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Tumor Suppressor RIZ1 in Carcinogenesis

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Abstract

Human retinoblastoma protein-interacting zinc-finger gene *RIZ* (*PRDM2*) encodes two protein products, tumor suppressor RIZ1 and proto-oncoprotein RIZ2, using alternative promoters. RIZ1 and RIZ2 regulate normal cell division in a Yin-Yang fashion with RIZ1 arresting cells in G2/M phase and inducing apoptosis and RIZ2 promoting cell proliferation. Silenced RIZ1 expression has been detected in various types of cancer. Because both RIZ isoforms contain multiple functional domains, their function mechanisms in suppressing or promoting tumor growth are complex. Based on the current knowledge, it is rational to propose four potential routes for RIZ1 to exert its tumor suppressing functions: directly repressing the promoters of growth factors such as insulin-like growth factor-1 *via* H3K9 (histone H3 lysine 9) methylation, regulating estrogen-induced *pS2* transcription through forming a complex with transcriptional co-activator p300, activating tumor suppressor p53 using a methylation-acetylation interplay, and blocking gene transcriptions by binding to PR-Set7 and establishing a H4K20^{me1} (histone H4 lysine 20 mono-methylation) - H3K9^{me1} (histone H3 lysine 9 mono-methylation) *trans*-tail 'histone code' at an ectopic locus.

Keywords: Tumor suppressor; Carcinogenesis; *RIZ* gene

Introduction

Human tumor suppressor RIZ1 (PRDM2) is encoded by the retinoblastoma protein-interacting zinc-finger gene *RIZ* (*PRDM2*), which was first identified from a functional screening for retinoblastoma tumor suppressor binding genes [1]. Gene *RIZ* is located on the distal short arm of human chromosome 1 (1q36.21), which also harbors other tumor suppressor genes such as *CHD5*. Besides RIZ1, gene *RIZ* encodes a second protein product, RIZ2, using an internal promoter other than the promoter that transcribes full-length RIZ mRNA [2-4]. Theoretically, it is possible to have other RIZ isoforms from alternative RNA splicing since gene *RIZ* contains more than 10 potential exons [3]. As shown in Figure 1, except for an N-terminal PR domain possessing histone methyltransferase (HMT) activity, RIZ1 and RIZ2 share the same amino acid sequences and both contain a Rb-binding domain, eight zinc finger motifs, a src homology 3 (SH3) domain, a putative GTPase domain, a proline-rich domain and a PR-binding motif (PRB). The expression level is almost identical between RIZ1 and RIZ2 among different human tissues except testes; and such an equivalent expression is essential for normal cell growth and functions [2,5,6]

Silencing of *RIZ1* during Carcinogenesis

RIZ1 and RIZ2 regulate normal cell division and functions in a Yin-Yang fashion [2-4]. RIZ1 acts as tumor suppressor to arrest cells in the G2/M phase of cell cycle and induce cell apoptosis; whereas RIZ2 functions as a proto-oncoprotein to promote cell proliferation [5,6]. Silenced or decreased RIZ1 expression, commonly associated with normal or increased RIZ2 expression, has been detected in various types of cancer [1,3-36]. The silencing of RIZ1 expression is through at least one of the following four mechanisms:

Methylation of the CpG islands in RIZ1 promoter

This is the mostly studied mechanism, but identity of the enzyme that methylates RIZ1 promoter is still not clear. Aberrant methylation of RIZ1 promoter has been observed in different types of cancer (Table 1) [4,7-27]. Nevertheless, a pairwise analysis by Feng et al. did not find increased methylation of gene *RIZ* between normal and malignant breast tissues [37]. Recently, RIZ1 promoter was shown to be up-regulated by silencing SMYD3 (SET and MYND domain-containing protein 3), a histone/protein methyltransferase, in human hepatoma [38] and down-regulated by silencing transcriptional repressor YY1 (Yin Yang 1) in human osteosarcoma [39]. Further studies are definitely warranted to understand how RIZ1 promoter is regulated by SMYD3, YY1, and even other histone/protein methyltransferases and transcriptional repressors

