Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

EIF2AK2 (eukaryotic translation initiation factor 2-alpha kinase 2)

William L Blalock, Lucio Cocco

IGM-CNR, Bologna, Rizzoli Orthopedic Institute,via di Barbiano, 1/10, 40136 Bologna, Italy (WLB), Cellular Signalling Laboratory, Department of Anatomical Sciences, University of Bologna, Via Irnerio, 48 I-40126 Bologna, Italy (LC)

Published in Atlas Database: March 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/EIF2AK2ID41866ch2p22.html
DOI: 10.4267/2042/47528

Identity

Other names: EIF2AK1, PKR, p68 kinase, PRKR

HGNC (Hugo): EIF2AK2

Location: 2p22.2

Local order: HEAT repeat containing 5B (HEATR5B); coiled-coil domain containing 75 (CCDC75); **Eukaryotic translation initiation factor 2-alpha kinase 2 (EIF2AK2)**; sulfotransferase family member, cytosolic, 6B, member 1 (SULT6B1); ribosomal protein L31 pseudogene 16 (RPL31P16).

DNA/RNA

Description

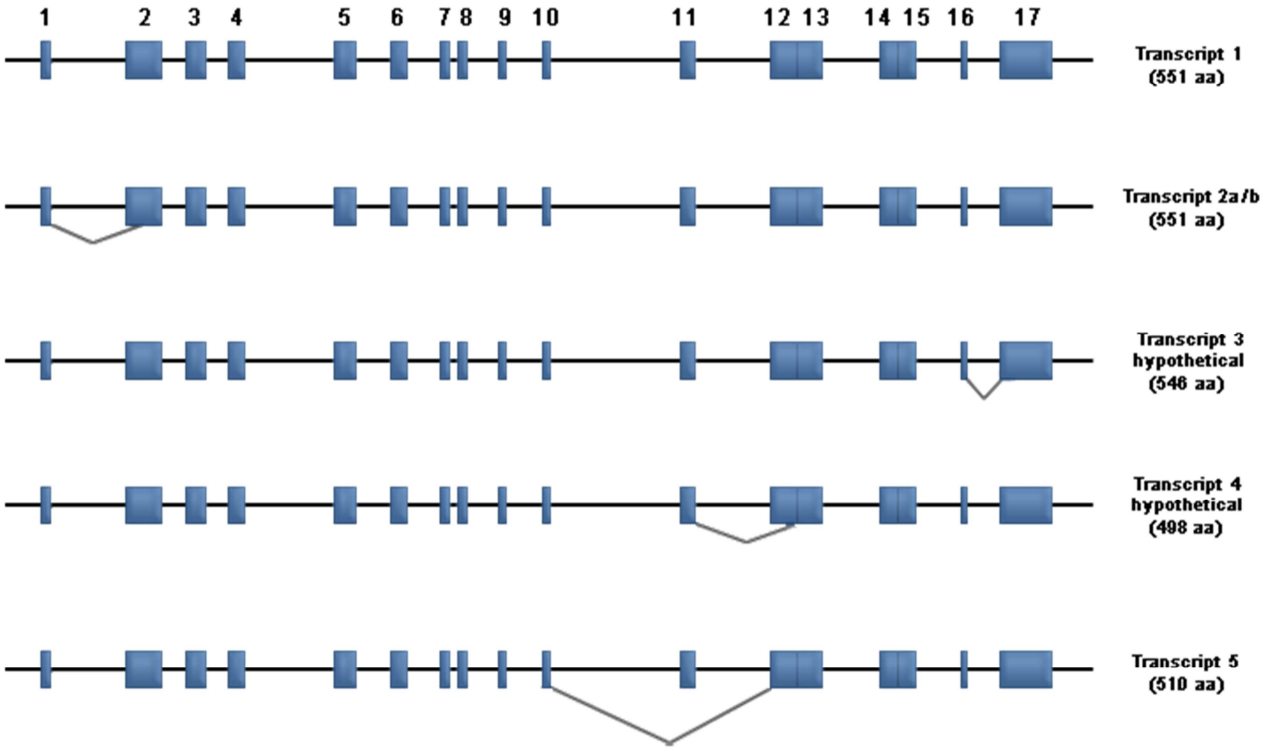
The EIF2AK2 gene spans approximately 50 kb and contains 17 exons.
The coding sequence initiates in exon 3 (Kuhen et al., 1996).

Transcription

Key Promoter Elements: TATA-less (No TATA Box).
1. KCS (Kinase Conserved Sequence): Nucleotides -67 to -81 from the transcriptional start site.
Required for basal expression utilizing Sp factors. Also required in combination with the ISRE for interferon-stimulated expression (Kuhen and Samuel, 1997; Kuhen et al., 1998; Kuhen and Samuel, 1999; Ward and Samuel, 2002).
2. ISRE (Interferon-stimulated response element): Nucleotides -50 to -62 from the transcriptional start site. Required for the interferon-inducible expression of EIF2AK2. Regulated by the binding of STAT1, STAT2 and IRF9 (Kuhen and Samuel, 1997; Kuhen and Samuel, 1999; Ward and Samuel, 2002; Ward and Samuel, 2003).
3. P53RE (p53 response element): Two p53RE domains were identified flanking the ISRE. Acts to enhance EIF2AK2 expression following genotoxic stress (Yoon et al., 2009).
Transcripts:
Three (3) transcripts have been identified based on alternate splicing of exon 1 with exon 2 in the 5'UTR. No change to the protein is observed with these transcripts (Kawakubo et al., 1999).
One (1) alternately spliced transcript (Tissue: Placenta) resulting in the loss of exon 12 (Gerhard et al., 2004).
One (1) alternately spliced transcript (Tissue: Brain/Lung) resulting in the loss of exon 11 (Gerhard et al., 2004).
One (1) transcript (Tissue: Brain) which results from an alternate splice acceptor site in exon 17 (Gerhard et al., 2004).

Pseudogene

None.



The stick diagram shows the splicing of the exons that compose PKR as well as confirmed and unconfirmed (suggested by cDNA libraries from the Mammalian Gene Collection (MGC) only) splicing products and the length of their resulting protein products. The coding sequence for PKR initiates in exon 3 at the 17th nucleotide. The coding sequence of PKR is 1656 base pairs; the individual exons contain the following coding nucleotides: exon 3 (1-118); exon 4 (119-240); exon 5 (241-389); exon 6 (390-516); exon 7 (517-593); exon 8 (594-687); exon 9 (688-722); exon 10 (723-785); exon 11 (786-908); exon 12 (909-1067); exon 13 (1068-1248); exon 14 (1249-1377); exon 15 (1378-1479); exon 16 (1480-1533); exon 17 (1534-1656).

Protein

Note

The protein product of the EIF2AK2 gene is typically referred to as PKR in the literature.

Description

EIF2AK2/PKR is a 551 amino acid protein with a predicted molecular weight of 62,1 kDa (68-72 kDa in SDS-PAGE) and a predicted pI of 8,58. PKR first described as an interferon-inducible antiviral kinase which phosphorylated eIF2-alpha on Ser 51, is now best described as a general stress/inflammatory kinase which phosphorylates an increasing list of substrates which includes eIF2-alpha (Colthurst et al., 1987), p53 (Cuddihy et al., 1999), B56-alpha (Xu and Williams, 2000), cyclin dependent kinase (CDK)-1 (Yoon et al., 2010), and vinsulin receptor substrate-1 (Nakamura et al., 2010).

Expression

Ubiquitous.

Localisation

Cytoplasm, nuclear, nucleolar.

Function

Major role

The double-stranded RNA dependent kinase (PKR) was initially identified as an innate immune anti-viral protein approximately 35 years ago (Roberts et al., 1976b; Roberts et al., 1976a).

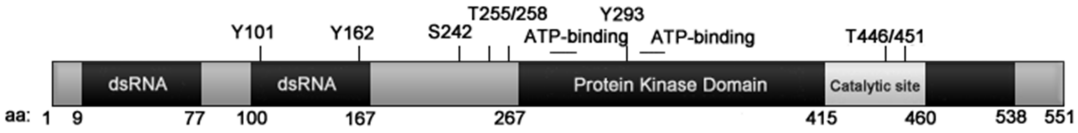
Since then PKR has been linked to normal cell growth and differentiation, inflammation, cytokine signaling and apoptosis (Garcia et al., 2006). Altered PKR activity has been shown to play a role in neurodegenerative diseases (Alzheimer's, Huntington's and Parkinson's) and cancer (Peel et al., 2001; Peel and Bredesen, 2003; Onuki et al., 2004; Peel, 2004; Bando et al., 2005; Eley et al., 2009).

