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Why YPEL3 represents a novel tumor suppressor

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1. ABSTRACT

Yippee-like 3 (YPEL3) was reported in 2004 as one of five family members of the Yippee protein with conservation in species down to slime molds. While reports of other YPEL family members have surfaced our laboratory was the first to report that YPEL3 is induced by the p53 tumor suppressor. Furthermore we demonstrated that YPEL3 is growth suppressive, triggering cellular senescence in human cell lines and is down-regulated in several human tumors. Studies with mouse YPEL3, originally named small unstable apoptotic protein (SUAP), confirmed that the gene encodes a growth suppressive highly unstable protein. In this review we show that transcriptionally active forms of p73 and p63, family members of p53, can transactivate the human YPEL3 gene. While there are several reported YPEL3 transcripts and potentially 2 protein isoforms, no clear protein structure has been reported. As evidence mounts that YPEL3 is a tumor suppressor gene, studies aimed at understanding its biological function, regulation of gene expression and impact on tumorigenesis will help determine the therapeutic potential of this novel cancer gene.

2. DISCOVERY OF YPEL3 AND ITS FAMILY MEMBERS

Yippee-like protein 3 (YPEL3) is one of five human homologs of the *Drosophila* gene *yippee*. *Yippee* was first discovered in *Drosophila* as a protein that interacted with hemolin from *Hyalophora cecropia* in a yeast two-hybrid screen (1). *Yippee* localized to the X chromosome showing strong sequence conservation in eukaryotes ranging from slime mold to humans. The *yippee* gene consists of 4 exons encoding a protein of 121 amino acids (13.7 kDa predicted molecular weight). Analysis of the amino acid sequence revealed the presence of a zinc binding Ring Finger domain, a motif conserved in all *yippee* homologs. While no other protein motifs were uncovered the authors did observe using the two-hybrid assay that *Yippee* appeared capable of forming homodimers.

As *Yippee* was being characterized Farlie and coworkers were studying genes involved in craniofacial development focusing on a cluster of human genes within chromosome 22q11.2 known as the 22q deletion syndrome.

Deletion of this region of human chromosome 22 is associated with a host of craniofacial development abnormalities most notably, DiGeorge syndrome (2). By using a similar Di George synteny in mice (3) they discovered that YPEL1 was found to be common in both deletion regions (4). They went on to clone mouse YPEL1, noted its high level of conservation among invertebrates and vertebrates and showed that it was expressed in the ventral portion of early embryos that develop into the brachial arches from which the face derives.

Recently, Abiatari and coworkers discovered that YPEL1 is downregulated in pancreatic cancer cell lines and tumor tissue. Paradoxically, a lower YPEL3 gene expression in pancreatic tumors correlated with a slight increase in survival (16 months vs. 13 months) (5).

YPEL1 is not the only *Yippee* homolog in humans. In 2004 a group from Japan reported the characterization of five human YPEL family members (6). Using bioinformatic approaches they identified the genomic location of each family member with YPEL3 being located on the short arm of chromosome 16. Based on amino acid comparisons human YPEL3 is 100% identical to mouse YPEL3 and shows high homology (>80%) to YPEL1, -2 and -4. YPEL5 most closely aligns to the *Drosophila Yippee* protein (70% identical). Semi-quantitative PCR showed that YPEL3 and YPEL5 were constitutively expressed in human and mouse tissues with the other family members having more restrictive gene expression patterns (6). Like previous reports on *yippee* and YPEL1, the group noted the high conservation of YPEL family members across a variety of species. Using indirect immunofluorescence they reported nuclear, centrosome localization, consistent with the nuclear localization reported for mouse YPEL1 (4, 6).

3. TRANSCRIPTIONAL REGULATION OF YPEL3

3.1. YPEL3 is regulated by the p53 tumor suppressor

Our laboratory became interested in YPEL3 following a study in which we examined how activation of the p53 tumor suppressor impacted the gene expression of MCF7 breast cancer cells. Reactivation of p53 in human tumors is an active area of research. Approximately 50% of all human tumors harbor mutations in the p53 gene (7). These mutations tend to be missense mutations that cluster in the region of the p53 gene that encodes the DNA binding domain. While half of all human tumors produce a mutant p53 incapable of transactiving genes, the other half of human tumors possess a wild-type p53 gene. Tumors harboring a wild-type p53 gene use a series of other genetic mechanisms to inactivate p53 (8). Numerous *in vitro* and *in vivo* approaches have been employed aimed at "reactivating" wild type p53 as a means to inhibit tumor cell growth. Using MCF7 cells that possess wild-type p53 inactive due to the overexpression of two p53 negative regulators HdmX and Hdm2, we employed RNAi to knockdown HdmX or Hdm2 (9).