Loss of heterozygosity (LOH) within the RIZ locus

Gene *RIZ* is located on the short arm of chromosome 1 (1p36), which is unstable and frequently lost in human malignancies *via* non-random deletions [40-42]. LOH within the *RIZ* locus in different types of cancers has been summarized in Table 2 [18,23,28-31]. However, a recent review on five candidate tumor suppressor genes, *CHD5*, *CAMTA1*, *KIF1B*, *CASZ1* and *miR-34a*, located on 1p36 showed that partial impairment instead of complete inactivation of their expression was enough to promote tumorigenesis [43], implicating that down-regulation of gene *RIZ* might follow the same mechanism in stimulating tumor development and growth.

Figure 1: Structural components in tumor suppressor RIZ1 and its alternatively transcribed proto-oncoprotein RIZ2. Except the PR domain located at the N-terminus of RIZ1, both RIZ isoforms containing a retinoblastoma-binding (Rb) domain, eight zinc finger motifs (shown in pink), a SH3 domain, a putative GTPase domain, a proline-rich region and a PR domain-binding motif (PRB).

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Cancer type	Sample size	Promoter methylation	References
Liver cancer	32 42 48 60 39 42	62% (20/32) 79% (33/42) 67% (32/48) 62% (37/60) 56% (22/39) 45% (20/42)	[4] [7] [8] [9] [10] [11]
Neuroblastoma	33	<10%	[12]
Breast cancer	25	44% (11/25)	[4]
Colorectal cancer	38	16% (6/38) (high-level MSI)	[13]
Ovarian cancer	89 69	22% (20/89) 7% (5/69)	[14] [15]
Gastric cancer	75 45 30	67% (50/75) 69% (31/45) 37% (11/30)	[16] [17] [18]
Prostate cancer	47 101	43% (20/47) 31% (31/101)	[19] [20]
Thyroid cancer	19	100% (19/19)	[21]
Cervical cancer	40	38% (14/40)	[22]
Parathyroid cancer	47	36% (17/37)	[23]
Malignant pheochromocytoma	4	50% (2/4)	[23]
Nasopharyngeal carcinoma	30 53	60% (18/30) 57% (30/53)	[24] [25]
Acute lymphoblastic leukemia	71 72	16% (T: 64%, B: 7%) 31% (22/72)	[26] [27]

Table 1: RIZ1 promoter methylation in various types of cancer.

Cancer type	Sample size	LOH within *RIZ* locus	References
Parathyroid cancer	47	28% (13/47)	[23]
Pheochromocytoma	23	39% (9/23)	[23]
Liver cancer	79	39% (31/79)	[28]
Colon cancer	47	23% (11/47)	[28]
Breast cancer	43	19% (8/43)	[28]
Gastric cancer	66 30	12% (8/66) 33% (10/30)	[28] [18]
Oral squamous cell carcinoma	27	33% (9/27)	[29]
Neuroblastoma	122	26% (32/122)	[30]
Melanoma	57	18% (10/57)	[31]

Table 2: LOH within the *RIZ* locus in various types of cancer.

Mutations within the RIZ gene

Both missense and frameshift mutations in *RIZ* have been observed in human cancers [18,32-35]. Frameshift mutations were detected in gene *RIZ* at two poly-A tracts, A_8 and A_9, within the coding region in gastric, pancreatic, colorectal and endometrial cancers [18,32-34]. Both mutations end up with truncated RIZ proteins (both RIZ1 and RIZ2) without the C-terminal PRB motif, which in turn may disrupt the Yin-Yang regulation of normal cell functions and lead to carcinogenesis due to eliminated PR-PRB interaction although this interaction has not yet been confirmed by any *in vivo* study. Searching for missense mutations in *RIZ* has been focused on the PR domain and its immediate C-terminal neighboring region. Missense mutation A563G (corresponding to amino acid Ile188Val mutation) happened in high incidence (29%, 11/35) in diffuse large B-cell lymphoma instead of other types of cancer [35]. Missense mutations G317A (corresponding to amino acid Cys106Tyr mutation) and C476T (corresponding to amino acid Ala159Val mutation) were identified in human osteosarcoma cell line Saos2 and neuroblastoma cell line SMS–KCNR, respectively [35].