PKR belongs to the eIF2α kinase family which also includes PKR-like endoplasmic reticulum kinase (PERK), general amino acid control of gene expression, non-derepressing 2 (GCN2) and heme-regulated kinase (HRI).

Whereas the activation of PERK, GCN2 and HRI are in response to more specific stresses; PKR is activated in response to diverse stress signals (Shi et al., 1998; Berlanga et al., 1999; Williams, 1999; Chen, 2007).

```
  1 MAGDLSAGFF MEELNTYRQK QGVVLKYQEL PNSGPPHDRR FTFQVIIDGR EFPEGEGRSK
 61 KEAKNAAAKL AVEILNKEKK AVSPLLLTTT NSSEGLSMGN YIGLINRIAQ KKRLTVNYEQ
121 CASGVHGPEG FHYKCKMGQK EYSIGTGSTK QEAKQLAAKL AYLQILSEET SVKSDYLSSG
181 SFATTCESQS NSLVTSTLAS ESSSEGDFSA DTSEINSNSD SLNSSSLLMN GLRNNQRKAK
241 RSLAPRFDLP DMKETKYTVD KRFGMDFKEI ELIGSGGFGQ VFKAKHRIDG KTYVIKRVKY
301 NNEKAEREVK ALAKLDHVNI VHYNGCWDGF DYDPETSDDS LESSDYDPEN SKNSSRSKTK
361 CLFIQMEFCD KGTLEQWIEK RRGEKLDKVL ALELFEQITK GVDYIHSKKL IHRDLKPSNI
421 FLVDTKQVKI GDFGLVTSLK NDGKRTRSKG TLRYMSPEQI SSQDYGKEVD LYALGLILAE
481 LLHVCDTAFE TSKFFTDLRD GIISDIFDKK EKTLLQKLLS KKPEDRPNTS EILRTLTVWK
541 KSPEKNERHT C
```

The primary amino acid sequence of PKR. The alternate exons to which the individual amino acids belong are indicated by shading. Translation of PKR initiates in exon 3 and terminates in exon 17.



The primary protein structure for PKR. Key domains of the protein and the amino acids that compose them are shown, as are the key phosphorylation site(s) which are required for kinase activity (T451) (Romano et al., 1998; Zhang et al., 2001) or enhance kinase activity (Y101, Y162, S242, T255, T258, Y293 and T446) (Romano et al., 1998; Alisi et al., 2005; Su et al., 2006).

As the first known substrate of PKR was eIF2α, much of the research involving PKR has centered on its ability to regulate translation under varying conditions.

Within the past ten years, PKR has been shown to play a significant role in signaling pathways involved in other cellular process such as cell proliferation, differentiation, metabolism, DNA repair and apoptosis (Garcia et al., 2006).

Among the targets that PKR has been demonstrated to phosphorylate or directly influence the phosphorylation of are: p53, signal transducer and activators of transcription factors STAT1 and STAT3, inhibitor κB kinase (IKK)-β, inhibitor κB (IκB)-β, the B56α regulatory subunit of PP2A, and RNA helicase (Garcia et al., 2006; Sadler et al., 2009). In addition to these targets, PKR has been shown to influence signaling through the phosphatidylinositol-3 kinase (PI3K)/AKT pathway and transcription factors NF-κB, C/EBPα, C/EBPβ and ATF3. PKR also influences signaling through the MAPK signal transduction pathways. PKR activity is required for activation of p38-MAPK and JNK in response to particular stresses, and signaling through these MAPKs is defective in PKR-/- cells. The PKR dependent mechanism involved in $p38^{MAPK}$and JNK activation may involve the interaction of PKR with ASK1 or MKK6. Additionally, inhibition of protein synthesis may reduce the level of negative regulators of these kinases (Garcia et al., 2006).

Activation

PKR activation was originally thought to occur only in the presence of double-stranded RNA (ex. viral infection). Over time increasing evidence has indicated that PKR activation is induced by cytotoxic cytokines (tumor necrosis factor (TNF)-α and IFNγ), growth factor deprivation, oxidative stress and DNA damage (Garcia et al., 2006).

PKR is potentially serine/threonine and tyrosine phosphorylated on 105 different sites (54 Ser, 33 Thr and 18 Tyr), including 15 suspected autophosphorylation sites. Of these, only 8 sites have so far been identified, and their significance to PKR activation determined. Phosphorylation of Thr451 in the catalytic domain of PKR is required for minimal kinase activity (Romano et al., 1998; Zhang et al., 2001). An additional phosphorylation of PKR on Thr446 serves to augment PKR activity (Romano et al., 1998; Alisi et al., 2005).

In addition to Thr446/451 phosphorylation, phosphorylation on three key tyrosine residues (Tyr101/162/293) is also required for maximal PKR activity (Su et al., 2006). In cell culture, PKR appears to be constitutively tyrosine phosphorylated, but the exact tyrosine sites that are phosphorylated have not been determined nor has the kinase(s) responsible for these phosphorylations. PKR kinase assays using wild-type eIF2α or mutants Ser51Thr or Ser51Tyr revealed that PKR could phosphorylate the residue at position 51 equally (Lu et al., 1999). One suggestion is that PKR possess tyrosine kinase ability and is able to autophosphorylate (Lu et al., 1999). This is supported by the finding that a catalytically-inactive mutant (K296R) of PKR is not tyrosine phosphorylated in vitro and in vivo (Su et al., 2006). More recent, findings indicate PKR is associated with JAK1 and TYK2 kinases in resting cells. Following interferon stimulation, exogenously expressed JAK1 and TYK2 were demonstrated to phosphorylate Tyr101 and Tyr293 (Su et al., 2007). Similarly the catalytic mutant of PKR was also tyrosine phosphorylated by the JAK kinases. As tyrosine phosphorylation of PKR in response to dsRNA is not affected in cells deficient in JAK kinases, other tyrosine kinases may potentially

phosphorylate these sites in response to different stresses (Su et al., 2007).
The role of PKR as a non-receptor tyrosine kinase remains controversial.

eIF2α

In order to properly initiate translation, the eIF2 complex must hydrolyze GTP to GDP in the presence of Met-tRNA and the 40S ribosomal subunit.
Efficient recycling of the complex then involves the removal of GDP and the re-loading of GTP to the eIF2 complex; a process carried-out by the GTP-exchange factor, eIF2B (Kimball et al., 1998). Phosphorylation of the eIF2α subunit turns the eIF2 complex into a competitive inhibitor. Those eIF2 complexes containing phosphorylated eIF2α demonstrate increased affinity for eIF2B and associate, blocking the eIF2 complex in the GDP bound state (Krishnamoorthy et al., 2001). As the eIF2 complex is in excess of eIF2B, a small amount of phosphorylated eIF2α can result in a shut-off of general translation (Kimball et al., 1998; Sudhakar et al., 2000; Krishnamoorthy et al., 2001; Nika et al., 2001; Wek et al., 2006). The inhibition of general translation is mainly thought to be pro-apoptotic, but recent evidence has suggested that this may be a cellular defense mechanism against stresses (Wek et al., 2006).
Phosphorylation of eIF2α results in a shut-off of general translation but at the same time allows for efficient translation of uORFs in particular mRNAs, such as ATF4, due to their 5' structure; or through what is termed internal ribosome entry site (IRES)-mediated translation (Fernandez et al., 2002; Gerlitz et al., 2002; Yaman et al., 2003). Many of these mRNAs encode proteins involved in the stress response (Koschmieder et al., 2007; van den Beucken et al., 2007; Lee et al., 2009). Short-term inhibition of general translation through eIF2α phosphorylation may in fact be pro-survival by allowing for cellular repair following a particular stress (Donze et al., 2004).

p53

PKR was shown to phosphorylate cytoplasmic p53 on Ser392 enhancing p53 tetramer stability and transcriptional activation of p53 targeted genes (Sakaguchi et al., 1997; Cuddihy et al., 1999; Keller et al., 2001). Among these are p21-Cip1, BAX, PUMA and several pro-caspases. The implications of this phosphorylation are a PKR-mediated cell cycle arrest and induction of apoptosis. Inhibition of constitutive PKR activity in several acute leukemia cells lines with a small molecule inhibitor has been observed to lead to p53 degradation (Unpublished results). Although the exact mechanism for p53 degradation has not been determined, it likely involves the activation of AKT, whose phosphorylation and activity are observed to increase, and AKT effects upon MDM2 (Blalock et al., 2009). Additionally, the cellular PKR activator RAX/PACT was demonstrated to result in increased cellular levels of p53, p53 transcriptional activity and growth arrest in a PKR dependent manner (Bennett et al., 2012). Expression of a siRNA to RAX, which blocks the ability of most stresses to activate PKR, resulted in the decreased expression of several p53 regulated genes such as $p21^{Cip1}$and PUMA and lower constitutive levels of p53. RAX resulted in the SUMOylation of p53 in a PKR independent manner, through direct interaction and activation of the E2 ligase Ubc9 (Bennett et al., 2012).

