RAD9A (RAD9 homolog A (S. pombe))

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Published in Atlas Database: March 2010


DOI: 10.4267/2042/44917

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Identity

Other names: RAD9, hRAD9
HGNC (Hugo): RAD9A
Location: 11q13.2
Note: Accession No. NM_004584.

DNA/RNA

Description
6461 bp, 11 exons.

Transcription
The transcript length is 1176 bp, full open reading frame cDNA clone, encodes a 391 amino acid, 42520 Da protein (Lieberman et al., 1996).

Protein

Function
The gene product is highly similar to Rad9 protein from S pombe. A cell cycle checkpoint protein with multiple functions for preserving genomic integrity (Ishikawa et al., 2006), such as the regulation of DNA damage response, cell cycle checkpoint, DNA repair, apoptosis, transcriptional regulation, exonuclease activity, ribonucleotide synthesis and embryogenesis.

hRad9 forms ring-shape heterotrimeric complex with hRad1 and hHus1 proteins (9-1-1 complex). All 3 proteins have sequence homology with proliferating cell nuclear antigen (PCNA). The 9-1-1 complex is recruited onto DNA-lesion by RAD17 and ATR - triggering checkpoint signaling pathway and acts to repair DNA damage (Volkmer and Karnitz, 1999; Rauen et al., 2000; Zou et al., 2002; Medhurst et al., 2008). Phosphorylation of hRad9 by protein kinase C delta (PKCD) is necessary for the formation of the 9-1-1 complex (Yoshida et al., 2003). NH2 terminus of hRad9 contains BH3-like domain which binds antiapoptotic proteins BCL2 and Bcl-x2, thereby promoting apoptosis (Komatsu et al., 2000). This interaction of hRad9 to Bcl2 is regulated also by PKCdelta (Yoshida et al., 2003).

RAD9, like P53 can regulate P21 at the transcriptional level. Overexpression of hRad was shown to cause an increase in P21 RNA and the encoded protein level in P53-null H1299 cells (Yin et al., 2004). This suggests that hRAD9 and P53 coregulate P21 to direct cell cycle progression. hRAD9 may also modulate transcription of other down-stream target genes.

C-terminal region of hRad9 protein acts to transport 9-1-1 complex into the nucleus (Hirai and Wang, 2002; Sohn and Cho, 2009).
hRad9 and ATM rapidly colocalize to regions containing DNA double-stranded breaks after DNA-damage (Greer et al., 2003; Medhurst et al., 2008) and Atm can phosphorylate Rad9 directly at Ser-272 during ionizing radiation (IR)-induced G1/S checkpoint activation (Chen et al., 2001). The 9-1-1 complex may attract DNA polymerase beta to sites of DNA damage, thus connecting checkpoint and DNA repair (Toueille et al., 2004). Thr-292 of hRad9 is subject to CDC2-dependent phosphorylation in mitosis. Four other hRad9 phosphorylation sites (Ser-277, Ser-328, Ser-336 and Thr-355) are regulated in part by Cdc2 (St Onge et al., 2001; St Onge et al., 2003; Ishikawa et al., 2006). Phosphorylation sites of the C-terminal region of hRad9 are essential for CHK1 activation following hydroxyurea, ionizing radiation and ultraviolet treatment (Roos-Mattjus et al., 2003). Crystal structure of the human Rad9-Hus1-Rad1 complex reveals a single repair enzyme binding site (Doré et al., 2009) and suggests that the C-terminal end of Rad9 protein is involved in the regulation of the complex in DNA binding (Sohn and Cho, 2009). hRad9 possesses 3'-5' exonuclease activity which may contribute to its role in sensing and repairing DNA damage (Bessho and Sancar, 2000). The exact mechanism of this exonucleolytic processing is still unclear.

**Implicated in**

**Various cancers**

**Oncogenesis**

Checkpoint genes are known to be involved in the maintenance of genomic integrity and their aberrant expression can lead to cancer. Paralogue of human HRad9 is called HRad9B. Gene product is structurally related to hRad9 protein (55% similar and 35% identical). HRad9B gene is expressed predominantly in the testis and found in decreased amount in testicular tumours, particularly seminomas (Hopkins et al., 2003).

**Prostate cancer**

**Oncogenesis**

Carboxy terminus of hRad9 contains a FXXLF motif which interrupts the androgen-induced interaction between the C and N terminus of androgen receptor (AR), acting as a co-regulator to suppress androgen-AR transactivation in prostate cancer cells (Wang et al., 2004). This denotes a possible tumour suppressor function of hRad9.