Down-regulation via histone H3 lysine 9 (H3K9) methylation

This is the least studied mechanism on silencing RIZ1 expression. A previous study by Zhang et al. showed extensive $H3K9^{me3}$ (H3K9 tri-methylation) at the silenced *RIZ1* promoter in human hepatocellular carcinoma cell line HepG2 [8]. As RIZ1 possesses H3K9 methylation activity, an interesting issue needs to be further addressed is whether there is a negative feedback on RIZ1 expression, *i.e.*, RIZ1 methylates H3K9 at its own promoter region. Reintroduction of RIZ1 *via* viral transfection was shown to suppress proliferation, arrest cell cycle in G2/M phase and induce apoptosis in cancer cells [44,45]. Furthermore, the expression level of RIZ1 has been related to tumor metastasis. Dong et al. reported that reduced RIZ1 expression was correlated positively with increased risk of tumor metastasis [46]; however, Sun et al. showed that RIZ1 mRNA expression was increased significantly at stage IV in various types of cancer [47]. Since patient survival rate drops dramatically for all types of cancer when tumor cells metastasize to distal organs, it is extremely important in future studies to identify whether RIZ1 expression is indeed increased at protein level as increases in mRNA expression do not always translate proportionally into protein expression, whether RIZ1 is in the wild-type or mutated form, and what role RIZ1 plays during metastasis, *i.e.*, increased RIZ1 expression in late-stage diseases promotes metastasis due to local stress resulted from increased tumor mass and reduced oxygen and nutrient supplies or counteracts tumor metastasis as a self-protective yet unsuccessful endeavour.

Structural Components and Their Biological Functions

Since RIZ contains multiple functional domains, its biological function is deemed to be complex. Studying its structural components (Figure 1) as well as their individual biological functions will definitely provide us a better understanding of RIZ1. The PR domain, which is located at the N-terminus of RIZ1 and the only structural difference between the two RIZ isoforms, possesses HMT activity and is structurally related to the suppressor of variegation-enhancer of zeste-trithorax (SET) domain of chromatin-associated proteins involved in gene expressions [48]. H3K9 methylation by RIZ1 is *via* the function of the PR domain [48,49]. The ability of RIZ1 to methylate H3K9 was depleted by the Ile188V mutation and decreased by the Cys106Tyr and Ala159Val mutations [49]. Transfection with cDNA encoding only the PR domain and its C-terminal neighboring region (amino acid residues 13-190) of RIZ1 significantly increased the cell death of hepatoma HuH7 cells, implicating that the PR domain possesses tumor suppressing activity even without the help of the other functional domains [47,50]. The Rb-binding domain interacts with the C-terminus of retinoblastoma protein (Rb), which is an important tumor suppressor [51].Since Rb is a common target for viral oncoproteins, it has been speculated that oncoviral proteins may structurally mimic RIZ proteins (RIZ1 and RIZ2) to interact with Rb and alter its biological function [51]. Extensive orthology is revealed between the Rb-binding domain of RIZ proteins and adenovirus oncoprotein E1A, which promotes cell proliferation, although they are evolutionally unrelated [51,52]. Eight zinc finger motifs are dispersed throughout the central and C-terminal regions of RIZ proteins. Zinc fingers 1-6 are C2-H2 type and zinc fingers 7-8 are C2-HC type [51]. The C2-H2 type zinc fingers are usually involved in transcriptional regulation; whereas the C2-HC type zinc fingers inhibit cell apoptosis [53]. In spite of that the functions of zinc fingers 4-8 remain unclear, zinc fingers 1-3 were shown to be essential for DNA binding [54]. Transfection and expression of these three zinc fingers increased cell proliferation in breast cancer cells [55]. Homology has been observed between the zinc fingers of RIZ proteins and the zinc fingers of