NF-κB

PKR association with inhibitor κB kinase (IKK) was demonstrated to induce NF-κB nuclear translocation and transcriptional activity (Gil et al., 2000; Zamanian-Daryoush, et al., 2000). While initially PKR kinase activity was implicated in the activation of NF-κB, PKR catalytic activity is not a requirement. Truncated forms of PKR consisting of the amino terminus were shown to associate with the IKK complex and stimulate IκBβ phosphorylation (Bonnet et al., 2000; Bonnet et al., 2006). Later, Donze et al. showed that PKR irregardless of catalytic activity could induce NF-κB activation and the synthesis of some NF-κB dependent transcripts, but NF-κB activity and transcription of other NF-κB dependent genes was greatly potentiated when PKR kinase activity remained intact (Donze et al., 2004). These data suggest that both PKR association with IKK and PKR catalytic activity are important for PKR mediated effects on NF-κB. To this end the current understanding is that PKR activity is required for the full effects of PKR on NF-κB, although whether PKR catalytic activity influences NF-κB activation at the point of IκB phosphorylation and release or at later points, has not been sorted-out.

STATs

PKR has also been demonstrated to affect the transactivation of STATs 1 and 3 (Karehed et al., 2007). STAT1 activity is enhanced by phosphorylation on Ser727. Phosphorylation of this site is defective in PKR-/- fibroblasts resulting in a decrease of STAT1 transactivation (Ramana et al., 2000). PKR kinase activity is not necessary for PKR effects on STAT1 (Wong et al., 1997); instead, PKR associates through its NH_2-terminus with STAT1, which apparently enhances mitogen activated protein kinase (MAPK)-mediated phosphorylation of STAT1 on Ser727 (Deb et al., 2001). Similar to STAT1, PKR has also been demonstrated to be required for proper phosphorylation and transactivation of STAT3. Like STAT1, PKR effects were mediated through MAPK-dependent phosphorylation of STAT3 (Deb et al., 2001). In the absence of PKR, activation of STAT3 by platelet derived growth factor (PDGF) is impaired (Deb et al., 2001).

PP2A

PKR was shown in a yeast-two hybrid system to associate with B56α in a manner dependent on PKR catalytic activity.
PKR phosphorylated B56α at multiple sites in vitro (among these Ser28) leading to enhanced PP2A activity (Xu and Williams, 2000).

The enhancement of PP2A activity via PKR phosphorylation of B56α resulted in decreased phosphorylation of eIF4E and a lower rate of translation. More recently additional effects of PKR on PP2A activity have been observed. The lymphocytic leukemia cell line REH contains both elevated levels of active PKR and a BCL2 targeted phosphatase activity. PKR was shown to phosphorylate B56α on Ser28 in REH cells which led to PP2A targeting to the mitochondria and dephosphorylation of BCL2 (Ruvolo et al., 2008). PKR activity was also shown to stabilize B56α, but this stabilization was not dependent on Ser28 phosphorylation but instead on eIF2α phosphorylation.

CDK1

Yoon et al. demonstrated that during genotoxic stress PKR is responsible for phosphorylating Cdc2 (CDK1) on Tyr4. Phosphorylation at this site was shown to result in ubiquitination and proteosomal degradation of Cdc2 thus resulting in a G2 arrest (Yoon et al., 2010).

IRS-1

PKR was found to link chronic inflammatory responses to metabolic signaling through the phosphorylation of the insulin response substrate (IRS)-1 on Ser312.
Phosphorylation at this site inhibits the phosphorylation of key tyrosine residues required for insulin induced signaling (Nakamura et al., 2010; Yang et al., 2010a).

Homology

H. sapiens: (100%)
P. troglodytes: (98%)
C. lupus: (55%)
B. taurus: (62%)
M. musculus: (58%)
R. norvegicus: (51%)
G. gallus: (39%)
D. rerio: (30%)

Mutations

Note

Although the 2p22-p21 locus is often rearranged in leukemia no data supports these alterations affecting EIF2AK2.
A single nucleotide mutation was documented in a single pediatric T-ALL patient.
The mutation occurred in the first double-stranded RNA binding domain and resulted in a protein that could not be activated by polyI:C (Murad et al., 2005).
In a murine model of chronic lymphocytic leukemia (CLL), a rearrangement in one locus of EIF2AK2 results in the deletion of 550 nucleotides and the production of a truncated protein with dominant-negative activity (Abraham et al., 1998).

Germinal

None.

Somatic

- DNA: nt50 (A to G); Protein: aa17 (Tyr to Cys); Source: Pediatric T-ALL; Influence on pathology not determined.
- DNA: nt1872 (C to G); Protein: aa439 (Leu to Val); Source: adenocarcinoma; Influence on pathology not determined.

Single Nucleotide Polymorphisms

SNP analysis revealed V428E (T1840A; source unknown), I506V (A2073G; source unknown).
Additional polymorphisms (1084) identified in the genomic sequence in the locus of EIF2AK2 can be found at PheGenI.

Phosphorylation

	Method of Identification	
Site	Biochem/Mol	Mass Spec
S83	X[a]	X[f,g]
T88	X[a]	
T89	X[a]	X[h]
T90	X[a]	X[h]
S92		X[h]
S93		X[h]
Y101	X[b]	
Y118		X[h]
Y133		X[h]
Y142		X[h]
Y162	X[b]	
S179		X[h]
S181		X[h]
S242	X[a,c]	X[i]
T255	X[a,c]	
T258	X[a,c]	
Y293	X[b]	X[h]
Y346		X[h]
T446	X[c,d]	X[c]
T451	X[c,e]	X[c]
S456		X[g]
S542		X[f]

Ubiquitination		
	Method of Identification	
Site	Biochem/Mol	Mass Spec
K268		X[j]
K299		X[j]
K304		X[h]
K385		X[h]
K388		X[h]
K400		X[j]
K408		X[h]
K416		X[h]
K426		X[j]
K429		X[h]
K440		X[h]
K509		X[h]
K517		X[k]
K521		X[h]
Methylation		
	Method of Identification	
Site	Biochem/Mol	Mass Spec
K61		X[h]
K69		X[h]

Post-translational modification. (Taylor et al., 2001)[a]; (Su et al., 2006)[b]; (Romano et al., 1998)[c]; (Alisi et al., 2005)[d]; (Zhang et al., 2001)[e]; (Olsen et al., 2010)[f]; (Dephoure et al., 2008)[g]; (CST Curation Set Data available from Phosphosite Plus at http://www.phosphosite.org)[h]; (Christensen et al., 2010)[i]; (Kim et al., 2011)[j]; (Wagner et al., 2011)[k].

Implicated in

Myelodysplastic syndromes (MDS)

Note

The presence of phospho-T451 PKR (p-T451 PKR) is slightly elevated in the cytoplasm of bone-marrow mononuclear cells (BMMC) from low-risk/INT-1 MDS patients. In contrast, BMMCs from INT-2/high-risk MDS patients show an enhanced presence of p-T451 PKR with primarily nuclear localization (Follo et al., 2008).

Inhibition of PKR kinase activity or expression reverses the suppressive effects of IFNγ and TNFα on colony formation from CD34+ hematopoietic progenitors and increases hematopoietic colony formation from human isolated MDS progenitors (Sharma et al., 2011).

Loss of PKR expression is observed in 5q- and 5q:31-33 myelodysplasias (Green et al., 1999; Giagounidis et al., 2004).

Disease

Bone marrow failure disorder.

Prognosis

The presence of p-T451 PKR in the cytoplasm is associated with low-risk disease.

The presence of p-T451 PKR in the nucleus is associated with high-risk disease and thus an enhanced probability of progression to acute myelogenous leukemia (AML).

Loss of PKR in 5q- and 5q32-33 myelodysplasias is associated with low-risk disease, while loss of PKR in 5q31 myelodysplasias with complex cytogenetics is associated with high-risk disease.

Oncogenesis

Progression to acute myelogenous leukemia.

Fanconi anemia (FA)

Note

PKR activity is constitutively elevated in bone marrow cells from Fanconi anemia patients and cells lines and contributes to the hypersensitivity of these cells to TNFα and IFNγ (Pang et al., 2001; Zhang et al., 2004).