The loss of either HdmX or Hdm2 triggered a dramatic cell cycle arrest with no detectable (sub G1) apoptosis (9). Consistent with the biological response analysis of the gene expression profiles from the HdmX or Hdm2 knock-down cells showed a predominance of p53 regulated genes that triggered growth arrest and a global loss of E2F regulated genes. Careful analysis of the p53 gene signature uncovered several genes with changes in expression that suggested each might represent a gene directly or indirectly regulated by p53 activation. YPEL3 represented one such gene.

Choosing to test whether YPEL3 was a direct target of the p53 tumor suppressor was based on two additional observations. First, we examined all of our novel p53 target genes against a database of putative p53 target genes uncovered through computational and microarray approaches (10). YPEL3 was identified based on computational analysis as a potential p53 regulated gene.

The second, more surprising result was the identification of another YPEL3 publication. In 2003 Stacey Baker detailed the discovery of an apoptosis-associated protein named SUAP for small unstable apoptotic protein (11). SUAP suppressed cell proliferation of 32Dcl3 myeloblastic cells and was upregulated in 32Dcl3 cells grown in the absence of IL-3, conditions that trigger apoptosis. Using an HA-tagged SUAP expression vector Dr. Baker demonstrated that SUAP was rapidly degraded by ubiquitin-mediated proteasome degradation and when overexpressed triggered an increase (3 to 8 %) in annexin-V positive cells. Unbeknownst at that time SUAP was in fact, mouse YPEL3. In our Cancer Research publication listed below, we were the first to make this connection between SUAP and YPEL3. Interestingly, we have confirmed that human YPEL3 protein is rapidly degraded by ubiquitin-mediated proteasome degradation (K. Miller, personal communication).

To confirm that p53 was capable of directly activating the human YPEL3 gene, we initially tested YPEL3 gene expression in tumor cell lines exposed to various DNA damaging agents. Using Taq-Man based RT-PCR we demonstrated that endogenous YPEL3 mRNA is induced in DNA damaged cells harboring wild-type p53 (12). A putative p53 response element was localized within the YPEL3 promoter and shown to respond to p53 induction. Interestingly, the YPEL3 p53 response element harbors three p53 half-sites; mutations in each were shown to eliminate p53 responsiveness. Finally, chromatin immunoprecipitation experiments were employed using HCT116 +/+ p53 colon carcinoma cells either treated with doxorubicin (damaged) or mock treated (undamaged). Under DNA damage conditions, p53 was shown to associate with the YPEL3 promoter (12). From this data, we conclude that the human YPEL3 gene represents a p53 regulated gene.

3.2. p53 family members regulate YPEL3

In the course of studies addressing the role of p53 in regulating YPEL3 gene expression we observed a low but reproducible induction of YPEL3 mRNA levels when HCT116 cells lacking p53 were exposed to doxorubicin