Recent study has confirmed that high levels of Rad9 expression is found in prostate cancer cells and the high protein levels in prostate adenocarcinomas were generally associated with more advanced disease (Zhu et al., 2008). Similar to previous findings in breast...
cancer (Cheng et al., 2005), the increased expression of Rad9 in prostate cancer cells was in part due to aberrant methylation or gene amplification (Zhu et al., 2008). The study failed to show that the role of Rad9 in prostate tumorigenesis was androgen dependent, since both androgen dependent CWR22 and LNCaP cell lines as well as androgen independent DU145 and PC-3 cell lines were found to contain high levels of Rad9 protein (Zhu et al., 2008).

**Lung cancer**

**Oncogenesis**

Presence of hyperphosphorylated forms of hRad9 has been found in the nuclei of surgically resected primary lung carcinoma cells (Maniwa et al., 2005). No mutation of the hRad9 gene was found in lung cancer cells, but a nonsynonymous single nucleotide polymorphism (SNP), His239Arg was found in 8 out of 50 lung adenocarcinoma patients, suggesting a possible association of this SNP with the development of cancer (Maniwa et al., 2006).

**Breast cancer**

**Oncogenesis**

Over-expression of hRad9 mRNA was found in breast cancer, which was shown to be correlated with tumour size ($p = 0.037$) and local recurrence ($p = 0.033$). Over-expression of Rad9 mRNA was partly due to increase in RAD9 gene amplification and aberrant DNA methylation at a putative Sp 1/3 binding site within the second intron of the RAD9 gene. Promoter assays indicate that the Sp 1/3 site in intron 2 may act as a silencer. Further experiments in silencing Rad9 expression by RNAi inhibit the proliferation of MCF-7 cell line in vitro. These findings suggested that Rad9 is a new oncogene candidate on Ch11q13 with a role in breast cancer progression (Cheng et al., 2005). In contrast to previous findings in testicular tumours, increased hRad9 protein was found in the nuclei of breast cancer cells. These were shown to exist as hyperphosphorylated forms, with molecular weights of 65 and 50 kDa. Since the theoretical molecular weight of hRad9 is 45 kDa (Lindsey-Boltz et al., 2001), these larger forms most likely represent hyperphosphorylated hRad9 and its hRad9-hRad1-hHus1 complex (Chan et al., 2008; St Onge et al., 1999). Localization of hyperphosphorylated forms of hRad in the nucleus of cancer cells is in keeping with its function in ameliorating DNA instability, whereby it inadvertently assists tumour growth.

**Colorectal cancer**

**Oncogenesis**

Rad9 interacts physically within the DNA mismatch repair (MMR) protein MLH1. Disruption of the interaction by a single point mutation in Rad9 leads to significantly reduced mismatch repair activity (He et al., 2008). The Rad9-MLH1 interaction might be a hotspot for mutation in tumour cells. The hMLH1 mutations lead to hereditary non-polyposis colorectal cancer (HNPPC) (Avdievich et al., 2008; Peltomäki et al., 2004) and various types of tumours (Avdievich et al., 2008; Hu et al., 2008). However, hRad9's function in MMR is not in the 9-1-1-complex form (He et al., 2008).

**References**


St Onge RP, Udell CM, Casselman R, Davey S. The human G2 checkpoint control protein hRAD9 is a nuclear phosphoprotein that forms complexes with hRAD1 and hHUS1. Mol Biol Cell. 1999 Jun;10(6):1985-95

Volkmer E, Karnitz LM. Human homologs of Schizosaccharomyces pombe rad1, hus1, and rad9 form a DNA damage-responsive protein complex. J Biol Chem. 1999 Jan 8;274(2):567-70

Bessho T, Sancar A. Human DNA damage checkpoint protein hRad9 is a ‘3’ to ‘5’ exonuclease. J Biol Chem. 2000 Mar 17;275(11):7451-4


Rauen M, Burtelow MA, Dufault VM, Karnitz LM. The human checkpoint protein hRad17 interacts with the PCNA-like proteins hRad1, hHus1, and hRad9. J Biol Chem. 2000 Sep 22;275(38):29767-71


Zou L, Cortez D, Elledge SJ. Regulation of ATR substrate selection by Rad17-dependent loading of Rad9 complexes onto chromatin. Genes Dev. 2002 Jan 15;16(2):198-208


Yoshida K, Wang HG, Miki Y, Kufe D. Protein kinase Cdelta is responsible for constitutive and DNA damage-induced phosphorylation of Rad9. EMBO J. 2003 Mar 17;22(6):1431-41


Doré AS, Kilkenny ML, Rzechozrek NJ, Pearl LH. Crystal structure of the rad9-rad1-hus1 DNA damage checkpoint complex--implications for clamp loading and regulation. Mol Cell. 2009 Jun 26;34(6):735-45


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