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Deep Insight Into YPEL3

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Abstract

Deep insight into YPEL3.

YPEL3 identification

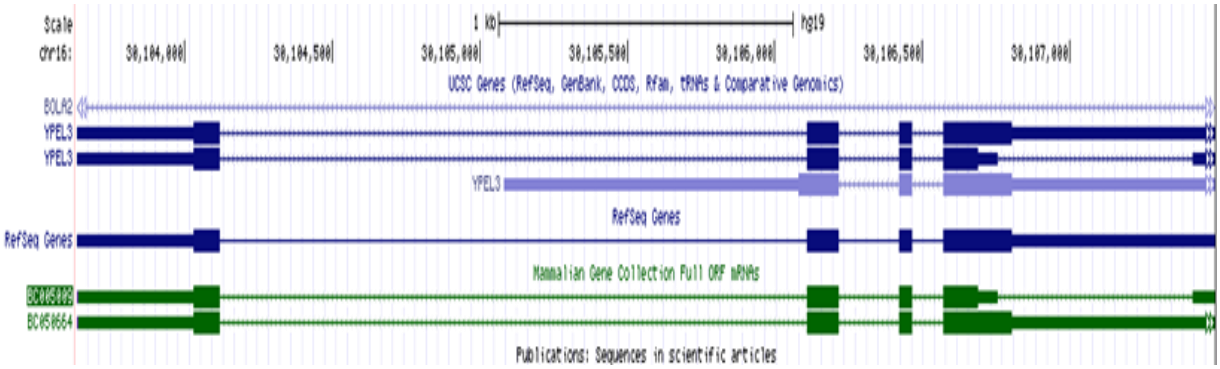
The Yippee gene was first identified in Drosophila through a yeast interaction trap screen for proteins that interact with Hemolin, a member of the immunoglobulin superfamily (Roxstrom-Lindquist et al., 2001). Later, five human Yippee-like genes, including YPEL3, were described in human and mouse tissues (Hosono et al., 2004). YPEL3, also known as Protein yippee-like 3, SUAP, RKSG5 or MGC10500, was found to be ubiquitously expressed in human fetal tissues and to have high sequence conservation between a wide ranges of species (Roxstrom-Lindquist et al., 2001). Human and mouse YPEL3 have 100% sequence identity (Hosono et al., 2004).

In the first publication to address the biology of YPEL3, Baker (2003) described a small unstable apoptotic protein (SUAP), subsequently determined to be YPEL3. Using a murine myeloid precursor cell line, apoptosis was induced by IL-3 deprivation and granulocyte colony stimulating factor treatment. The RNA of these cells was then analyzed. YPEL3 was induced in the apoptotic myeloid precursor cells compared to normal, growing cells with IL-3 present (Baker, 2003). Additionally, YPEL3 was also found to be rapidly degraded by the proteasome which led to the descriptive name of small unstable apoptotic protein.

YPEL3 gene

YPEL3 is located in the region of 16p11.2 along with 22 other genes. The importance of this region in relation to development and pathologic syndromes is discussed in detail later. The Mammalian Genome Project was completed in March 2009. The objective of this project was to provide researchers with access to sequence-validated full-length protein-coding cDNA clones for various mammalian genomes. A search for YPEL3 clones on the Mammalian Genome Clone Homepage resulted in two clones. One denoted as MGC:10500 (Accession: BC005009) differs from the YPEL3 sequence by 39 base pairs according to the GenBank sequence alignment. This clone has been determined synonymous with YPEL3. However, the GenBank records were frozen in 2009 and sequence revisions have been performed since then so we have performed this analysis through the assistance of other tools to verify these results.

Further investigation through UCSC Genome Browser resulted in an 86.33% exon structure similarity to the transcript 1 sequence and 100% exon structure similarity to the transcript 2 sequence. These similarities are based on the BLAT genomic alignments of the CDS of the MGC clone with the alignments of the RefSeq mRNA CDSs. Additionally, the alignment of the mRNA had 100% identity with a 95.84% alignment.



