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# THE RETINOBLASTOMA PROTEIN-INTERACTING ZINC FINGER GENE RIZ IN 1P36-LINKED CANCERS

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## 1. ABSTRACT

Mutations or changes in protooncogenes and tumor suppressor genes are casually linked to human cancer pathogenesis. The *RIZ* gene is isolated based on the capacity its gene products to bind to the retinoblastoma tumor suppressor protein. Consistent with a potential role in the Rb pathway, *RIZ* may play an important role in human cancer pathogenesis. *RIZ* maps to human chromosome band 1p36, a region commonly altered in many types of human cancers. *RIZ* is the founding member of the PR-domain family of zinc finger genes. Similar to other members of this family, *RIZ* is involved in human cancers in an unusual yin-yang fashion. Two products are produced from the *RIZ* locus which differ by the presence or absence of the PR domain; the PR-plus product RIZ1 is commonly lost or underexpressed whereas the PR-minus product RIZ2 is always present in cancer cells. This yin-yang imbalance in the amount of the two *RIZ* products may be an important cause of malignancy.

## 2. RIZ GENE PRODUCTS AS RB-BINDING PROTEINS

One of the best studied tumor suppressor genes is the retinoblastoma susceptibility gene Rb. Rb is believed to act as a cell cycle break to stop cell growth when the need arises, such as when cells are committed to undergo differentiation. Rb acts by protein complex formation with DNA binding proteins to modulate nuclear DNA related events (1, 2). This activity of Rb is regulated by G1-specific cyclin-dependent kinases (3). The essential role of Rb in tumorigenesis is underscored by the observation that nearly all of the known components of the Rb pathway are altered in tumor cells (4). In retrospect, isolation of components of the Rb pathway may represent a productive way of discovering novel cancer genes.

The Rb-interacting zinc finger gene *RIZ* was isolated in a functional screening for Rb-binding proteins (5) and independently as a *GATA-3*-binding protein *G3B* (6) and as a DNA-binding protein *MTB-Zf* (7). Several features of *RIZ* are consistent with a role in Rb function. First, *RIZ* encodes zinc-finger type DNA binding proteins capable of transcriptional repression (8). *RIZ* products can bind to GC rich Sp1 binding sites and the so called MTE element GTCATATGAC (7). *RIZ* is a relative of the SET domain family of nuclear proteins involved in chromatin mediated gene expression (9). A potential role for *RIZ* products in chromatin regulation and transcription repression is consistent with the role of Rb in transcriptional repression.

Secondly, *RIZ* shares sequence homology with the E1A viral oncoprotein. Rb is best known as a target of viral oncoproteins (1, 10). It is remarkable that different viral proteins, E1A, E7, and T, share a conserved Rb-binding motif LXCXE. The X-ray structure of Rb in complex with the E7's LXCXE motif reveals an overwhelming conservation of residues that make up the LXCXE binding site (11). This observation suggests that cellular proteins with an important role in the Rb pathway might have contributed to the high conservation of this site, and further strengthens the long-held notion that viral proteins are structural homologs of key cellular Rb-binding proteins. It remains an open question as to what those proteins are but several cellular LXCXE-containing genes have been identified as candidates, including *RIZ* and proteins of the histone acetylase/deacetylase complex. The best known Rb-binding protein E2F1 can be clearly excluded as a candidate because it lacks the LXCXE motif and binds to a different site on Rb. Among the cellular LXCXE containing proteins that have been shown to bind Rb at least in vitro, *RIZ* gene products contain the most extensive homology to viral proteins which extends to the nearby sequences of the LXCXE motif (5, 12). Also, *RIZ* products are antigenically related to E1A, which is mediated by a novel conserved motif designated CE1.

Thirdly, *RIZ* gene products have the capacities to induce G2/M cell cycle arrest and/or apoptosis (13). Several lines of investigation suggest a role of Rb in inhibiting apoptosis of differentiated cells. Mouse embryos deficient in Rb display excessive apoptosis in the lens and neurons of the central nervous system and the peripheral nervous system (14-17). Rb expression is shown to protect cells from radiation induced cell death (18). Rb blocks apoptosis mediated by Rb binding proteins such as E2F1 (19). It will be important to determine whether Rb may inhibit apoptosis mediated by *RIZ* gene products.

