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Review

RRM2 (ribonucleotide reductase M2)

Ali Afrasiabi, Hamid Fiuji, Reza Mirhafez, Amir Avan

Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran and Department of ENT-Head and Neck Surgery, ENT-Head and Neck Surgery Research Center, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, Iran (AAf), Department of Biochemistry, Faculty of Science, Payame Noor University, Mashhad, Iran (HF), Department of New Sciences and Technology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran (RM), Department of Medical Oncology, VU University Medical Center, Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands (HF, AAv)

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Abstract

Ribonucleotide reductase subunit M2 (RRM2) is located in chromosome-2 p25-p24, converts ribonucleotides to deoxynucleotides which is required for DNA polymerization and repair. It has been shown that RMM2 plays a key role in DNA synthesis, cell growth, and drug resistance of cancer cells. There is accumulating evidence that alteration in the expression level of RRM2 can have a substantial impact on the biological characteristics of cancer cells, including tumor initiation and progression, suggesting its role as a prognostic factor and a possible therapeutic target for cancer therapy. Therefore, this review highlights several recent and clinically relevant aspects of the expression and function of RRM2 in human cancer.

Identity

Other names: R2, RR2, RR2M

HGNC (Hugo): RRM2

Location: 2p25.1

Local order

Based on MapViewer, gene flanking RRM2 oriented on 2p25-p24 are:
- KLF11 (Kruppel-like factor 11); 2p25,
- CYS1 (cystin 1); 2p25.1,
- RRM2 (ribonucleotide reductase M2); 2p25-p24,
- C2orf48 (chromosome 2 open reading frame 48); 2p25.1,
- MIR4261 (microRNA 4261); chromosome 2,
- HPCAL1 (hippocalcin-like 1); 2p25.1.

Exon No.	Size (bp)	Intron No.	Size (bp)
1	330	1	85
2	75	2	329
3	146	3	204
4	115	4	863
5	134	5	2010
6	95	6	118
7	134	7	1635
8	105	8	88
9	114	9	80
10	1263		

Table 1. Exons and introns of RRM2 gene.

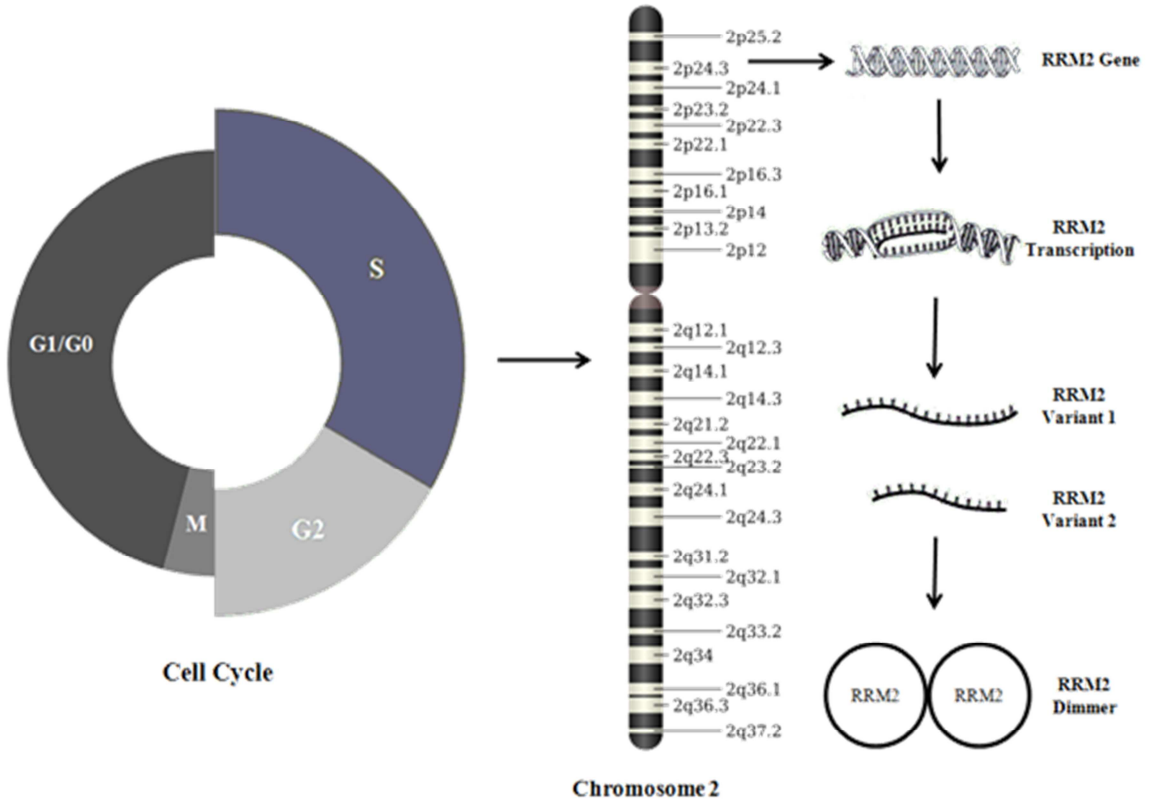

Figure 1. Ribonucleotide reductase subunit M2 (RRM2) is located in chr 2p25-p24. Synthesis of the encoded protein RRM2 is regulated in a cell-cycle dependent fashion and elevated to maximal levels during S-phase of cell cycle. RRM2 has two isoforms with different N-terminal lengths, variant 1 and 2, which contains 3452 and 3284 bp, respectively.