Inhibition of PKR activity by either expressing a dominant negative PKR kinase or a dominant-negative form of the cellular PKR activator RAX/PACT (S18A) reduces apoptosis and sensitivity to TNFα and IFNγ (Pang et al., 2001; Bennett et al., 2006).

Disease

Bone marrow failure disorder.

Prognosis

Unknown.

Oncogenesis

Progression to acute myelogenous leukemia.

Acute myelogenous leukemia (AML)

Note

PKR is overexpressed in blasts from AML patients, and is a functional kinase (Basu et al., 1997). AML derived cell lines contain elevated levels of p-T451 PKR as compared to control peripheral blood lymphocytes (Blalock et al., 2009).

AML cell lines were highly dependent on PKR activity for cell maintenance as treatment of the cells with the commercial PKR inhibitor resulted in cell cycle arrest and cell death (Blalock et al., 2009).

Disease
Cancer; myelo-/monocytic leukemia.

Prognosis
Unknown.

Oncogenesis
Contributes to cancer cell maintenance.

Acute lymphocytic leukemia (ALL)

Note
PKR is overexpressed in blasts from ALL patients, and is a functional kinase (Basu et al., 1997).
T-ALL derived cell lines contain elevated levels of p-T451 PKR as compared to control peripheral blood lymphocytes (Blalock et al., 2009).
T-ALL cell lines were highly dependent on PKR activity for cell maintenance as treatment of the cells with the commercial PKR inhibitor resulted in cell cycle arrest (Blalock et al., 2009).
A somatic point mutation was detected in the coding region of dsRNA-binding domain I (coding nucleotide 50 (A to G); amino acid Y17C) of PKR in a patient with T-ALL.
Although activation of the mutant PKR kinase by polyI:C was impaired, the exact role of this mutation in the T-ALL was not determined (Murad et al., 2005).

Disease
Cancer; T-cell derived lymphoblastic leukemia.

Prognosis
Unknown.

Cytogenetics
Somatic point mutation in the coding region of dsRNA-binding domain I (coding nucleotide 50 (A to G); amino acid Y17C); Source: T-ALL.

Oncogenesis
Contributes to cancer cell maintenance.

Chronic lymphocytic leukemia (CLL)

Note
PKR mRNA is underexpressed in CLL as compared to controls, and the kinase is inactive due to the presence of a soluble cellular inhibitor (Basu et al., 1997; Hii et al., 2004).

Disease
Cancer; B-cell lymphocytic leukemia.

Prognosis
Unknown.

Lung carcinoma

Note
Elevated phospho-T446 PKR and/or p-S51 eIF2α were associated with longer median survival in patients with non-small cell lung cancer (NSCLC). Combinations of p-PKR/PKR expression or p-eIF2α/PKR expression were valuable prognostic markers for survival (Pataer et al., 2010; He et al., 2011). Lower levels of PKR expression though correlated with aggressive tumor behavior, increased lymph node metastasis and shorter survival in the patients (Pataer et al., 2010).
In contrast to NSCLC, a high level of PKR expression was associated with shorter overall survival in patients with small-size lung adenocarcinomas (Roh et al., 2005).

Disease
Cancer; Non-small cell lung cancer (NSCLC) and small cell adenocarcinoma of the lung.

Prognosis
PKR expression and activation as determined by immunocytochemistry (p-T446 PKR) are associated with a positive prognosis in NSCLC.
PKR expression in small-size lung adenocarcinomas is associated with a poor prognosis.

Oncogenesis
Low levels of PKR expression favor aggressive behavior and metastasis in NSCLC.

Breast carcinoma

Note
Breast carcinoma cells contain elevated PKR protein and activity (7-40 fold) as compared to controls (Kim et al., 2000; Nussbaum et al., 2003). Stimulation of the PKR promoter ISRE is responsible for enhanced PKR expression (Nussbaum et al., 2003).
Elevated PKR activity is further linked to macrophage-migration inhibitory factor (MIF) expression which favors breast cancer cell growth, but also sensitizes breast cancer cells to PKR-mediated killing as the system is already primed (Armstrong et al., 2008; Pervin et al., 2008).
PKR may assist in the therapeutic response of 5'Florourocil (5'FU) in p53-null breast cancer (Garcia et al., 2011).

Disease
Cancer; breast.

Prognosis
Unknown.

Oncogenesis
Activated PKR may promote growth of breast carcinoma cells.

Colon carcinoma

Note
Elevated PKR expression and activity are associated with progressive transformation from normal mucosa to adenoma and colon carcinoma (Kim et al., 2002).
The activation state of PKR also influences the drug sensitivity of colon cancer cells (Yoon et al., 2009; Yang et al., 2010b; Garcia et al., 2011).

Disease
Cancer; colon adenoma and colon carcinoma.

Prognosis
Unknown; associated with progressive transformation and drug-sensitivity.

Oncogenesis
Progressive transformation to adenomas or carcinomas.

Melanoma

Note
Melanomas contain elevated levels of PKR protein, p-S51 eIF2α and PKR activity as compared to controls (Kim et al., 2002).
PKR was highly expressed in melanoma lymph node metastasis (Kim et al., 2002).
Knock-down of PKR mRNA and protein in B16-F10 melanoma tumor cells using shRNA led to decreased metastatic nodes in mice (Delgado Andre and De Lucca, 2007).

Disease
Cancer; skin (melanoma).

Prognosis
Elevated PKR activity associated with disease progression and metastasis.

Oncogenesis
Elevated PKR expression and activity are associated with metastasis.

Thyroid cancer

Note
PKR is overexpressed in 90% of thyroid cancers, and its expression is higher in papillary versus nonpapillary carcinoma.
Elevated PKR expression was associated with vascular invasion and satellite tumor nodules. PKR expression was linked to a low proliferative activity of the tumor (Terada et al., 2000a).

Disease
Cancer; thyroid.

Prognosis
Unknown.

Oncogenesis
Increased invasiveness and satellite tumor formation.

Pancreatic cancer

Note
PKR is upregulated during interferon treatment of pancreatic cancer where lower PKR expression predicted a shorter anti-cancer response and length of survival following IFN treatment (Zhou et al., 1998).

Disease
Cancer; neuroendocrine.

Prognosis
Enhanced expression is associated with a favorable outcome to interferon therapy. Could represent a prognostic indicator.

Oncogenesis
Role uncharacterized.

Gastric cancer

Note
Levels of phosphorylated forms of PKR and eIF2α were elevated in the rectus abdominus muscle of oesophago-gastric cancer patients as compared to control (Eley et al., 2008).

Disease
Cancer-related cachexia.

Prognosis
Poor; Phospho-PKR and Phospho-eIF2α are associated with muscle wasting.

Rectal carcinoma

Note
PKR protein expression is associated with smaller sized tumors, a lower relapse rate and greater 5-year disease-free and overall survival (Kwon et al., 2005).

Disease
Cancer; lymph node negative rectal carcinoma.

Prognosis
Favorable; PKR expression is associated with a lower relapse rate and higher disease free and overall survival.

Oncogenesis
Role uncharacterized.

Hepatocellular carcinoma (HCC)

Note
PKR mRNA and protein are overexpressed and PKR kinase activity enhanced in hepatocellular carcinoma (Hiasa et al., 2003; Alisi et al., 2005). PKR protein levels were observed to increase in bile duct tissue during progression to carcinoma, and this increase was associated with duct inflammation and duct cell proliferation (Terada et al., 2000b).
Increased PKR expression was associated with both chronic hepatitis and HCC (Shimada et al., 1998).
Importantly, elevated PKR expression is associated with better differentiated HCC and cholangiocarcinoma (Shimada et al., 1998; Terada et al., 2000b).
The core protein of hepatitis C virus (HCV), a major contributor to HCC, was seen to bind to and activate PKR (pT446) in HCC cells and tissue (Delhem et al., 2001; Alisi et al., 2005).
In contrast, hepatitis B virus infected HCC liver tissue showed decreased PKR expression as determined by real-time PCR and immunohistochemistry and no association between the status of tumor differentiation was observed (Chen et al., 2004).

Disease
Cancer; hepatocellular carcinoma (HCC) HCV-associated HCC, HBV-associated HCC.

Oncogenesis
Expression increases with progression toward HCC but is associated with better differentiated tumors (except in HBV-associated HCC).

Alzheimer's disease

Note

Phospho-PKR accumulates in the nuclei of AD brain tissue (Onuki et al., 2004).