other PR-domain containing proteins [51]. RIZ proteins contain a putative GTPase domain [54]. Both RIZ1 and RIZ2 can suppress the transcription of a herpes simplex virus thymidine kinase promoter [54]. A point mutation (Lys755Asn) in the GTPase domain disrupted its GTPase activity but did not change the transcriptional repression action of the RIZ proteins [54]. Interestingly, the SH3 domain, which is located immediately N-terminal to the GTPase domain, was involved in this repression action as revealed by point mutation studies [54]. The SH3 domain helps in assembling protein complexes *via* binding to proline-rich peptides [56]. RIZ proteins also contain a proline-rich region; however, it is unknown whether there is an interaction between the SH3 domain and the proline-rich region. The LXXLL motif in the proline-rich region is essential to receive estrogen receptor signaling and change the distribution of RIZ proteins inside cells [57]. The C-terminal PR-domain binding (PRB) motif was revealed from an *in vitro* assay [58]; however the interaction between PR and PRB has not yet been observed under *in vivo* conditions. The important Yin-Yang regulation roles played by the RIZ proteins during carcinogenesis warrant further investigations on how these functional domains coordinate together to fulfil the tumor-suppressing function for RIZ1 and tumorigenic action for RIZ2.

Functional Mechanism

Contrary to the large amount of information on silencing RIZ1 expression during carcinogenesis, little is known about the functional mechanisms of RIZ1, RIZ2 and their Yin-Yang regulations under *in vivo* conditions. The very limited research on the functional mechanism of RIZ1 has been focused on its HMT activity since PR domain is the only structural difference between RIZ1 and RIZ2. Furthermore, histone modification is closely related to DNA methylation [59]. Histone modification undergoes a dramatic change from $H3^{Ac}$ (histone H3 acetylation), $H4^{Ac}$ (histone H4 acetylation) and $H3K4^{me2/3}$ (histone H3 lysine 4 di- or tri-methylation) in normal cells with un-methylated CpG islands to $H3K9^{me2/3}$ (histone H3 lysine 9 di- or tri-methylation) and/or $H3K27^{me3}$ (histone H3 lysine 27 di- or tri-methylation) in cancer cells with aberrant methylation of the CpG islands [59-61]. Based on the limited information on the functions of RIZ1, it is still rational to propose the following four potential regulatory routes to explain the tumor suppressing and anti-metastasis functions of RIZ1 (Figure 2).

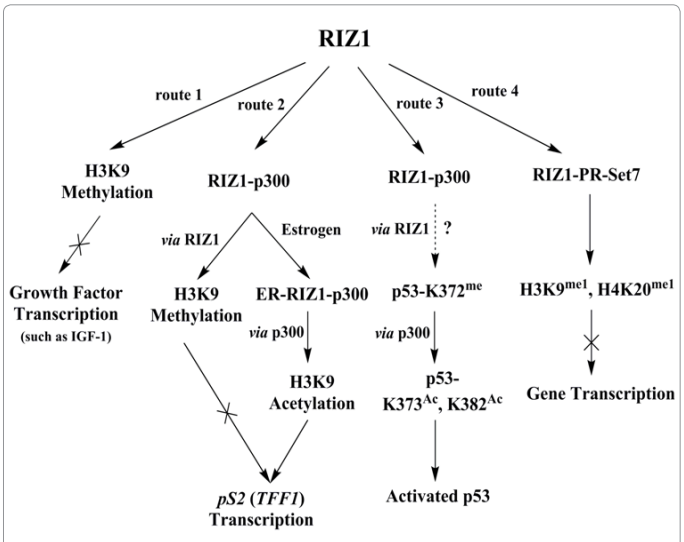

Figure 2: Four potential regulatory routes for the tumor-suppressing and anti-metastasis functions of RIZ1.