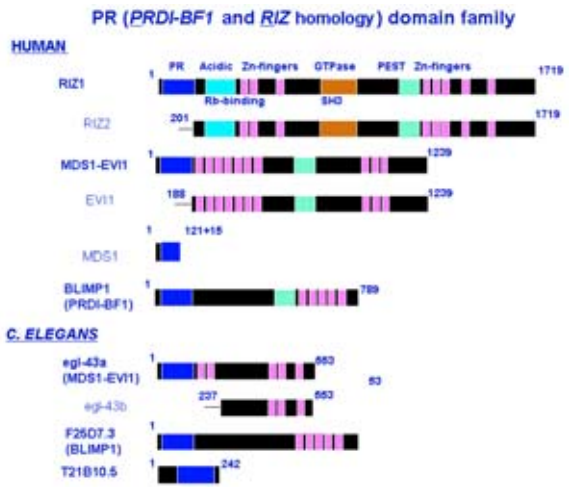


**Figure 1.** PR domain family members. Schematics of protein products of three human PR genes and three C. elegans genes are shown. MDS1-EVI1 and BLIMP1 genes have C. elegans homologs. PEST: Pro, Glu, Ser, and Thr rich sequence.

## 3. THE PR/SET DOMAIN

One novel motif recognized from the *RIZ* gene product is the PR domain. This domain represents a ~100-amino acid region of homology first found between *RIZ* and the previously cloned *PRDI-BF1* protein (*PRDI-BF1-RIZ1* homologous region) (5, 20). The murine homolog of *PRDI-BF1* was later independently cloned as *Blimp1* (21, 22). When the PR domain peptide sequence was later used as a query to search the translated nucleotide database of Genbank (by the tblastn program), we found that a portion of the 5' untranslated region of the EVI1 oncogene encodes the B and C boxes of the PR domain, and the MDS1 gene 5' to the *EVI1* locus encodes the A box of PR (23). Indeed, the expression of the fusion *MDS1-EVI1* gene has been experimentally confirmed (23). Furthermore, the *Caenorhabditis elegans* homolog of *MDS1-EVI1* gene *egl-43*, which controls motor neuron migration, also has a PR domain (24). Thus, the *MDS1-EVI1* gene is a PR gene that normally produces at least two different length products, the PR-containing MDS1-EVI1 protein and the PR-lacking EVI1 protein. Because the former is disrupted and the latter is activated in leukemia cells, the MDS1-EVI1 locus appears to encode both tumor suppressive and oncogenic products.

The recently completed *C. elegans* genome sequence revealed two more PR domain-containing open reading frames. One of these F25D7.3 is the homolog of *BLIMP1* because the zinc finger domains are also highly homologous. The other T21B10.5 is devoid of zinc finger domains and is the first example of a PR protein without any zinc finger domains. EST clones of PR domain genes are also found in the *Drosophila* EST databases. However, no PR peptides can be detected in the yeast genome. Thus, the PR domain may have evolved as a result of the special need of multicellular organisms.

Using a recently developed, more powerful database-searching program (PSI-BLAST), the PR domain was found to be homologous to the previously recognized SET domain (9). The SET domain is a 130-amino acid, evolutionarily conserved sequence motif present in chromosomal proteins that function in modulating gene activities from yeast to mammals (25, 26). It is important to note that the shared residues between PR and SET are also among the most conserved residues in each domain, suggesting they may share a common function.

A common function of the PR domain is likely to be mediating protein-protein interaction. The PR domain of RIZ products functions as a protein-binding interface (9). Recombinant PR domain protein can bind to in vitro translated *RIZ* products in vitro. Binding is mediated by residues conserved among different PR domains, suggesting that similar functions may be shared among different PR domains. Several different SET domains have recently been shown to mediate protein-protein interactions (27-29). Thus, PR and SET are related protein-protein interaction modules.