Neurons from AD patient brains contain elevated levels of p-T446 and/or T451 PKR, and p-S51 eIF2α (Peel and Bredesen, 2003; Suen et al., 2003) and treatment of cell lines with Aβ peptide results in PKR activation, eIF2α phosphorylation and the co-localization of p-PKR with Redd1 and FADD in the nucleus (Suen et al., 2003; Morel et al., 2009b; Couturier et al., 2010a).

Phospho-PKR is associated with phospho-Tau and phospho-p38 in AD brain (Peel and Bredesen, 2003).

Inhibition of PKR attenuates inflammation as well as TNFα, IL-1α, IL-1β, IL-6 expression and apoptosis stimulated by Aβ peptide (Couturier et al., 2010b; Couturier et al., 2011).

Elevated levels of p-PKR, p-eIF2α and secretion of TNFα, IL-1α, IL-1β and IL-6 are observed in peripheral blood mononuclear cells from AD patients (Morel et al., 2009a; Couturier et al., 2010b).

Disease

Neurodegenerative.

Prognosis

The presence of elevated p-PKR in brain neuronal tissue is an indicator of cellular stress and degeneration. Possible disease indicator.

An EIF2AK2 SNP (C/T; rs2254958) at position 250 in the 5'UTR was found to be associated with Alzheimer's disease (Bullido et al., 2008).

Cytogenetics

Alzheimer's associated EIF2AK2 SNP (C/T; rs2254958).

Parkinson's disease (PD)

Note

Hippocampal neurons from PD patients contain elevated levels of nuclear p-T446 PKR (Bando et al., 2005).

Disease

Neurodegenerative.

Prognosis

Unknown.

Huntington chorea

Note

PKR binds CAG repeats in mutated Huntington transcripts.

Affected Huntington tissues contain elevated levels of p-PKR (active) with a particular increase in the nuclei of hippocampal neurons (Peel et al., 2001; Bando et al., 2005).

Disease

Neurodegenerative.

Prognosis

Unknown.

Creutzfeldt-Jakob disease (CJD)

Note

Neuronal tissue (frontal, occipital, temporal cortex, striatum and cerebellum) from CJD patients contained elevated levels of p-T451 PKR localized exclusively to the nucleus.

The levels of p-T451 PKR were associated with apoptosis, spongiosis, astrocytosis and disease severity (Paquet et al., 2009).

Disease

Neurodegenerative.

Prognosis

The levels of p-T451 PKR are associated with disease severity in CJD patients.

Amyotrophic lateral sclerosis (ALS)

Note

The presence of p-T451 PKR increases in spinal cord tissue from ALS patients 2600% (cytosolic) and 3300% (particulate) as compared to controls (Hu et al., 2003).

Disease

Neurodegenerative.

Prognosis

Unknown.

References

Roberts WK, Hovanessian A, Brown RE, Clemens MJ, Kerr IM. Interferon-mediated protein kinase and low-molecular-weight inhibitor of protein synthesis. Nature. 1976a Dec 2;264(5585):477-80

Roberts WK, Clemens MJ, Kerr IM. Interferon-induced inhibition of protein synthesis in L-cell extracts: an ATP-dependent step in the activation of an inhibitor by double-stranded RNA. Proc Natl Acad Sci U S A. 1976b Sep;73(9):3136-40

Colthurst DR, Campbell DG, Proud CG. Structure and regulation of eukaryotic initiation factor eIF-2. Sequence of the site in the alpha subunit phosphorylated by the haem-controlled repressor and by the double-stranded RNA-activated inhibitor. Eur J Biochem. 1987 Jul 15;166(2):357-63

Kuhen KL, Shen X, Carlisle ER, Richardson AL, Weier HU, Tanaka H, Samuel CE. Structural organization of the human gene (PKR) encoding an interferon-inducible RNA-dependent protein kinase (PKR) and differences from its mouse homolog. Genomics. 1996 Aug 15;36(1):197-201

Basu S, Panayiotidis P, Hart SM, He LZ, Man A, Hoffbrand AV, Ganeshaguru K. Role of double-stranded RNA-activated protein kinase in human hematological malignancies. Cancer Res. 1997 Mar 1;57(5):943-7

Kuhen KL, Samuel CE. Isolation of the interferon-inducible RNA-dependent protein kinase Pkr promoter and identification of a novel DNA element within the 5'-flanking region of human and mouse Pkr genes. Virology. 1997 Jan 6;227(1):119-30

Sakaguchi K, Sakamoto H, Lewis MS, Anderson CW, Erickson JW, Appella E, Xie D. Phosphorylation of serine 392 stabilizes the tetramer formation of tumor suppressor protein p53. Biochemistry. 1997 Aug 19;36(33):10117-24

Wong AH, Tam NW, Yang YL, Cuddihy AR, Li S, Kirchhoff S, Hauser H, Decker T, Koromilas AE. Physical association

between STAT1 and the interferon-inducible protein kinase PKR and implications for interferon and double-stranded RNA signaling pathways. EMBO J. 1997 Mar 17;16(6):1291-304

Abraham N, Jaramillo ML, Duncan PI, Méthot N, Icely PL, Stojdl DF, Barber GN, Bell JC. The murine PKR tumor suppressor gene is rearranged in a lymphocytic leukemia. Exp Cell Res. 1998 Nov 1;244(2):394-404

Kimball SR, Fabian JR, Pavitt GD, Hinnebusch AG, Jefferson LS. Regulation of guanine nucleotide exchange through phosphorylation of eukaryotic initiation factor eIF2alpha. Role of the alpha- and delta-subunits of eiF2b. J Biol Chem. 1998 May 22;273(21):12841-5

Kuhen KL, Vessey JW, Samuel CE. Mechanism of interferon action: identification of essential positions within the novel 15-base-pair KCS element required for transcriptional activation of the RNA-dependent protein kinase pkr gene. J Virol. 1998 Dec;72(12):9934-9

Romano PR, Garcia-Barrio MT, Zhang X, Wang Q, Taylor DR, Zhang F, Herring C, Mathews MB, Qin J, Hinnebusch AG. Autophosphorylation in the activation loop is required for full kinase activity in vivo of human and yeast eukaryotic initiation factor 2alpha kinases PKR and GCN2. Mol Cell Biol. 1998 Apr;18(4):2282-97

Shi Y, Vattem KM, Sood R, An J, Liang J, Stramm L, Wek RC. Identification and characterization of pancreatic eukaryotic initiation factor 2 alpha-subunit kinase, PEK, involved in translational control. Mol Cell Biol. 1998 Dec;18(12):7499-509

Shimada A, Shiota G, Miyata H, Kamahora T, Kawasaki H, Shiraki K, Hino S, Terada T. Aberrant expression of double-stranded RNA-dependent protein kinase in hepatocytes of chronic hepatitis and differentiated hepatocellular carcinoma. Cancer Res. 1998 Oct 1;58(19):4434-8

Zhou Y, Gobl A, Wang S, Jacobsen MB, Janson ET, Haines GK 3rd, Radosevich JA, Oberg K. Expression of p68 protein kinase and its prognostic significance during IFN-alpha therapy in patients with carcinoid tumours. Eur J Cancer. 1998 Dec;34(13):2046-52

Berlanga JJ, Santoyo J, De Haro C. Characterization of a mammalian homolog of the GCN2 eukaryotic initiation factor 2alpha kinase. Eur J Biochem. 1999 Oct;265(2):754-62

Cuddihy AR, Wong AH, Tam NW, Li S, Koromilas AE. The double-stranded RNA activated protein kinase PKR physically associates with the tumor suppressor p53 protein and phosphorylates human p53 on serine 392 in vitro. Oncogene. 1999 Apr 29;18(17):2690-702

Green WB, Slovak ML, Chen IM, Pallavicini M, Hecht JL, Willman CL. Lack of IRF-1 expression in acute promyelocytic leukemia and in a subset of acute myeloid leukemias with del(5)(q31). Leukemia. 1999 Dec;13(12):1960-71

Kawakubo K, Kuhen KL, Vessey JW, George CX, Samuel CE. Alternative splice variants of the human PKR protein kinase possessing different 5'-untranslated regions: expression in untreated and interferon-treated cells and translational activity. Virology. 1999 Nov 10;264(1):106-14

Kuhen KL, Samuel CE. Mechanism of interferon action: functional characterization of positive and negative regulatory domains that modulate transcriptional activation of the human RNA-dependent protein kinase Pkr promoter. Virology. 1999 Feb 1;254(1):182-95