Splign is a tool that is used for accurate and rapid alignment of spliced cDNA sequences against their genomic counterparts. It has been found to be more accurate than a BLAST analysis since BLAST does not include the nonaligning intronic segments and lacks precision at splice junctions. Using the Splign alignment tool through NCBI website inputting BC005009 for cDNA and selecting Homo sapiens for the whole genome resulted in a 100% match in all categories.

Two functional YPEL3 transcript variants have been identified by NCBI. One variant (transcript 2) is a 940-bp transcript (NCBI Reference Sequence: NM_001145524.1) and translates into a 119 amino acid protein that is approximately 13.6kDa. This isoform is the 'canonical sequence (NCBI Reference Sequence: NM_001138996.1). A 1588-bp alternative spliced transcript (transcript 1, NCBI Reference Sequence: NM_031477.4) has also been reported by NCBI. This isoform codes for a 157 amino acid protein that is approximately 17.5kDa. This isoform has an additional 29 amino acids sequence at the N-terminus. Both YPEL3 isoforms possess 2 putative zinc finger motives that are common in all members of the YPEL3 family (Hosono et al., 2004). There have been at least 10 other transcripts identified from different normal and tumor human tissues.

YPEL3 protein structure

The Yippee gene consists of 4 exons encoding a protein of 121 amino acids (13.7 kDa predicted molecular weight). Amino acid sequence revealed the presence of a zinc binding ring finger domain, a motif that is 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 (Roxstrom-Lindquist et al., 2001).

It has proven difficult to study YPEL3 at the protein level for a number of reasons. It is a small protein that is rapidly degraded by ubiquitin mediated proteasome degradation (Baker, 2003 and personal communication Kelly Miller). There is currently no published complete structural data and this is an area of ongoing research. Attempts are underway to purify this protein for additional structural studies.

YPEL3 protein localization

The Hosono Lab (2004), using immunofluorescent staining in COS-7 cells, found that the YPEL1-4 proteins localize in the nucleoli and centrosome during interphase. During mitosis, YPEL1-4 proteins were found to localize to an unknown structure on or close to the mitotic apparatus and the mitotic spindle. Since the antibody used in this study was not specific for YPEL3, it is impossible to discern the precise location of YPEL3 and the resulting localizations could contain any of the YPEL 1-4 proteins.

Unpublished data in the Berberich lab using an antibody specific to YPEL3 suggests that YPEL3 localization is weakly nuclear with punctate perinuclear staining.

Both the localization of YPEL3 and potential binding partners of the YPEL3 protein are ongoing areas of research.

YPEL3 and p53 family

In order to study novel p53 regulated genes, a microarray experiment was completed where the negative regulators of p53 (Hdm2 and HdmX) were silenced in MCF7 breast carcinoma cells using siRNA technology (Heminger et al., 2009). MCF7 cells contain wild-type p53; therefore, knocking down Hdm2 and HdmX allowed for the non-genotoxic stress induction of p53.

This led to a G1 phase cell cycle arrest along with sensitization of the arrested MCF7 cells to DNA damage (Heminger et al., 2009). From analysis of the microarray data, a novel p53 target was discovered named YPEL3. Further validation studies, including chromatin immunoprecipitation (ChIP), confirmed that YPEL3 is a direct p53 target gene (Kelley et al., 2010). TA forms of p63 and p73 (p53 family members) have been shown to induce the YPEL3 promoter (Berberich et al., 2011). The biologic relevance of this is an ongoing area of research.