## 4. THE YIN-YANG OF *RIZ* IN TUMORIGENESIS

An unusual feature of PR genes is the generation of an alternative product that lacks PR but is otherwise identical to the PR-plus product (figure 1). This was first found for *the MDS1-EVI1* gene as mentioned above. The EVI1 product lacks the PR domain whereas MDS1-EVI1 has. Both products are expressed in normal tissues. EVI1 is generated by an internal promoter located within the *MDS1-EVI1* gene (30). The promoter for the full length *MDS1-EVI1* gene has yet to be isolated. The MDS1 exon is located >170 kb 5' of the EVI1 promoter, indicating that the *MDS1-EVI1* gene is very large (23). In addition, *egl-43*, the *C. elegans* homolog of *MDS1-EVI1*, produces an alternative product lacking the PR domain (figure 1), suggesting that expression of the PR-minus product by a PR gene is evolutionarily conserved. A large body of data show that the *MDS1-EVI1* locus is altered in human and mouse leukemia in an unusual yin-yang fashion; while MDS1-EVI1 is disrupted in tumor cells, EVI1 is activated.

The *RIZ* gene also produces a PR-minus product. When the protein products of *RIZ* were first identified in tumor cell lines, only a single protein species of 250 kDa was recognized (5). This protein was later found to be lacking the PR domain and was designated RIZ2 protein. The full-length PR-containing product RIZ1 was identified as a 280-kDa protein that is at a much lower level than RIZ2 in all tumor cell lines examined (31). Characterization of the human *RIZ* gene genomic structure established that RIZ2 is produced by an internal promoter (31). *RIZ* gene is very large (>150 kb) and consists of at least 10 exons. A complete genomic sequence for the 3' end of *RIZ* is available in Genbank (AL031277), which is ~120 kb (figure 2). This sequence contains a single CpG island, which is known to be indicative of promoters. Indeed, the RIZ2 promoter we identified previously is located within this CpG island. The PR domain is encoded

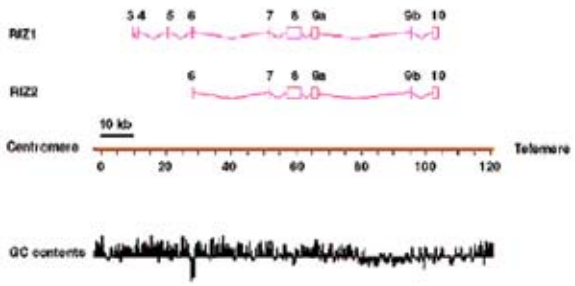


**Figure 2.** RIZ locus genomic structure. The genomic structure of the 3' end of RIZ based on the complete genomic sequence of the BAC clone dJ1177E10 was obtained from the Sanger Center. The telemere to centromere direction of 1p is from right to left. RIZ exons are numbered according to previously published designations (31). RIZ and MTB-zf differ due to alternative splicing of exon 9; RIZ uses exon 9b and terminates with exon 10 while MTB-zf uses 9a and terminates with 9a.

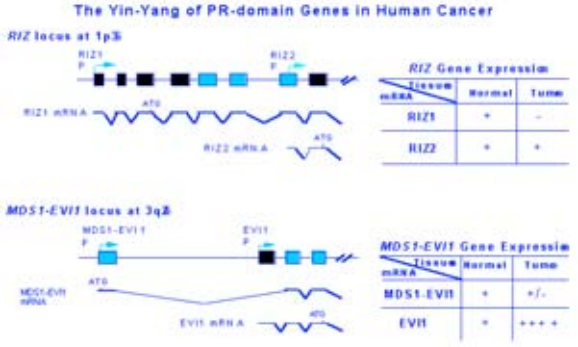


**Figure 3.** The yin-yang imbalance of RIZ and MDS1-EVI1 gene products in tumor cells. Partial genomic and mRNA structures (PR domain region only) of the 5'-end of RIZ and MDS1-EVI1 genes are shown schematically. P: promoter. Open boxes represent exons; the shaded boxes represent PR domain exons; thin lines represent introns. Thick horizontal lines designate mRNA. The expression of MDS1-EVI1 in tumors is likely to be reduced in dosage (+/-) due to the allelic inactivation by translocation.

by three small exons 4-6. The majority of the RIZ1 cDNA is encoded by one large exon 8. RIZ2 mRNA is produced by an internal promoter located at the intron-exon boundary of exon 6. The RIZ2 promoter from human, rat, and mouse genes have been isolated and sequenced. The promoter is highly conserved and shows features of a typical TATA-less GC-rich promoter of a housekeeping gene, consistent with the ubiquitous expression of RIZ2 in all normal and tumor tissues examined (31).