Lu J, O'Hara EB, Trieselmann BA, Romano PR, Dever TE. The interferon-induced double-stranded RNA-activated protein kinase PKR will phosphorylate serine, threonine, or tyrosine at residue 51 in eukaryotic initiation factor 2alpha. J Biol Chem. 1999 Nov 5;274(45):32198-203

Williams BR. PKR; a sentinel kinase for cellular stress. Oncogene. 1999 Nov 1;18(45):6112-20

Bonnet MC, Weil R, Dam E, Hovanessian AG, Meurs EF. PKR stimulates NF-kappaB irrespective of its kinase function by interacting with the IkappaB kinase complex. Mol Cell Biol. 2000 Jul;20(13):4532-42

Gil J, Alcamí J, Esteban M. Activation of NF-kappa B by the dsRNA-dependent protein kinase, PKR involves the I kappa B kinase complex. Oncogene. 2000 Mar 9;19(11):1369-78

Kim SH, Forman AP, Mathews MB, Gunnery S. Human breast cancer cells contain elevated levels and activity of the protein kinase, PKR. Oncogene. 2000 Jun 22;19(27):3086-94

Ramana CV, Grammatikakis N, Chernov M, Nguyen H, Goh KC, Williams BR, Stark GR. Regulation of c-myc expression by IFN-gamma through Stat1-dependent and -independent pathways. EMBO J. 2000 Jan 17;19(2):263-72

Sudhakar A, Ramachandran A, Ghosh S, Hasnain SE, Kaufman RJ, Ramaiah KV. Phosphorylation of serine 51 in initiation factor 2 alpha (eIF2 alpha) promotes complex formation between eIF2 alpha(P) and eIF2B and causes inhibition in the guanine nucleotide exchange activity of eIF2B. Biochemistry. 2000 Oct 24;39(42):12929-38

Terada T, Maeta H, Endo K, Ohta T. Protein expression of double-stranded RNA-activated protein kinase in thyroid carcinomas: correlations with histologic types, pathologic parameters, and Ki-67 labeling. Hum Pathol. 2000a Jul;31(7):817-21

Terada T, Ueyama J, Ukita Y, Ohta T. Protein expression of double-stranded RNA-activated protein kinase (PKR) in intrahepatic bile ducts in normal adult livers, fetal livers, primary biliary cirrhosis, hepatolithiasis and intrahepatic cholangiocarcinoma. Liver. 2000b Dec;20(6):450-7

Xu Z, Williams BR. The B56alpha regulatory subunit of protein phosphatase 2A is a target for regulation by double-stranded RNA-dependent protein kinase PKR. Mol Cell Biol. 2000 Jul;20(14):5285-99

Zamanian-Daryoush M, Mogensen TH, DiDonato JA, Williams BR. NF-kappaB activation by double-stranded-RNA-activated protein kinase (PKR) is mediated through NF-kappaB-inducing kinase and IkappaB kinase. Mol Cell Biol. 2000 Feb;20(4):1278-90

Deb A, Zamanian-Daryoush M, Xu Z, Kadereit S, Williams BR. Protein kinase PKR is required for platelet-derived growth factor signaling of c-fos gene expression via Erks and Stat3. EMBO J. 2001 May 15;20(10):2487-96

Delhem N, Sabile A, Gajardo R, Podevin P, Abadie A, Blaton MA, Kremsdorf D, Beretta L, Brechot C. Activation of the interferon-inducible protein kinase PKR by hepatocellular carcinoma derived-hepatitis C virus core protein. Oncogene. 2001 Sep 13;20(41):5836-45

Keller DM, Zeng X, Wang Y, Zhang QH, Kapoor M, Shu H, Goodman R, Lozano G, Zhao Y, Lu H. A DNA damage-induced p53 serine 392 kinase complex contains CK2, hSpt16, and SSRP1. Mol Cell. 2001 Feb;7(2):283-92

Krishnamoorthy T, Pavitt GD, Zhang F, Dever TE, Hinnebusch AG. Tight binding of the phosphorylated alpha subunit of initiation factor 2 (eIF2alpha) to the regulatory subunits of guanine nucleotide exchange factor eIF2B is required for inhibition of translation initiation. Mol Cell Biol. 2001 Aug;21(15):5018-30

Nika J, Rippel S, Hannig EM. Biochemical analysis of the eIF2beta gamma complex reveals a structural function for eIF2alpha in catalyzed nucleotide exchange. J Biol Chem. 2001 Jan 12;276(2):1051-6

Pang Q, Keeble W, Diaz J, Christianson TA, Fagerlie S, Rathbun K, Faulkner GR, O'Dwyer M, Bagby GC Jr. Role of double-stranded RNA-dependent protein kinase in mediating hypersensitivity of Fanconi anemia complementation group C cells to interferon gamma, tumor necrosis factor-alpha, and double-stranded RNA. Blood. 2001 Mar 15;97(6):1644-52

Peel AL, Rao RV, Cottrell BA, Hayden MR, Ellerby LM, Bredesen DE. Double-stranded RNA-dependent protein kinase, PKR, binds preferentially to Huntington's disease (HD) transcripts and is activated in HD tissue. Hum Mol Genet. 2001 Jul 15;10(15):1531-8

Taylor DR, Tian B, Romano PR, Hinnebusch AG, Lai MM, Mathews MB. Hepatitis C virus envelope protein E2 does not inhibit PKR by simple competition with autophosphorylation sites in the RNA-binding domain. J Virol. 2001 Feb;75(3):1265-73

Zhang F, Romano PR, Nagamura-Inoue T, Tian B, Dever TE, Mathews MB, Ozato K, Hinnebusch AG. Binding of double-stranded RNA to protein kinase PKR is required for dimerization and promotes critical autophosphorylation events in the activation loop. J Biol Chem. 2001 Jul 6;276(27):24946-58

Fernandez J, Yaman I, Merrick WC, Koromilas A, Wek RC, Sood R, Hensold J, Hatzoglou M. Regulation of internal ribosome entry site-mediated translation by eukaryotic initiation factor-2alpha phosphorylation and translation of a small upstream open reading frame. J Biol Chem. 2002 Jan 18;277(3):2050-8

Gerlitz G, Jagus R, Elroy-Stein O. Phosphorylation of initiation factor-2 alpha is required for activation of internal translation initiation during cell differentiation. Eur J Biochem. 2002 Jun;269(11):2810-9

Kim SH, Gunnery S, Choe JK, Mathews MB. Neoplastic progression in melanoma and colon cancer is associated with increased expression and activity of the interferon-inducible protein kinase, PKR. Oncogene. 2002 Dec 12;21(57):8741-8

Ward SV, Samuel CE. Regulation of the interferon-inducible PKR kinase gene: the KCS element is a constitutive promoter element that functions in concert with the interferon-stimulated response element. Virology. 2002 Apr 25;296(1):136-46

Hiasa Y, Kamegaya Y, Nuriya H, Onji M, Kohara M, Schmidt EV, Chung RT. Protein kinase R is increased and is functional in hepatitis C virus-related hepatocellular carcinoma. Am J Gastroenterol. 2003 Nov;98(11):2528-34

Hu JH, Zhang H, Wagey R, Krieger C, Pelech SL. Protein kinase and protein phosphatase expression in amyotrophic lateral sclerosis spinal cord. J Neurochem. 2003 Apr;85(2):432-42

Nussbaum JM, Major M, Gunnery S. Transcriptional upregulation of interferon-induced protein kinase, PKR, in breast cancer. Cancer Lett. 2003 Jul 10;196(2):207-16

Peel AL, Bredesen DE. Activation of the cell stress kinase PKR in Alzheimer's disease and human amyloid precursor protein transgenic mice. Neurobiol Dis. 2003 Oct;14(1):52-62

Suen KC, Yu MS, So KF, Chang RC, Hugon J. Upstream signaling pathways leading to the activation of double-stranded RNA-dependent serine/threonine protein kinase in beta-amyloid peptide neurotoxicity. J Biol Chem. 2003 Dec 12;278(50):49819-27

Ward SV, Samuel CE. The PKR kinase promoter binds both Sp1 and Sp3, but only Sp3 functions as part of the interferon-inducible complex with ISGF-3 proteins. Virology. 2003 Sep 1;313(2):553-66

Yaman I, Fernandez J, Liu H, Caprara M, Komar AA, Koromilas AE, Zhou L, Snider MD, Scheuner D, Kaufman RJ, Hatzoglou M. The zipper model of translational control: a small upstream ORF is the switch that controls structural remodeling of an mRNA leader. Cell. 2003 May 16;113(4):519-31