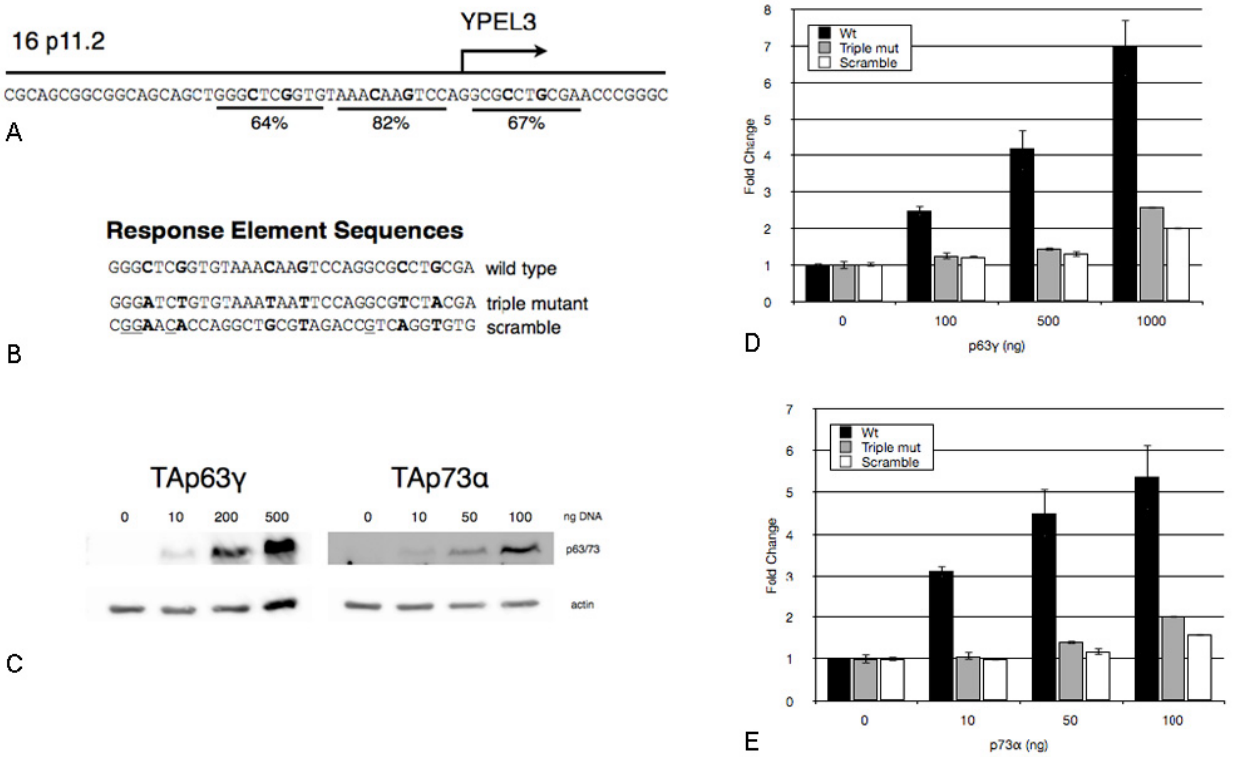

Figure 1. The YPEL3 p53 response element cluster sites. (A) Cluster site of p53 response elements. The start site of transcription is indicated with an arrow. The three p53 response element half sites are underlined with percent consensus indicated below each site. (B) The response element sequences used for luciferase assays. A 50 bp region of the YPEL3 promoter was used to generate firefly luciferase constructs for luciferase assays. A triple mutant was generated which changed the consensus C and G bases (bold) to A or T. A randomly generated scramble sequence was also created where underlined bases indicate bases that remained the same as the wild type sequence. (C) Western blot showing expression of TAp63γ (left) and TAp73α (right) protein following transfection of expression vectors into H1299 cells. Actin serves as a loading control. (D/E) TAp63γ and TAp73α transactivate the 50 bp cluster site. H1299 cells were cotransfected with increasing amounts of TAp63γ (D) or TAp73α (E) expression construct, Renilla luciferase, and indicated firefly luciferase construct. 24 hours after transfection, cells were lysed and subjected to dual luciferase assay. Luciferase readings were measured in relative light units and firefly luciferase values were normalized to the Renilla luciferase values. Values were plotted as fold change relative to the 0 ng p63/p73 controls. Error bars indicate standard deviation between three biological replicates. Experiments were done a minimum of three times in biological triplicate each time.

(12). Given that these cells were p53 null we tested the hypothesis that p53 family members p63 and p73 might also regulate YPEL3 expression. Using a 50 bp region of the YPEL3 promoter harboring the wild-type p53 response element or two mutant versions of this 50 bp region, we were able to demonstrate that TA-forms of p63 and p73 can induce the YPEL3 promoter (Figure 1). As discussed later, the biological relevance of the potential regulation of YPEL3 by p53 family members is a future area of research.