The expression of p53 varies based on the type of stimulus (Purvis et al., 2012). Double-strand DNA breaks induces p53 expression in a series of repeated pulses. This type of p53 expression allows cells to recover from DNA damage. However, when p53 expression is sustained using a sequence of timed drug additions, the cell fate is altered and senescence is induced. When p53 expression is sustained different downstream genes are targeted mediating the senescence response. The Purvis lab sustained the p53 signal using Nutlin-3 which binds to p53 inhibitor Mdm2. They then compared the genetic expression levels of various genes after treatments with either gamma radiation or Nutlin-3. YPEL3 expression did not mirror the oscillatory pattern of p53 expression and was not induced by p53 pulses. Post Nutlin-3 treatment, YPEL3 showed a delayed increase in expression under the sustained p53 signaling. This suggests that as p53 pulses it selectively activates genes in response to DNA damage and selectively activates a different set of genes for terminal cell fates by holding a sustained expression level. This substantiates the Berberich lab's previous finding that YPEL3 is a crucial gene for inducing cellular senescence (Kelley et al., 2010).

YPEL3 and p17

Recently, Klaus Heese (2013) showed that YPEL3 interacts with p17. p17 is localized in the cellular cytoplasm of proliferating cells, where it modulates cell survival and drives the cell cycle into the G0/G1 phase. The significance of this interaction has yet to be elucidated. There were also other tumor suppressor genes found to interact with p17 in this study again implicating YPEL3 in the pathway to tumorigenesis.

YPEL3 and estrogen receptor

The Cicatiello lab (2010) performed an expression profile of ZR-75-1 cells eleven times during a 32 hour treatment with a physiological dose of 17β-estradiol. The changes were monitored against hormone starved cells. They found deprivation of estrogen induced G1 arrest which could be overcome by the addition of estrogen. During this transcriptome analysis, YPEL3 was found to be down regulated after treatment with B-estradiol. It was grouped in estrogen cluster 1 with other genes found to be suppressed by estrogen. The clusters were made to organize the genes according to similarities in relative inhibition or activation. Cluster 1 includes genes that required 1 to 4 hours of hormone treatment for a progressive decrease in mRNA expression to be first detected. These results were confirmed in an independent microarray study previously done by the Finlin lab (2001).

These findings led to the further investigation of YPEL3 regulation by the estrogen receptor. YPEL3 is down regulated by the estrogen receptor (ER-alpha) in ER+ breast cancer cells (Tuttle, et al. 2012). Additionally, depletion of estrogen or treatment of ER+ cells with Tamoxifen leads to induction of cellular senescence that is dependent on YPEL3. The estrogen receptor regulation of YPEL3 occurred independently of p53. This demonstrates yet another signaling pathway where YPEL3 plays a crucial role and implicates YPEL3 as a tumor suppressor. Current studies are underway to investigate the relevance of these findings at the protein level in human breast tumors.

YPEL3 and IGF-1

Insulin and insulin-like growth factor-1 (IGF-1) exert specificity on metabolism and growth through homologous receptors (Boucher, et al., 2010). Several studies have shown that both hormones may mediate the same physiological response. However, it is not known whether or not insulin receptor (IR) and insulin-like growth factor 1 receptor (IGF1R) have distinct or overlapping functions. The Boucher Lab used several strategies to assess the contribution both of these receptors have on gene expression post induction by their respective ligands.

One such strategy included the use of pre and post differentiated adipocytes. After a 6 hour treatment with IGF-1 in wild-type brown preadipocytes, YPEL3 was found to be down-regulated by almost 75%. They repeated this experiment with insulin which mediated similar but lower magnitude of genetic expression. In the case of YPEL3, 6 hours post insulin treatment decreased YPEL3 expression by slightly more than 50%. This data suggests that decreased levels of YPEL3 may be required for growth to occur, again contributing to the growth suppressive role of YPEL3.

YPEL3 mutations

The Cancer Genome Atlas has sequenced thousands of tumors allowing for the expansion in the discovery of genetic mutations (Kandoth, et al., 2013). The Kandoth Lab analyzed over 3000 tumors from 12 cancer types looking for mutated genes in order to elucidate the mechanisms of cancer initiation and progression.

They identified four different mutations of YPEL3 in uterine corpus endometrial carcinoma. Two mutations that occurred were silent mutations, and two were missense mutations.