Chen GG, Lai PB, Ho RL, Chan PK, Xu H, Wong J, Lau WY. Reduction of double-stranded RNA-activated protein kinase in hepatocellular carcinoma associated with hepatitis B virus. J Med Virol. 2004 Jun;73(2):187-94

Donzé O, Deng J, Curran J, Sladek R, Picard D, Sonenberg N. The protein kinase PKR: a molecular clock that sequentially activates survival and death programs. EMBO J. 2004 Feb 11;23(3):564-71

Gerhard DS, Wagner L, Feingold EA, Shenmen CM, Grouse LH, Schuler G, Klein SL, Old S, Rasooly R, Good P, Guyer M, Peck AM, Derge JG, Lipman D, Collins FS, Jang W, Sherry S, Feolo M, Misquitta L, Lee E, Rotmistrovsky K, Greenhut SF, Schaefer CF, Buetow K, Bonner TI, Haussler D, Kent J, Kiekhaus M, Furey T, Brent M, Prange C, Schreiber K, Shapiro N, Bhat NK, Hopkins RF, Hsie F, Driscoll T, Soares MB, Casavant TL, Scheetz TE, Brown-stein MJ, Usdin TB, Toshiyuki S, Carninci P, Piao Y, Dudekula DB, Ko MS, Kawakami K, Suzuki Y, Sugano S, Gruber CE, Smith MR, Simmons B, Moore T, Waterman R, Johnson SL, Ruan Y, Wei CL, Mathavan S, Gunaratne PH, Wu J, Garcia AM, Hulyk SW, Fuh E, Yuan Y, Sneed A, Kowis C, Hodgson A, Muzny DM, McPherson J, Gibbs RA, Fahey J, Helton E, Ketteman M, Madan A, Rodrigues S, Sanchez A, Whiting M, Madari A, Young AC, Wetherby KD, Granite SJ, Kwong PN, Brinkley CP, Pearson RL, Bouffard GG, Blakesly RW, Green ED, Dickson MC, Rodriguez AC, Grimwood J, Schmutz J, Myers RM, Butterfield YS, Griffith M, Griffith OL, Krzywinski MI, Liao N, Morin R, Palmquist D, Petrescu AS, Skalska U, Smailus DE, Stott JM, Schnerch A, Schein JE, Jones SJ, Holt RA, Baross A, Marra MA, Clifton S, Makowski KA, Bosak S, Malek J. The status, quality, and expansion of the NIH full-length cDNA project: the Mammalian Gene Collection (MGC). Genome Res. 2004 Oct;14(10B):2121-7

Giagounidis AA, Germing U, Haase S, Hildebrandt B, Schlegelberger B, Schoch C, Wilkens L, Heinsch M, Willems H, Aivado M, Aul C. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. Leukemia. 2004 Jan;18(1):113-9

Hii SI, Hardy L, Crough T, Payne EJ, Grimmett K, Gill D, McMillan NA. Loss of PKR activity in chronic lymphocytic leukemia. Int J Cancer. 2004 Apr 10;109(3):329-35

Onuki R, Bando Y, Suyama E, Katayama T, Kawasaki H, Baba T, Tohyama M, Taira K. An RNA-dependent protein kinase is involved in tunicamycin-induced apoptosis and Alzheimer's disease. EMBO J. 2004 Feb 25;23(4):959-68

Peel AL. PKR activation in neurodegenerative disease. J Neuropathol Exp Neurol. 2004 Feb;63(2):97-105

Zhang X, Li J, Sejas DP, Rathbun KR, Bagby GC, Pang Q. The Fanconi anemia proteins functionally interact with the protein kinase regulated by RNA (PKR). J Biol Chem. 2004 Oct 15;279(42):43910-9

Alisi A, Mele R, Spaziani A, Tavolaro S, Palescandolo E, Balsano C. Thr 446 phosphorylation of PKR by HCV core protein deregulates G2/M phase in HCC cells. J Cell Physiol. 2005 Oct;205(1):25-31

Bando Y, Onuki R, Katayama T, Manabe T, Kudo T, Taira K, Tohyama M. Double-strand RNA dependent protein kinase (PKR) is involved in the extrastriatal degeneration in Parkinson's disease and Huntington's disease. Neurochem Int. 2005 Jan;46(1):11-8

Kwon HC, Moon CH, Kim SH, Choi HJ, Lee HS, Roh MS, Hwang TH, Kim JS, Kim HJ. Expression of double-stranded RNA-activated protein kinase (PKR) and its prognostic significance in lymph node negative rectal cancer. Jpn J Clin Oncol. 2005 Sep;35(9):545-50

Murad JM, Tone LG, de Souza LR, De Lucca FL. A point mutation in the RNA-binding domain I results in decrease of PKR activation in acute lymphoblastic leukemia. Blood Cells Mol Dis. 2005 Jan-Feb;34(1):1-5

Roh MS, Kwak JY, Kim SJ, Lee HW, Kwon HC, Hwang TH, Choi PJ, Hong YS. Expression of double-stranded RNA-activated protein kinase in small-size peripheral adenocarcinoma of the lung. Pathol Int. 2005 Nov;55(11):688-93

Bennett RL, Blalock WL, Abtahi DM, Pan Y, Moyer SA, May WS. RAX, the PKR activator, sensitizes cells to inflammatory cytokines, serum withdrawal, chemotherapy, and viral infection. Blood. 2006 Aug 1;108(3):821-9

Bonnet MC, Daurat C, Ottone C, Meurs EF. The N-terminus of PKR is responsible for the activation of the NF-kappaB signaling pathway by interacting with the IKK complex. Cell Signal. 2006 Nov;18(11):1865-75

García MA, Gil J, Ventoso I, Guerra S, Domingo E, Rivas C, Esteban M. Impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. Microbiol Mol Biol Rev. 2006 Dec;70(4):1032-60

Su Q, Wang S, Baltzis D, Qu LK, Wong AH, Koromilas AE. Tyrosine phosphorylation acts as a molecular switch to full-scale activation of the eIF2alpha RNA-dependent protein kinase. Proc Natl Acad Sci U S A. 2006 Jan 3;103(1):63-8

Wek RC, Jiang HY, Anthony TG. Coping with stress: eIF2 kinases and translational control. Biochem Soc Trans. 2006 Feb;34(Pt 1):7-11

Chen JJ. Regulation of protein synthesis by the heme-regulated eIF2alpha kinase: relevance to anemias. Blood. 2007 Apr 1;109(7):2693-9

Delgado André N, De Lucca FL. Knockdown of PKR expression by RNAi reduces pulmonary metastatic potential of B16-F10 melanoma cells in mice: possible role of NF-kappaB. Cancer Lett. 2007 Dec 8;258(1):118-25

Kårehed K, Dimberg A, Dahl S, Nilsson K, Oberg F. IFN-gamma-induced upregulation of Fcgamma-receptor-I during activation of monocytic cells requires the PKR and NFkappaB pathways. Mol Immunol. 2007 Jan;44(4):615-24

Koschmieder S, D'Alò F, Radomska H, Schöneich C, Chang JS, Konopleva M, Kobayashi S, Levantini E, Suh N, Di Ruscio A, Voso MT, Watt JC, Santhanam R, Sargin B, Kantarjian H, Andreeff M, Sporn MB, Perrotti D, Berdel WE, Müller-Tidow C, Serve H, Tenen DG. CDDO induces granulocytic differentiation of myeloid leukemic blasts through translational up-regulation of p42 CCAAT enhancer binding protein alpha. Blood. 2007 Nov 15;110(10):3695-705

Su Q, Wang S, Baltzis D, Qu LK, Raven JF, Li S, Wong AH, Koromilas AE. Interferons induce tyrosine phosphorylation of the eIF2alpha kinase PKR through activation of Jak1 and Tyk2. EMBO Rep. 2007 Mar;8(3):265-70

van den Beucken T, Magagnin MG, Savelkouls K, Lambin P, Koritzinsky M, Wouters BG. Regulation of Cited2 expression provides a functional link between translational and transcriptional responses during hypoxia. Radiother Oncol. 2007 Jun;83(3):346-52

Armstrong ME, Gantier M, Li L, Chung WY, McCann A, Baugh JA, Donnelly SC. Small interfering RNAs induce macrophage migration inhibitory factor production and proliferation in breast cancer cells via a double-stranded RNA-dependent protein kinase-dependent mechanism. J Immunol. 2008 Jun 1;180(11):7125-33

Bullido MJ, Martínez-García A, Tenorio R, Sastre I, Muñoz DG, Frank A, Valdivieso F. Double stranded RNA activated EIF2 alpha kinase (EIF2AK2; PKR) is associated with Alzheimer's disease. Neurobiol Aging. 2008 Aug;29(8):1160-6