3.3. YPEL3 promoter analysis

As mentioned above YPEL3 is located on the minus strand of chromosome 16p11.2 (16:3001136-30015022) between the T-box transcription factor 6 gene (TBX6; 16:30010706-300004618) and the glycerolphosphodiester phosphodiesterase domain containing 3 (GPDP3; 16:33032379-33032632) genes. Using the UCSC genome browser CpG islands were identified 5' and 3' of the YPEL3 gene (Figure 2, green boxes). We demonstrated that in ovarian cancer cell lines a CpG DNA hypermethylation within the YPEL3 gene correlates with transcriptional regulation (12). While the p53 binding site was identified using both bioinformatic and chromatin immunoprecipitation assays to identify other potential cis-acting elements that might regulate YPEL3 expression we searched for transcription factor bindings sites that were conserved in human, mouse and rat. Figure 2 shows that transcription factor DNA binding sites for CREB, POU2F1 and the FOXO family were identified within the YPEL3 promoter region. While YPEL3 gene regulation by the growth suppressive FOXO transcription factor family is intriguing additional experimentation will be required to validate that any of these transcription factors, identified based on sequence comparison with consensus binding sites, impact YPEL3 expression under biologically relevant conditions.

3.4. Multiple YPEL3 mRNA transcripts

RefSeq identifies two YPEL3 transcripts named transcript variant 1 and transcript variant 2. Transcript

Table 1. YPEL3 gene expression in 8 different solid tumors was compared with normal tissues

Tumor Type	Decrease	No Change	Increase
Breast	22%	11%	67%
Colon	89%	11%	0%
Kidney	44%	44%	11%
Liver	33%	11%	56%
Lung	89%	11%	0%
Ovary	100%	0%	0%
Prostate	30%	22%	44%
Thyroid	22%	0%	78%

TissueScan Cancer Survey Tissue qPCR Array, CSRT101, was purchased from OriGene. Each tumor type consisted of cDNAs from nine tumor samples with three normal tissue speciments. cDNA was rehydrated according to manufacturer's instructions and RT-PCR was performed as described below except that the GAPDH Assay on Demand was multiplexed with the YPEL3 Assay on Demand (Applied Biosystems, validated targets). An increase or decrease was met if the YPEL3 expression normalized to GAPDH was greater than 2 fold (increase) or less than 50% (decrease) of the average expression from the three normal samples. Note for the ovarian dataset, one normal specimen was removed.

variant 1 (NM_001145524.1) represents a 1588 nucleotide length mRNA that encodes an isoform 1 protein of 157 amino acids. Transcript variant 2 (NM_001145524.1) represents a smaller mRNA (940 nucleotides) encoding an isoform 2 protein of 119 amino acids. The primary difference between the two protein isoforms is that the larger protein (isoform 1) contains an additional amino-terminal 38 amino acids not present in isoform 2. Translation programs predict that the downstream ATG in transcript variant 1 would be the preferred translation start site suggesting that both transcripts would encode the smaller, isoform 2 protein. However, AceView (13) reports the existence of 9 prospective YPEL3 mRNA transcripts and more than two potential translation reading frames. Clearly more work will be needed to resolve the expression patterns of these various YPEL3 transcripts and the potential protein isoform expressed.

4. YPEL3 BIOLOGICAL FUNCTION

4.1. YPEL3 triggers growth arrest

Towards understanding more about the cellular function of YPEL3 the human YPEL3 cDNA was subcloned into a tetracycline inducible retroviral expression vector and transduced into various human cell lines. The induction of YPEL3 led to cell cycle arrest in human tumor (MCF7, U20S) and primary (IMR90) cells. This was observed using flow cytometry (increased G1/S phase ratio), MTT and colony formation assays. Unlike the induction of apoptosis when mouse YPEL3 (SUAP) was overexpressed in 32Dcl3 myeloblastic cells (11), no increase in sub-G1 or annexin-V positivity was observed when human YPEL3 was induced. Whether this is the result of differences between the cell lines (human vs. mouse) or the level of induction will require further experimentation. We noted in our Cancer Research publication that the tetracycline addition was sufficient to increase YPEL3 mRNA levels comparable to that observed when cells were damaged with doxorubicin.