Several observations suggest that RIZ1 is a tumor suppressor whereas RIZ2 is not (figure 3). RIZ1 expression is commonly lost in human breast cancer cell lines and tumor specimens as well as in several other types of tumors examined, including neuroblastoma, lung cancer, and osteosarcoma (13). In contrast, RIZ2 is uniformly expressed in all cases examined. Loss of RIZ1 but never RIZ2 is most common in hepatoma cell lines. 80% of hepatoma cells showed undetectable expression of RIZ1 but all showed uniform expression of RIZ2 (Jiang, G., Buyse, I.M., Simon, D., and Huang, S., submitted). The results suggest an especially important role of RIZ1 in hepatoma tumorigenesis. This is consistent with RIZ's location on 1p36.23 next to the marker D1S228 (7, 32). This region commonly undergoes deletions, rearrangements, or LOH in a broad spectrum of human tumors, including mammary cancer (33), ovarian cancer (34), primary hepatoma (35), colorectal cancer (36), chronic myelocytic leukemia (37), non-Hodgkin's lymphoma (38), melanoma (39), parathyroid adenoma (40), Merkel cell carcinoma (41), pheochromocytoma (42), and neuroblastoma (43). A consensus deletion region in neuroblastoma has been defined (44), which is distal to the center of deletion in hepatoma (35, 45), suggesting that different genes are involved in these two different types of cancers. Because *RIZ* is proximal to the consensus deletion region of neuroblastoma, *RIZ* may be more commonly involved in hepatoma than neuroblastoma. Indeed, decreased RIZ1 expression is not common in neuroblastoma cell lines and tumor specimens (13).

The uniform presence of RIZ2 suggests that loss of RIZ1 is not a random-occurring event. There may be a specific negative selection for RIZ1 versus RIZ2 in tumors. Consistently, forced RIZ1 expression causes G2/M cell cycle arrest and/or apoptosis in breast cancer and osteosarcoma cells (13). Adenovirus mediated RIZ1 expression caused G2/M arrest and apoptosis in hepatoma cell lines and inhibited hepatoma tumor growth in nude mice (Jiang, G., Buyse, I.M., Simon, D., and Huang, S., submitted).

Inactivating gene expression rather than intragenic mutations affecting protein structure appears to be the basis of RIZ1 alteration in malignant cells. Whether tumor-associated 1p36 alterations may inactivate RIZ1 expression requires future investigation. Relative to the RIZ1 abnormality, the uniform presence of RIZ2 is striking and may indicate a positive role for RIZ2 in oncogenesis. A need to maintain RIZ2 expression in tumor cells may explain the lack of gross mutations in *RIZ* because RIZ2 shares 89% of the coding region with RIZ1. Of course, mutations in the PR region of RIZ1 should not affect RIZ2. Such mutations, however, must be subtle (undetectable by Southern-blot analysis). Moreover, if such mutations exist, they are likely to be rare because tumors primarily display RIZ1 underexpression. However, it is possible that certain nucleotide changes could lead to destabilization of transcripts. Given that RIZ1 and RIZ2 are produced by different promoters, it seems likely that the RIZ1 promoter may represent a specific target of inactivation in tumor cells.

Although loss of RIZ1 expression may be common in human cancers, the present lack of data of intragenic mutations in RIZ1 makes it difficult to distinguish causality from correlation. To prove that loss of RIZ1 is causal to human tumorigenesis, animal models will be needed where RIZ1 but not RIZ2 is specifically

inactivated or knocked out. We have in fact generated such models in the mouse and found those animals to be tumor prone (Steele-Perkins, G., Jiang, G-L., Yu, J.X., Yang, X.H., Liu, J., Bronson, R, and Huang, S., manuscript in preparation). Thus, for all practical purposes, RIZ1 represents a bona-fide tumor suppressor.

## 5. SUMMARY

Several lines of investigation suggest that the *RIZ* locus on 1p36 plays an important role in human cancers. The RIZ1 product of this locus is a strong candidate tumor suppressor. Loss of RIZ1 may be common in a variety of sporadic human cancers associated with 1p36 alterations. The mechanisms of RIZ1 loss, either genetic or epigenetic, remains to be determined by future studies. Also, studies of RIZ1 knock out mice should further establish the role of RIZ1 in tumor suppression and its relationship with other tumor suppressors.

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