Dephoure N, Zhou C, Villén J, Beausoleil SA, Bakalarski CE, Elledge SJ, Gygi SP. A quantitative atlas of mitotic phosphorylation. Proc Natl Acad Sci U S A. 2008 Aug 5;105(31):10762-7

Eley HL, Skipworth RJ, Deans DA, Fearon KC, Tisdale MJ. Increased expression of phosphorylated forms of RNA-dependent protein kinase and eukaryotic initiation factor 2alpha may signal skeletal muscle atrophy in weight-losing cancer patients. Br J Cancer. 2008 Jan 29;98(2):443-9

Follo MY, Finelli C, Mongiorgi S, Clissa C, Bosi C, Martinelli G, Blalock WL, Cocco L, Martelli AM. PKR is activated in MDS patients and its subcellular localization depends on disease severity. Leukemia. 2008 Dec;22(12):2267-9

Pervin S, Tran AH, Zekavati S, Fukuto JM, Singh R, Chaudhuri G. Increased susceptibility of breast cancer cells to stress mediated inhibition of protein synthesis. Cancer Res. 2008 Jun 15;68(12):4862-74

Ruvolo VR, Kurinna SM, Karanjeet KB, Schuster TF, Martelli AM, McCubrey JA, Ruvolo PP. PKR regulates B56(alpha)-mediated BCL2 phosphatase activity in acute lymphoblastic leukemia-derived REH cells. J Biol Chem. 2008 Dec 19;283(51):35474-85

Blalock WL, Grimaldi C, Fala F, Follo M, Horn S, Basecke J, Martinelli G, Cocco L, Martelli AM. PKR activity is required for acute leukemic cell maintenance and growth: a role for PKR-mediated phosphatase activity to regulate GSK-3 phosphorylation. J Cell Physiol. 2009 Oct;221(1):232-41

Eley HL, McDonald PS, Russell ST, Tisdale MJ. Inhibition of activation of dsRNA-dependent protein kinase and tumour growth inhibition. Cancer Chemother Pharmacol. 2009 Mar;63(4):651-9

Lee YY, Cevallos RC, Jan E. An upstream open reading frame regulates translation of GADD34 during cellular stresses that induce eIF2alpha phosphorylation. J Biol Chem. 2009 Mar 13;284(11):6661-73

Morel M, Couturier J, Lafay-Chebassier C, Paccalin M, Page G. PKR, the double stranded RNA-dependent protein kinase as a critical target in Alzheimer's disease. J Cell Mol Med. 2009a Aug;13(8A):1476-88

Morel M, Couturier J, Pontcharraud R, Gil R, Fauconneau B, Paccalin M, Page G. Evidence of molecular links between PKR and mTOR signalling pathways in Abeta neurotoxicity: role of p53, Redd1 and TSC2. Neurobiol Dis. 2009b Oct;36(1):151-61

Paquet C, Bose A, Polivka M, Peoc'h K, Brouland JP, Keohane C, Hugon J, Gray F. Neuronal phosphorylated RNA-dependent protein kinase in Creutzfeldt-Jakob disease. J Neuropathol Exp Neurol. 2009 Feb;68(2):190-8

Sadler AJ, Latchoumanin O, Hawkes D, Mak J, Williams BR. An antiviral response directed by PKR phosphorylation of the RNA helicase A. PLoS Pathog. 2009 Feb;5(2):e1000311

Yoon CH, Lee ES, Lim DS, Bae YS. PKR, a p53 target gene, plays a crucial role in the tumor-suppressor function of p53. Proc Natl Acad Sci U S A. 2009 May 12;106(19):7852-7

Christensen GL, Kelstrup CD, Lyngsø C, Sarwar U, Bøgebo R, Sheikh SP, Gammeltoft S, Olsen JV, Hansen JL. Quantitative phosphoproteomics dissection of seven-transmembrane

receptor signaling using full and biased agonists. Mol Cell Proteomics. 2010 Jul;9(7):1540-53

Couturier J, Morel M, Pontcharraud R, Gontier V, Fauconneau B, Paccalin M, Page G. Interaction of double-stranded RNA-dependent protein kinase (PKR) with the death receptor signaling pathway in amyloid beta (Abeta)-treated cells and in APPSLPS1 knock-in mice. J Biol Chem. 2010a Jan 8;285(2):1272-82

Couturier J, Page G, Morel M, Gontier C, Claude J, Pontcharraud R, Fauconneau B, Paccalin M. Inhibition of double-stranded RNA-dependent protein kinase strongly decreases cytokine production and release in peripheral blood mononuclear cells from patients with Alzheimer's disease. J Alzheimers Dis. 2010b;21(4):1217-31

Nakamura T, Furuhashi M, Li P, Cao H, Tuncman G, Sonenberg N, Gorgun CZ, Hotamisligil GS. Double-stranded RNA-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. Cell. 2010 Feb 5;140(3):338-48

Olsen JV, Vermeulen M, Santamaria A, Kumar C, Miller ML, Jensen LJ, Gnad F, Cox J, Jensen TS, Nigg EA, Brunak S, Mann M. Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis. Sci Signal. 2010 Jan 12;3(104):ra3

Pataer A, Raso MG, Correa AM, Behrens C, Tsuta K, Solis L, Fang B, Roth JA, Wistuba II, Swisher SG. Prognostic significance of RNA-dependent protein kinase on non-small cell lung cancer patients. Clin Cancer Res. 2010 Nov 15;16(22):5522-8

Yang X, Nath A, Opperman MJ, Chan C. The double-stranded RNA-dependent protein kinase differentially regulates insulin receptor substrates 1 and 2 in HepG2 cells. Mol Biol Cell. 2010a Oct 1;21(19):3449-58

Yang H, Park SH, Choi HJ, Moon Y. The integrated stress response-associated signals modulates intestinal tumor cell growth by NSAID-activated gene 1 (NAG-1/MIC-1/PTGF-beta). Carcinogenesis. 2010b Apr;31(4):703-11

Yoon CH, Miah MA, Kim KP, Bae YS. New Cdc2 Tyr 4 phosphorylation by dsRNA-activated protein kinase triggers Cdc2 polyubiquitination and G2 arrest under genotoxic stresses. EMBO Rep. 2010 May;11(5):393-9

Couturier J, Paccalin M, Morel M, Terro F, Milin S, Pontcharraud R, Fauconneau B, Page G. Prevention of the β-amyloid peptide-induced inflammatory process by inhibition of double-stranded RNA-dependent protein kinase in primary murine mixed co-cultures. J Neuroinflammation. 2011 Jun 23;8:72

García MA, Carrasco E, Aguilera M, Alvarez P, Rivas C, Campos JM, Prados JC, Calleja MA, Esteban M, Marchal JA, Aránega A. The chemotherapeutic drug 5-fluorouracil promotes PKR-mediated apoptosis in a p53-independent manner in colon and breast cancer cells. PLoS One. 2011;6(8):e23887

He Y, Correa AM, Raso MG, Hofstetter WL, Fang B, Behrens C, Roth JA, Zhou Y, Yu L, Wistuba II, Swisher SG, Pataer A. The role of PKR/eIF2α signaling pathway in prognosis of non-small cell lung cancer. PLoS One. 2011;6(11):e24855

Kim W, Bennett EJ, Huttlin EL, Guo A, Li J, Possemato A, Sowa ME, Rad R, Rush J, Comb MJ, Harper JW, Gygi SP. Systematic and quantitative assessment of the ubiquitin-modified proteome. Mol Cell. 2011 Oct 21;44(2):325-40

Sharma B, Altman JK, Goussetis DJ, Verma AK, Platanias LC. Protein kinase R as mediator of the effects of interferon (IFN) gamma and tumor necrosis factor (TNF) alpha on normal and dysplastic hematopoiesis. J Biol Chem. 2011 Aug 5;286(31):27506-14

Wagner SA, Beli P, Weinert BT, Nielsen ML, Cox J, Mann M, Choudhary C. A proteome-wide, quantitative survey of in vivo ubiquitylation sites reveals widespread regulatory roles. Mol Cell Proteomics. 2011 Oct;10(10):M111.013284

Bennett RL, Pan Y, Christian J, Hui T, May WS Jr. The RAX/PACT-PKR stress response pathway promotes p53 sumoylation and activation, leading to G□ arrest. Cell Cycle. 2012 Jan 15;11(2):407-17

This article should be referenced as such:

Blalock WL, Cocco L. EIF2AK2 (eukaryotic translation initiation factor 2-alpha kinase 2). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(9):601-613.