4.2. YPEL3 plays a role in cellular senescence

The flattened morphology of cell cycle arrested, YPEL3 induced cells suggested that these cells might be undergoing cellular senescence. To examine this possibility beta-galactosidase activity and senescent associate heterochromatin foci (SAHFs), two hallmarks of cellular senescence (14), were monitored in MCF7 and U2OS cells where YPEL3 induction was controlled by tetracycline. In both cell lines, an increase in beta-galactosidase positive cells with SAHFs was observed (12). Using primary diploid fibroblasts and activated ras, we went on to demonstrate that YPEL3 induction could trigger senescence in primary fibroblasts and that the p53 dependency of ras-mediated cellular senescence could be compensated by the induction of YPEL3. Surprisingly, the knock-down of YPEL3 completely abrogated ras-mediated senescence. Taken together these findings implicate YPEL3 as an important protein in oncogene-mediated cellular senescence. Given that inducing cellular senescence can result in increased tumor clearance *in vivo* (15, 16), these findings point to YPEL3 activation as a potential therapeutic approach in the treatment of human cancers.

5. YPEL3 GENE EXPRESSION DOWN-REGULATED IN HUMAN TUMORS

Based on its growth suppressive activities we predicted that YPEL3 would be down-regulated in human tumors. In an initial pilot study of 8 solid tumors where each tumor type consisted of 9 tumor and 3 normal specimens, YPEL3 showed decreased mRNA expression in lung, colon and ovarian (Table 1). In our Cancer Research paper we pursued the YPEL3 decrease in ovarian tumors by comparing 30 ovarian tumor samples with 6 normal ovarian tissues. A statically significant decrease in YPEL3 gene expression in ovarian tumors was detected when compared to normal specimens. Interestingly this decrease was seen in both early and late stage ovarian tumors suggesting that YPEL3 down-regulation may represent an early event in the progression towards more aggressive ovarian tumors. While it was not possible to examine the YPEL3 gene locus in these ovarian samples we were able to demonstrate using ovarian cell lines that the decrease in YPEL3 expression correlated with a hypermethylation of the CpG island located near the YPEL3 promoter. Furthermore treatment of these ovarian cell lines with the DNA methylation inhibitor 5-azadeoxycyctidine led to a marked increase in YPEL3 gene expression.

Towards examining the expression of YPEL3 in colon carcinomas we collected 22 colon tumor samples with matched, normal controls and analyzed them for YPEL3 gene expression using RT-PCR and CpG hypermethylation of the YPEL3 promoter by base specific PCR analysis (R. Tuttle et.al., manuscript under review). Results showed that while YPEL3 is preferentially down-regulated in human colonic adenocarcinomas DNA hypermethylation does not appear to be the primary mechanism of YPEL3 down-regulation in colon carcinomas. However preliminary data suggest that histone acetylation may be a relevant epigenetic modulator of