The relevance of these mutations has yet to be elucidated. In that only 127 significant mutations were found in over 3000 genes, these results suggest that the number of mutations required during oncogenesis is fairly small and suggest that other factors such as epigenetic regulation play a critical role for YPEL3 in tumorigenesis.

YPEL3 Biologic Functions

Uncovering the biologic function of YPEL3 is an ongoing area of research. The unifying theme is that YPEL3 appears to be growth suppressive. Unlike in the mouse model with SUAP, induction of YPEL3 in human tumor (MCF7, U2OS) or primary cells (IMR90) did not cause apoptosis, but rather cell cycle arrest. Using flow cytometry, there is an increase in G1/S phase cells after YPEL3 induction. There is also a decrease in colony number in colony formation assays after the expression of YPEL3 (Kelley et al., 2010). Using senescence associated beta-galactosidase staining and SAHF (senescence associated heterochromatin formation) to assess senescence, induction of YPEL3 in MCF7, U2OS and IMR90 cells induced senescence (Kelley et al., 2010). Also, using a Ras-mediated senescence model, YPEL3 was shown to act down-stream of p53 during Ras-mediated senescence and is required for Ras-mediated senescence in IMR90 cells. This data supported the conclusion that YPEL3 is a growth suppressive gene and further supported a role for YPEL3 in tumorigenesis. It is unclear if this difference (apoptosis versus senescence) is related to the method of expression of YPEL3 or the different model system (mouse versus human).

Rapamycin is known to induce G1 arrest and apoptosis (Kasukabe, et al., 2005). Rapamycin has been a candidate for cancer therapy; however, the different cancer types possess varying sensitivities to the growth inhibition effects of Rapamycin. The Kasukabe Lab aspired to elucidate a chemical agent that when paired with rapamycin would elicit the most enhanced growth-inhibitory effects. They found that the optimal agent tested was cotylenin A which induced growth arrest in G1 phase as well as led to induced senescence associated β-gal activity rather than apoptosis. In MCF-7 cells after rapamycin exposure plus CN-A for 12 hours, YPEL3 was upregulated 3.72 fold, with just rapamycin treatment YPEL3 was induced 2.18 fold, and with just CN-A treatment YPEL3 was induced only 2.29 fold. These results suggest that a synergistic effects occurs when Rapamycin and CN-A are used together. Additionally, the induction of YPEL3 may be involved and required for the SA-β-gal activity that was observed after treatment.

There are a vast amount of nanomaterials in consumer products such as: cosmetics, electronic appliances, clothes, biomedical applications, and solar cells (Park et al., 2013). These nanomaterials contain silver (Ag), Copper-doped titanium dioxide (Cu-TiO2), and pure titanium dioxide (TiO2). The increasing consumption of these materials may influence human health. After exposing zebra fish embryos to the three different nanoparticles, they evaluated expression profiles and selected genes that had a fold change of greater than 2 or less than 0.5 when compared to a control with a p-value of less than 0.05. YPEL3 was grouped with the apoptosis genes and had a fold change of approximately 3.58 when embryos were treated with Cu-TiO2. Again, suggesting YPEL3 as a growth suppressive gene. It was suggested that genes in the apoptosis category may also have other functions such as endocytosis and immune responses; however, further studies are needed to address the effects of these genes after NP treatments.

Morphology Associated Syndromes

YPEL3 is located in the region of 16p11.2 along with 22 other genes. It has been previously shown that duplication or disruption of this interval may contribute to neurodevelopmental disorders such as: autism, mental retardation, and schizophrenia. The high recurrence of rearrangements of this region may be mediated by low copy repeats that make this region susceptible to non-allelic homologous recombination. Recently, it was reported that a patient who suffered from infantile seizures and symptoms with malignant migrating partial seizures of infancy had de novo microduplications in the 16p11.2 region (Bedoyan, et al., 2010). This suggests that disruption of YPEL3 may have a role in infantile seizures.