DNA/RNA

Description

RRM2 gene has ten exons, nine introns and alternative promoters (Table 1). The alternative promoters are resulting in two isoforms with different N-terminal lengths (variants 1 and 2; Figure 1). Variants 1 and 2 contain 3452 and 3284 bp, respectively. Variant 1 is the longest isoform with respect to the variant 2.

Transcription

Promoter of RRM2 gene has two transcription start sites, TATA box, three CCAAT boxes and several GC rich in 5' of the downstream transcription initiation site. Variant 2 has a shorter 5' UTR and uses a downstream translational start codon, compared to the variant 1. Regions of -204 to +1 and -659 to -257 act as a promoter for the variant 1 (1.65 kbp) and variant 2 (3.4 kbp), respectively. Several studies are currently ongoing for the role of the 3' UTR in the regulation of RRM2 expression. Moreover, three CCAAT boxes exist in the region between transcription initiating sites at positions -82, -109, -139 and -436. Also, the transcription of 1.65 kbp RRM2 mRNA initiates from +1, while 3.4 kbp mRNA RRM2 initiates at position -187 (Zhou and Yen, 2001).

Synthesis of the encoded protein (RRM2) is regulated in a cell-cycle dependent fashion and elevated to maximal levels during S-phase of cell cycle (Figure 1). RRM2 promoter has transcription factor binding sites for SP1, c-Ets, MZF1, E2F, Lyf-1, GATA-X, HSF2, AP-1, CdxA, IK-2, Sox-5, SRY, Brn-2, HNF-1, STATx, GATA-1, USF (c-Myc), Pbx-1, Oct-1, GATA-2, CRE-Bp and Nkx-2. 3.4 kbp RRM2 mRNA is the major form in kidney, placenta and lung, while 1.65 kbp RRM2 mRNA is the main form in small intestine, colon, testis and thymus. RRM2 gene expression level is high in small intestine, colon thymus and testis tissues. In addition RRM2 mRNA in heart is very higher with respect to other tissues. Conversely, the expression level of RRM2 gene is low in lung and liver tissues, and its level is very low level in prostate, skeletal muscle, brain and leukocyte tissues (Zhou and Yen, 2001; Park and Levine, 2000).

Pseudogene

Related pseudogenes have been identified on chromosomes 1 and X (1p33→p31, 1q21→q23 and Xp21→p11).

Species	Symbol	Identity (%)	
H.sapiens	RRM2	Protein	DNA
vs. M.mulatta	RRM2	94.8	95.7
vs. C.lupus	RRM2	96.7	91.7
vs. B.taurus	RRM2	94.9	91.4
vs. M.musculus	Rrm2	91.5	88.2
vs. R.norvegicus	LOC100359539	90.2	86.9
vs. R.norvegicus	RRM2	90	86.6
vs. G.gallus	RRM2	89.1	80.1
vs. D.melanogaster	RnrS	81.6	70.5
vs. A.gambiae	AgaP_AGAP006818	82.8	70.6
vs. C.elegans	mr-2	70.1	64.9
vs. S.cerevisiae	RNR2	69.6	64.4
vs. K.lactis	KLLA0F15103g	71.7	64.2
vs. E.gossypii	AGOS_AAL136C	72	67.6
vs. S.pombe	suc22	71	64.4
vs. M.oryzae	MGG_06408	71.6	65.6
vs. N.crassa	NCU07887	69.5	66
vs. A.thaliana	RNR2A	65.9	62.5

Table 2. Percentage of identity/homology of RRM2 in DNA and protein levels in eukaryotes with respect to human.

Protein

Description

The building blocks of DNA, deoxyribonucleotide triphosphates (dNTPs), is provided/generated by ribonucleotide reductases (RNR). In fact RNR have a vital role in preserving the appropriate amount of dNTPs (dATP, dGTP, dCTP, dTTP) pool for DNA replication and repair by converting ribonucleotide diphosphates (NDP) to deoxyribonucleotide diphosphates (dNDP). RNR enzymes are divided into three different classes: I, II and III. Human RNR belongs to the class I. Furthermore, RNR has two subunits, RRM1 and RRM2. RRM1 is the larger subunit of RNR with respect to the RRM2. RRM2 isoform 1 and 2 have 449 and 389 residues, respectively. In particular, isoform 1 has 60 residues more than isoform 2 inits N-terminal region. RRM2 interact with RRM1 through its C-terminus region (Nordlund and Reichard, 2006; Eklund et al., 2001; Thelander, 2007).

