated IkappaB kinase beta (IKKbeta). The suppressive activity of DNAJA3 on IKKbeta required a functional J domain that mediates association with heat shock proteins and resulted in prolonging the half-life of the NF-kappaB inhibitors IkappaBalpha and IkappaBBeta (Cheng et al., 2002).

**AKT:** overexpression of DNAJA3 in HNSCC cells inhibited cell proliferation, migration, invasion, anchorage-independent growth, and xenotransplantation tumorigenicity. Overexpression of DNAJA3 attenuated EGFR activity and blocked the activation of AKT in HNSCC cells, which are known to be involved in the regulation of survival in HNSCC cells. Conversely, ectopic expression of constitutively active AKT greatly reduced apoptosis induced by DNAJA3 overexpression (Chen et al., 2009).

**JAK2:** DNAJA3L and DNAJA3S interacted with Jak2 in vivo in COS-1 cells. Interaction was primarily in the cytoplasm and predominantly with the active kinase domain of Jak2 (Sarkar et al., 2001).

**c-MET receptor tyrosine kinase (MetR):** MetR interacted with DNAJA3L and DNAJA3S, but showed preferential binding to DNAJA3S. Interaction occurred through the J domain. In RCC cells, overexpression of DNAJA3S enhanced HGF-mediated MetR autophosphorylation, while DNAJA3L showed modest inhibition of MetR activity. Modulation of MetR phosphorylation levels was independent of pVHL. DNAJA3S enhanced HGF-mediated cell migration and modulated HGF-mediated MAPK phosphorylation. DNAJA3 knockdown inhibited MetR activation and migration in response to HGF (Copeland et al., 2011).

**Signal transducers and activators of transcription (STAT) 5b:** DNAJA3 specifically interacted with STAT5b but not STAT5a in hematopoietic cell lines. Interaction involved the DNAJ domain. DNAJA3 negatively regulated the expression and transcriptional activity of STAT5b and suppressed the growth of hematopoietic cells transformed by an oncogenic form of STAT5b (Dhennin-Duthille et al., 2011).

**Cell Fate**

DNAJA3 was shown to be required for the T-cell transition from double-negative 3 to double-positive stages. Mice with dnaja3 specifically deleted in T cells developed thymic atrophy, with dramatic reduction of...
double-positive and single-positive thymocytes in the dnaja3(-/-) thymus. DNAJA3 deficiency inhibited cell proliferation and enhanced cell death of DN4 cells. The expression profile of genes involved in cytokine receptor signaling was altered in DN4 T-cells. Expression of human bcl-2 transgene restored T lymphocyte proliferation and differentiation in the dnaja3 knockout mice. These results suggest that dnaja3 is critical in early thymocyte development, especially during transition from the DN3 to double-positive stages, possibly through its regulation of bcl-2 expression, which provides survival signals.

**Homology**

Mouse (laboratory): Dnaja3
Rat: Dnaja3
Cattle: DNAJA3
Chimpanzee: DNAJA3
Dog (domestic): DNAJA3

**Mutations**

**Note**

The SF767 glioma cell line exhibits an aberrant 52 kD molecular weight protein. Sequence analysis of cDNA generated from this line showed two mutations: an additional thymine at nucleotide position 1438 and an additional cytosine at nucleotide position 1449. These mutations alter the reading frame of the DNAJA3 sequence, introducing an additional 71 amino acids following the penultimate threonine residue at position 479. The mutations appear to increase the steady-state abundance of the mutant protein, resulting in aberrantly high levels of the DNAJA3 mutant variant (Trentin et al., 2004).

**Implicated in**

**Colon cancer**

**Disease**

DNAJA3 and INT6 protein levels, as well as DNAJA3 and Patched protein levels, were positively correlated in human colon tumor tissues (Traicoff et al., 2007). However, there were no correlations between DNAJA3 and p53, c-Jun, or phospho-c-Jun protein levels (Traicoff et al., 2007). These results were demonstrated by multiplex tissue immunoblotting of tissue microarrays (Traicoff et al., 2007). Progression of colorectal cancers correlated with overexpression and loss of polarization of expression of DNAJA3. These changes were associated with upregulation of Hsp70 and loss of compartmentalization of APC (Kurzik-Dumke et al., 2008).

**Breast cancer**

**Disease**

DNAJA3 protein expression showed a strong correlation with negative or weakly positive expression of ErbB2 in human breast cancer tissue samples. High DNAJA3 levels were strongly correlated with high levels of CHIP (carboxyl terminus of heat shock cognate 70 interacting protein). Lower expression of DNAJA3 had a higher risk of unfavorable tumor grade, later pathological stage, larger tumor size, and microscopic features of a more malignant histology (Jan et al., 2011). Higher expression of DNAJA3 correlated with increased 10-year overall and disease-free survival rate (Jan et al., 2011).

The expression of the three DNAJA3 isoform transcripts was examined in human breast cancer carcinomas by RT-PCR. Aberrant expression of all three forms correlated with malignant transformation. Furthermore, elevated DNAJA3L expression was associated with less aggressive tumors (Kurzik-Dumke et al., 2010). Immunohistochemical analysis demonstrated high levels of DNAJA3 protein in tumors of the luminal A subtype, but significantly lower levels of DNAJA3 protein in the luminal B subtype, triple negative tumors, and the HER-2 subtype which overexpresses HER-2 (Kurzik-Dumke et al., 2010).

Multiplex tissue immunoblotting of human breast tumor tissue microarrays was used to test correlations between DNAJA3 protein levels and a set of tumor suppressor proteins. DNAJA3 protein levels showed strongly positive correlations with p53, Patched, and INT6 proteins (Traicoff et al., 2007). Additionally, DNAJA3 protein levels showed moderate positive correlations with c-Jun and phospho-c-Jun proteins (Traicoff et al., 2007).

**Head and neck squamous cell carcinoma (HNSCC)**

**Disease**

The clinical association between DNAJA3 expression and progression of HNSCC was explored using immunohistochemical analysis of primary HNSCC patient tumor tissue. DNAJA3 expression was negatively associated with tumor T stage, overall stage, survival, and recurrence. Patients with higher expression of DNAJA3 were predicted to have better overall survival than those with low or undetectable expression of DNAJA3 protein (Chen et al., 2009). Highly malignant HNSCC cell lines also demonstrated low or undetectable levels of DNAJA3, in contrast to less aggressive lines where DNAJA3 protein was easily detected (Chen et al., 2009).

**Ovarian cancer**

**Disease**

Multiplex tissue immunoblotting of ovarian tumor tissues demonstrated that DNAJA3 protein levels showed moderate positive correlations with INT6, c-Jun, phospho-c-Jun, and p53. No correlations were observed between DNAJA3 and Patched (Traicoff et al., 2007).
Lung cancer

Disease
Multiple tissue immunoblotting of lung tumor tissues demonstrated that DNAJA3 protein levels were strongly correlated with INT6. DNAJA3 protein levels were moderately correlated with Patched, c-Jun, and p53. However, DNAJA3 proteins showed negative correlation with phospho-c-Jun in these samples (Traicoff et al., 2007).

Cardiomyopathy

Note
Mice deficient in Dnaja3 developed dilated cardiomyopathy (DCM) and died before 10 weeks of age (Hayashi et al., 2006). Progressive respiratory chain deficiency and decreased copy number of mitochondrial DNA were observed in cardiomyocytes lacking Dnaja3 (Hayashi et al., 2006).

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