Deleted or duplicated intervals of the genome are known as copy number variant regions (CNVs). They cause a plethora of diseases from autoimmune disease to speech and developmental delays and autism. The Blaker-Lee lab (2012) analyzed the activity of CNV genes in region 16p11.2 in zebra fish. Utilizing antisense morpholino oligonucleotides (MO) injected into embryos, they analyzed the loss of function of 21 genes. Twenty-four hours after fertilization they examined the embryos and scored the brain for various development features. They found that the loss of several genes, including YPEL3, resulted in the formation of a straight midbrain with the hinge point absent. Embryos that experienced loss of YPEL3 function had a wider midbrain-hindbrain boundary when compared to control embryos. Additionally, the loss of YPEL3 led to a unique hindbrain and midbrain-hindbrain boundary phenotype when compared to the phenotypes generated by the loss of other genes. Co-injection of human YPEL3 cDNA with the YPEL3, MO restored the phenotype ameliorating both morphological and behavioral defects previously observed with the loss of function. These results suggest that YPEL3 is very active in and required for early for both brain and body development. In addition to aberrant brain development, the loss of YPEL3 also led to movement and axon tract deficiencies. Loss of YPEL3 led to abnormal muscle activity; although, the axon tract appeared normal, suggesting a

potential defectiveness in the synaptic transmission. These results suggest the YPEL3 may be important in normal neuro-development.

YPEL3 regulation/methylation

DNA methylation is one well known method of epigenetic regulation of various genes. Given that YPEL3 gene expression was determined to be decreased in colon tumor samples compared to patient matched control DNA (Tuttle, et al., 2011), the possibility of DNA hypermethylation was considered as the mechanism.

These authors found that DNA hypermethylation of the CpG island has no role in the regulation of YPEL3. They did suggest some potential role for histone acetylation which has yet to be further studied.

Epigenetic regulations may be responsible for the connection between susceptibility to disease and environmental exposure (Pascual, et al., 2011). One epigenetic regulation that occurs during intrauterine growth is DNA methylation. Studies have shown that mice possess enhanced sensitivity of allergic diseases when they are exposed to diets high in methyl donors during pregnancy. Thus, the Pascual lab compared B lymphocytes from allergic asthmatic, type I hypersensitive patients with patients that had bronchial asthma, nasal polyps, and an intolerance to aspirin (a non IgE form of hypersensitivity), and a control population that had no known evidence of allergies. In a listing of genes that are most differentially methylated between allergic and control groups by HELP assay, YPEL3 had a 1.56 fold reduction in methylation with a p-value of 0.0151. Further investigation of the relevance of this finding to allergic disease has yet to be uncovered.

Curcumin, a dietary compound, has been found to suppress cell proliferation, induce apoptosis, and inhibit metastasis (Skommer et al., 2007). Due to its tumor suppressing functions, it has been critical to elucidate the mechanisms behind the anticancer properties of curcumin. After exposure to curcumin, YPEL3 gene expression was reduced by slightly over 50%, after a 36 hour treatment in HF4.9 cells. This is actually inverse to the prediction that YPEL3 expression would be increased in growth suppressive conditions. The authors did not further investigate the molecular mechanism for the decreased expression of YPEL3 under these conditions. There is also no protein level data under these conditions; therefore, the biologic relevance of the finding is unknown.

YPEL3 Expression in Tumors:

Oncomine is a cancer-profiling database that contains data that has been analyzed and standardized by Compendia Bioscience.

This database includes data from over 500 cancer types that includes changes in genetic expression and DNA amplification from over 40,000 experiments.

When YPEL3 was examined using Oncomine it was immediately observed that YPEL3 is underexpressed in a variety of cancer types.

These results substantiate previous findings that YPEL3 is downregulated in both lung and colon cancer (Tuttle, et al., 2011).

These results support the hypothesis that YPEL3 is a novel tumor suppressor due to its significant underexpression in a variety of cancer tumors.