Expression

RRM2 protein expression is increased to maximal level during S-phase due to E2F, as an activator of DNA synthesizing enzymes, however, its exression is reduced during G1 by E2F4 (Eklund et al., 2001; Nordlund and Reichard, 2006).

Function

RRM2 contains a KEN-box on the N-terminus that is recognized during the mitosis by the Cdh1-anaphase-promoting complex and thereby becomes poly-ubiquitinated or depredates by proteasome (Nordlund and Reichard, 2006; Eklund et al., 2001; Thelander, 2007). RRM2 is responsible for producing a stable tyrosyl radical for the active site of RNR that is located in RRM1. In addition, p53R2 is 80% similar to RRM2, which can bind to RRM1 and form the active structure. According to the vital role of RNR in cell cycle and proliferation, RNRs can be considered as suitable targets for cancer treatment.

Several studies have been demonstrated that inhibition of RRM2 can inhibit cancer cell growth and overcomes drug resistance (Aimiuwu et al., 2012; Zhou et al., 2013).

In particular, Zhou and colleagues showed that inhibition of RRM2 by novel RNR inhibitor COH29 inhibited the proliferation of most cell lines in the human cancer panel, mostly ovarian cancer and leukemia. In mouse xenograft models of human cancer, COH29 treatment reduced tumor growth with respect to the control group (Zhou et al., 2013).

Homology

The RRM2 gene is conserved in Rhesus monkey, dog, chicken, cow, mouse, rat, K. lactis, fruit fly, mosquito, C. elegans, M. oryzae, S. cerevisiae, S. pombe, E. gossypii, N. crassa, and A. thaliana. Percentage of identity or homology of RRM2 in DNA and protein levels in eukaryots with respect to human is shown in Table 2.

Mutations

Note

More than 1215 single nucleotide variations (SNPs) have been reported in RRM2 gene (until 5th of March 2014, dbSNP), such as rs15516, rs1130609, rs1138727, rs1138728, rs1138729, rs4668664, etc.

Implicated in

Pancreatic cancer

Note

Youns and colleagues recently showed that RRM2 is overexpressed in the pancreatic cancer cell lines. They performed a gene expression profiling to identify novel molecular targets modulating the growth inhibitory effects of COX-2 inhibitor NS-398 in pancreatic cancer. They found that RRM2 was down-regulated in BxPC-3, MiaPaCa-2 and ASPC-1 cell lines after treatment with NS-398. Moreover, they identified RRM2 as a biomarker for the chemo-preventive effect of NS-398 in pancreatic cancer cells (Youns et al., 2011). Previous study illustrated that over-expression of RRM2 was associated with resistance to gemcitabine in pancreatic cancer (Nakano et al., 2007). In this study the expression level of RRM2 was analysed by q-PCR in different subclones during the development of acquired resistance to gemcitabine. This analysis showed that the expression level of RRM2 enhanced during the development of gemcitabine resistance. Moreover, they also evaluated the expression levels of other genes, RRM1, dCK, hENT1. This results illustrated that expression ratio significantly correlated with gemcitabine sensitivity in eight pancreatic cancer cell lines, whereas no single gene expression level correlated with the sensitivity, indicating that the sensitivity of pancreatic cancer cells to gemcitabine is dependent on the ratio of four factors involved in gemcitabine transport and metabolism. On the one hand, the ratio of the four gene expression associated with acquired gemcitabine-resistance in pancreatic cancer cells (Nakano et al., 2007). Moreover, Duxbury et al., showed that small interfering RNA targeting RRM2 enhanced chemosensitivity to gemcitabine in pancreatic adenocarcinoma (Duxbury et al., 2004), suggesting its role as an attractive target for pancreatic cancer.

Lung cancer

Note

Several studies have been shown that RRM2 is overexpressed in lung cancer. In particular, Souglakos and colleagues showed that patients with low level of RRM2 had a significantly higher response rate (60% vs 14.2%), time to progression (9.9 vs 2.3 months), and overall survival (15.4 vs 3.6 months) in metastatic lung adenocarcinoma patients treated with gemcitabine plus docetaxel with respect to the patients with high level of RRM2 (Souglakos et al., 2008). Furthermore, Boukovinas et al., evaluated the effect of RRM2 expression on outcome to gemcitabine plus docetaxel in advanced non-small-cell lung cancer (NSCLC) patients. RRM1, RRM2 and BRCA1 mRNA levels were determined by quantitative PCR and correlated with response, time to progression and survival. This study showed that the probability of response decreased (RRM2: Odds Ratio, 0.94; $p<0.0001$) and the risk of progression increased (RRM2: HR, 1.005; $p = 0.01$) in patients samples with high expression of RRM2, compared to the samples with low expression (Boukovinas et al., 2008). In another recent study the prognostic value of RRM2 was determined in 418 patients with NSCLC who received adjuvant chemotherapy (Wang et al., 2014).