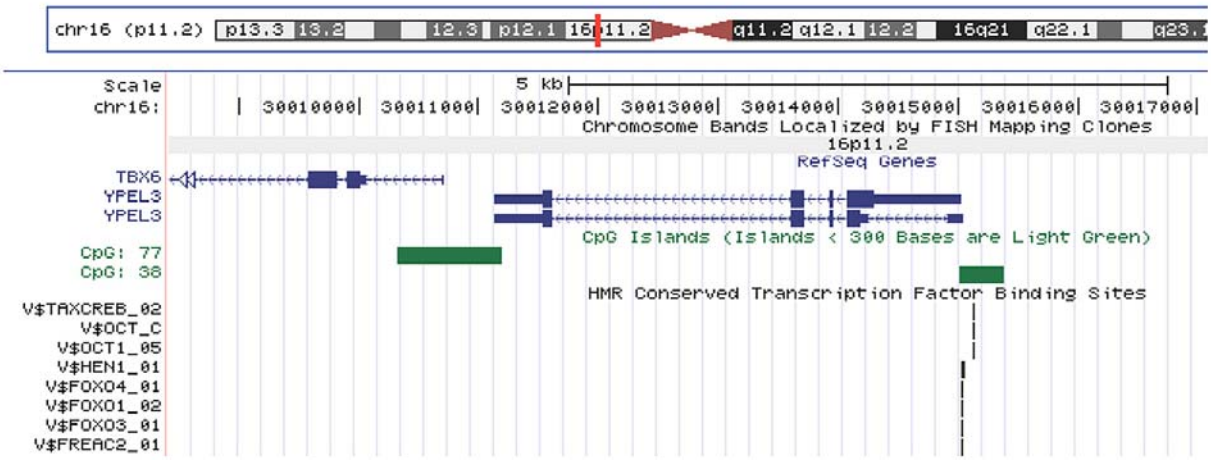

Figure 2. Analysis of the YPEL3 genomic region for CpG islands and evolutionarily conserved transcription factor binding sites. Both searches were performed using the appropriate tracks in the UCSC Genome Browser. CpG islands are listed in green. CREB site: V$TAXCREB_02; POU2F site: V$OCT_C or V$OCT1_05; FOXO binding sites: remaining V$ sites.

Table 2. Decreased YPEL3 gene expression detected in Oncomine DNA microarray data from various human tumors

Tumor Type	P-value	Fold Change	Source
Glioblastoma	1.66E-14	-2.001	Sun
Acute Meyloid Leukemia	7.99E-11	-2.462	Anderson
T-Cell ALL	8.57E-09	-4.412	Anderson
Squamous Cell Lung Carincoma	5.87E-07	-2.875	Garber
Invasive Breast Carcinoma	1.95E-06	-4.520	Finak

An analysis of Oncomine's database was performed comparing tumor verse normal specimens where YPEL3 probe sets were decreased in the tumor samples with a P-value of less than 10E-5. The fold change represents the average decrease in expression from which the values were obtained.

YPEL3. Finally, using Oncomine to examine microarray data for tumors showing YPEL3 down-regulation we discovered several human tumors with decreased YPEL3 expression (Table 2). Interestingly, no tumors showed elevated YPEL3 expression when compared to normal specimens. Taken together these studies provide compelling evidence that YPEL3 gene expression is frequently down-regulated in several human tumor types.

6. FUTURE PERSPECTIVES

While YPEL3 spent 6 years as a homolog of a family of conserved proteins with unknown function recent work from our laboratory suggests that YPEL3 possesses many of the attributes of a tumor suppressor gene. The discovery that the p53 tumor suppressor protein transactivates the YPEL3 gene was the first evidence that YPEL3's activity might be growth suppressive. We subsequently demonstrated the growth suppressive activity of YPEL3 in studies where YPEL3 re-expression negatively impacted cell growth in human and normal cells. Data from our laboratory and others have confirmed that YPEL3 gene expression is down-regulated in several human tumor types, a result consistent with that of many tumor suppressor genes. Future studies examining the molecular basis of this down-regulation and a better understanding of the regulation of various YPEL3 transcripts in normal and tumor samples will hopefully shed light on issues such as YPEL3 mutants and the growth suppression of putative protein isoforms.

Although YPEL3 was first identified as a p53 regulated gene our recent findings that TAp63 isoforms can induce YPEL3 gene expression (Figure 1) suggest that there may be other roles for YPEL3. Given the critical role for p63 in keratinocyte differentiation it will be interesting to determine how YPEL3 impacts skin development.

The fact that human and mouse YPEL3 are 100% identical at the amino acid sequence (6) and that mouse YPEL3 (SUAP) showed growth suppressing effects in a myeloblastic cell line (11) provide compelling reasons to examine the putative tumor suppressor activity of mouse YPEL3 through knock-out studies. We are collaborating with another group to establish a YPEL3 knockout mouse model and believe that the analysis of the tumor incidence of these mice will help to address YPEL3's putative tumor suppressor activity.

Besides testing if YPEL3 is a classic tumor suppressor it is clear that the biological function of YPEL3 remains an enigma. Using yeast 2-hybrid assays recent results with other family members, namely YPEL5 (17) and YPEL4 (18), suggest that the YPEL proteins may function in cell signaling based on their association with RanBPM/RanBP10 and MVP respectively. The ability of YPEL3 to trigger cellular senescence implies that it too may impact signaling pathways.

A final interesting area of future study will likely involve assessing if the various YPEL family members interact. This is based first on the observation with *Yippee*

showing it was capable of forming homodimers (1) suggesting the possibility that the human homologs may in fact heterodimerize. That taken with our preliminary data that YPEL5 may also be a p53 regulated gene (S. Berberich, personal communication) suggests that studies into the interplay of these YPEL family members or a subset of them may be the critical next experiments.

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