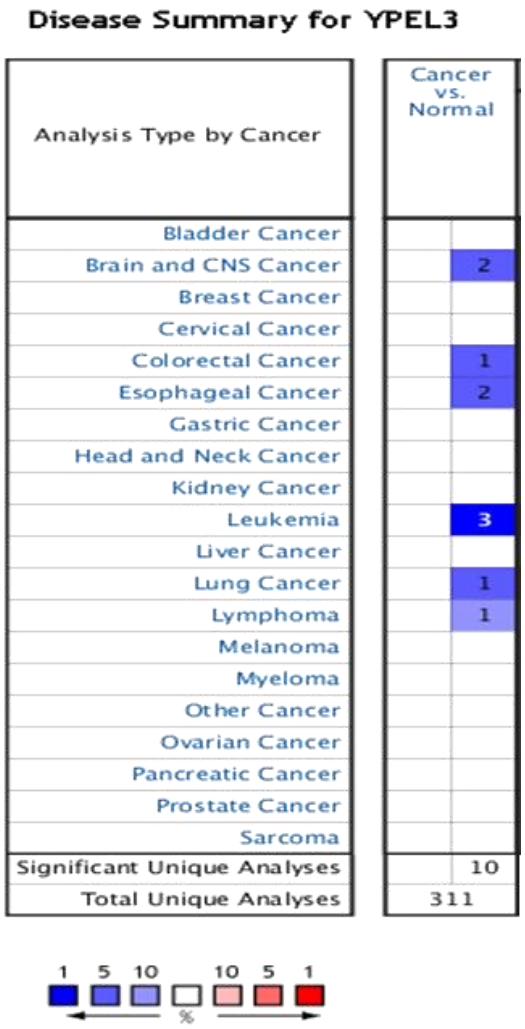


Figure 1: An overview of the expression level of YPEL3 in Cancer vs. Normal in various Cancer Types. The Following Parameters were set: Fold Change-2, P-Value-1E-4, Gene Rank-Top 10%, and Data Type- All.

Additionally, pancreatic cancer, is associated with rapid death and low survival rates due to the inability to detect it in the early stages. Pancreatic cancer often metastasizes to the liver, among other locations. Varying genetic expression has an impact on metastatic potential. When NOG

(NOD/SCID/γcnull) mice were injected with metastatic cell populations derived from BxPC-3 cells, a human pancreatic cancer, a highly metastatic line (LM-Bx-PC-3) was generated (Suemizu, et al., 2007). Analysis of the expression profiles between Bx-PC-3 and LM-BxPC-3 resulted in 9 candidate genes having altered expression profiles. These 9 genes were analyzed in 6 other human pancreatic cancer cell lines. YPEL3 was one of the genes found to be over expressed in LM-BxPC-3 when compared to the parental BxPC-3 line. The 7 fold increase in expression level was validated by RT-PCR. These results suggest that YPEL3 may play a role in pancreatic cancer-liver metastasis.

Gene expression analysis in elderly patients with acute myeloid leukemia was complete by Home and colleagues in 2010. Following an mRNA microarray analysis from 67 adult myeloid leukemia patients ranging in age from 17-80 years old, it was found that YPEL3 had a 0.436 positive correlation, meaning age related change in expression of YPEL3 mRNA in AML blasts was identified. Again, the relevance of this at the protein level, to the disease process or prognosis has yet to be studied.

Conclusion

YPEL3 has been uncovered as a p53 target gene with growth suppressive properties. It has been shown to induce senescence and apoptosis under various conditions. Given the down-regulation of this gene in various human tumors, it makes it a nice potential molecular target for anti-cancer therapies. There is much investigation that remains including more protein level studies to determine if the gene related changes that have been uncovered translate to similar protein level findings and finally biologic functions. There is also interesting data to suggest that YPEL3 may also be a molecular marker for disease diagnosis and/or prognosis. This is another exciting area of investigation which may have impact on future clinical practice.

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