This analysis demonstrated that patients with low expression of RRM2 had a significantly higher responce to platinum-based chemotherapy (OR = 1.64, 95 % CI = 1.09-2.48) and a longer time to progression and overall survival time, with hazard ratio of 0.57 (0.38-0.86) and 0.47 (0.31-0.71), respectively (Wang et al., 2014).

Breast cancer

Note

It has been shown that RRM2 is overexpressed in human breast carcinoma tissue (DCIS, Jensen et al., 1994). Recently Kretschmer and colleagues identified molecular markers for the ductal carcinoma in situ using WAP-TNP8 mouse model. In particular, they identified seven marker genes (RRM2, MUC1, SPP1, FOXM1, EXO1, NUSAP1 and DEPDC1), which were overexpressed at a very early stage of premalignancy and preneoplasia of breast carcinomas (Kretschmer et al., 2011).

Ovarian cancer

Note

Ferrandina and colleagues found a association between RRM2 expression level and relative risk of death in ovarian cancer.

In this study they evaluated the mRNA expression levels of several genes involved in transportation and metabolism of gemcitabine, including RRM2, in 25 primary ovarian carcinomas using q-PCR. They showed that samples with high RRM2 expression had a less overall survival, OS, (median OS=19 months) with respect to the samples with low RRM2 level (median OS=36 months; Ferrandina et al., 2010).

Osteosarcoma

Note

Fellenberg et al., in 2007 investigated the prognostic value of eight genes including RRM2 in 35 formalin-fixed osteosarcoma biopsies. They observed a significant relation between RRM2 expression with overall survival of the patients. However, the prognostic value of this gene did not confirm by multivariate analysis and further studies are needed to evaluate the prognostic role of RRM2 in osteosarcoma (Fellenberg et al., 2007).

Bladder cancer

Note

Lu and colleagues investigated whether global gene expression profiling can help in predecting the suitability of rodent models of bladder cancer for the detection of cancer-related genes and prediction of cancer prevention in human bladder cancer and carcinogen-induced rodent models.

They found that 13~34% of whole genome were differentially expressed between tumor and normal tissues in humans, Fischer-344 rats, and B6D2F1 mice.

Approximately 20% of these differentially expressed genes overlapped among species, corresponding to 2.6 to 4.8% of whole genes in the genome.

A number of genes were consistently dysregulated in bladder tumors in both humans and rodents. Among these genes, RRM2 was up-regulated in tumor tissue across three species, suggesting its role as a potential factor in contributing to bladder carcinogenesis (Lu et al., 2010).

Hepatocellular carcinoma

Disease

Patients with hepatocellular carcinoma (HCC) suffer from chronic hepatitis or liver cirrhosis. Satow and colleagues performed whole-genome RNA interference-based functional screening in order to identify genes that sensitize lung cancer cells to drug and genes required for proliferation and survival of HCC cells.

In this study four genes (AKR1B10, HCAP-G, RRM2, and TPX2) were found to be expressed strongly in HCC, suggeting their role as potential therapeutic targets in hepatocellular carcinoma (Satow et al., 2010).

Gastric cancer

Note

Morikawa et al., in 2010, explored the prognostic value of RRM2 in 112 gastric cancer samples using immunohistochemistry (Morikawa et al., 2010). They found that RRM2 expression was limited to the neck regions of gastric pits, in normal gastric mucosa.

Moreover, they observed RRM2 overexpression in 72 cases (64.3%), among 112 gastric cancer tissues. In vitro analysis and inhibition of RRM2 systhesis by small interfering RNA, inhibited the growth of three gastric cancer cell lines, MKN-1, MKN-7, and SNU-719.

Furthermore, they demonstarted that overexpression of RRM2 was associated with the gastric cancer progression and suppression of its function could be considered as a potential therapeutic strategy in gastric cancer (Morikawa et al., 2010).

Parkinson disease

Note

The inhibitory effect of dopamine on RRM1/2 has been reported in Parkinson disease. Dopamine inhibits RNR through two pathways: (I) dopamine acts as an effective radical scavenger and scavenge the tyrosyl radical of RRM2, which is important for initiating of catalytic process in RRM1 active site and (II) chelates the iron center of RRM2 which acts as a chelator for iron and other metals. In addition nitric oxide induces dopaminergic neuronal cells through inhibiting RNR (Woldman et al,. 2005; Ebadi and Sharma, 2003).

To be noted

Note

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