Gene Section

Review

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

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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).
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; Berflanga et al., 1999; Williams, 1999; Chen, 2007).
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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 processes 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 (IkB)-β, the B56α regulatory subunit of PP2A, and RNA helicase (Garcia et al., 2006). Within the past ten years, PKR has been shown to play a significant role in signaling pathways involved in other cellular processes such as cell proliferation, differentiation, metabolism, DNA repair and apoptosis (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 (Koschmider 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 p21Cip1, 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 p21Cip1 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 IκB 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 on Ser727. Phosphorylation of this site is defective in PKR-/- fibroblasts resulting in a decrease of STAT1 activation and the synthesis of some NF-κB dependent genes was greatly potentiated when PKR kinase activity remained intact (Donze et al., 2004). Similar to STAT1, PKR has also been demonstrated to be required for proper phosphorylation and transactivation of STAT3 by platelet derived growth factor (PDGF) is impaired (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 (Ruvo 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**

<table>
<thead>
<tr>
<th>Species</th>
<th>Similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. sapiens</em></td>
<td>100%</td>
</tr>
<tr>
<td><em>P. troglodytes</em></td>
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<tr>
<td><em>C. lupus</em></td>
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<td><em>B. taurus</em></td>
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<td><em>M. musculus</em></td>
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<tr>
<td><em>G. gallus</em></td>
<td>39%</td>
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<tr>
<td><em>D. rerio</em></td>
<td>30%</td>
</tr>
</tbody>
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**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.
**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 IFN\(\gamma\) and TNF\(\alpha\) 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 TNF\(\alpha\) and IFN\(\gamma\) (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 TNF\(\alpha\) and IFN\(\gamma\) (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'Florouracil (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
Enhanced expression is associated with a favorable outcome to interferon therapy. Could represent a prognostic indicator.

Oncogenesis
Role uncharacterized.

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.

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