RIZ1 directly represses the promoters of growth factors involved in carcinogenesis via H3K9 methylation

This route is proposed based on the observation that RIZ1 suppressed the insulin-like growth factor-1 (IGF-1) signaling pathway by directly repressing the *IGF-1* promoter *via* H3K9 methylation in chronic myeloid leukemia [45].The promoter repression would, in turn, reduce the transcription level of the growth factors and attenuate their downstream signaling.

RIZ1 exerts its histone modification functions via binding to p300

RIZ1 was observed to form a complex with transcriptional co-activator p300 to augment estrogen-induced transcription of gene *pS2* (*TFF1*) in human breast cancer MCF7 cells [62]. Gene *pS2* (*TFF1*) encodes a small protease-resistant secretory protein TFF1 (trefoil factor 1), which acts as a tumor suppressor in gastric cancer [63,64] but a tumorigenesis and metastasis promoter in prostate and pancreatic cancers [65-67]. The role TFF1 plays in breast cancer is controversial. Amiry et al. showed that *TFF1* functioned as an oncogene and forced expression of TFF1 increased the oncogenicity of human breast cancer MCF7 and T47D cells [68]. On the contrary, Buache et al. reported *TFF1* acted as a beneficial factor rather than an oncogene in the breast and knockout of TFF1 augmented the tumorigenicity of breast cancer cells and stimulated breast tumor development [69]. Although TFF1 enhanced the migration and invasion of breast cancer MDA-MB-231, MCF7 and ZR75.1 cells under *in vitro* conditions, its expression is usually depleted in highly metastatic breast cancer cell lines such as MDA-MB-231 [69]. A simple working model on how RIZ1 affects the estrogen-induced *pS2* transcription has been proposed taking in consideration that the RIZ1-p300 complex possesses both histone methylation and acetylation activities [62,70]. The complex methylates H3K9 *via* the HMT activity of RIZ1 and silences the *pS2* promoter in the absence of estrogen. Upon estrogen activation, the complex binds to the estrogen receptor (ER), switches the histone modification from H3K9 methylation to H3K9 acetylation *via* the histone acetyltransferase (HAT) activity of p300, and promotes *pS2* transcription.The delicate H3K9 modification by RIZ1-p300 may be essential in controlling the expression level of TFF1 and its biological function.

RIZ1 expresses its tumor suppressing activity via tumor suppressor p53

The expression of p53 was increased by RIZ1 in monocytic leukemia and malignant meningioma [71-73]. However, the exact mechanism is unknown. A previous study on p53 towards DNA damage showed a methylation-acetylation interplay was important for its activation and stabilization [74]. Set7/9, which possesses HMT activity at H3K4, methylated p53 at residue Lys372 [74]. $Lys372^{me}$ then activated p53 *via* enhancing its acetylation at residues Lys373 and Lys382 by p300 [74]. The methylation-acetylation interplay also increased the acetylation of histone 4 at the promoter region of tumor suppressor p21, leading to its up-regulation to suppress cell cycle [74-76]. Here, we hypothesize that the RIZ1-p300 complex activated p53 using a similar methylation-acetylation interplay mechanism, *i.e.*, RIZ1 could methylate Lys372 of p53. Subsequently, the activated p53 can decrease tumor metastasis *via* CD82 [76-79]. In addition, the RIZ1-p300 complex might counteract the inhibitory effect of Mdm2 (mouse double minute 2 homolog) on p53 acetylation.

RIZ1 shows its tumor suppressing activity through direct binding to PR-Set7

A very recent study by Congdon et al. showed that RIZ1 was recruited to chromatin by PR-Set7 *via* direct binding of their C-terminal domains [80]. The RIZ1-PR-Set7 complex was able to establish an H4K30^{me1}-H3K9^{me1} *trans*-tail 'histone code' at an ectopic locus to repress gene transcriptions [80]. Regardless of which route/routes RIZ1 may use to carry out its tumor suppressing functions, it is still unknown how the different functional domains of RIZ proteins coordinate one another during tumor-suppressing by RIZ1 or carcinogenesis by RIZ2. It will definitely be a big boost of our understanding about RIZ1 as well as other tumor suppressors if the coordination of these functional domains is clearly elucidated.

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