Gene Section

Review

YEATS4 (YEATS domain containing 4)
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Abstract
This entry reviews the structure, function and clinical significance of YEATS4, a gene originally identified from an amplicon on 12p15 found in a glioblastoma cell line and originally named glioma-amplified sequence (GAS41). The gene is amplified in several other cancers and translocations or rearrangements of chromosome 12 with breakpoints in YEATS4 are noted in such cancers as glioblastoma, lung cancer and soft tissue sarcomas. Several frameshift and one nonsense mutations have also been detected in cancer. As the YEATS4 protein is involved in chromatin modeling, transcriptional regulation and mitotic regulation, such aberrations are likely to deregulate cellular mechanisms involved in the normal control of cellular proliferation and cell death.

Keywords
YEATS4, glioblastoma, chromatin, centrosome

Identity

Other names
Gas41, NuBI1, YAF9

HGNC (Hugo)
YEATS4

Location
12q15; Extends between Chromosome 12: 69,359,703-69,390,796, (according to hg38-Dec 2013)(Fig. 1)
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Fig. 1. Location of the YEATS4 gene is shown within a 500kb region of 12p15. A) Protein-coding genes; B) Genes for non-coding and microRNAs; C) Processed pseudogenes.

Fig. 2. Genomic structure of YEATS4. The exon distributions for the two alternatively spliced products (RefSeq accessions NM_006530 and NM_001300950 are shown, with the intron sizes given in base pairs (bp). Coding regions are shown in thicker lines; non-coding regions (5' untranslated and 3' untranslated regions) are depicted as thinner lines.

Description
YEATS4 is encoded by 7 exons spread over 31,094bp (Fig. 2). The gene encodes two alternatively spliced products (RefSeq accessions NM_006530 and NM_001300950). Transcript 1 (NM_006530) is 1501 nucleotides in length and encodes a protein of 227 amino acids. Transcript 2 (NM_001300950) is 1339 nucleotides long and encodes a protein of 173 amino acids.

Protein

Fig. 3. Structure of the YEATS4 protein. Location of exon boundaries (vertical lines) are shown relative to the protein structure. The YEATS and Coiled domains are involved in the functional interactions of the protein. Alternative splicing removes exon 3 and 4, yielding transcript 2, such that isoform 2 (NP_001287879) misses 55 amino acids of the YEATS domain.

Description
The YEATS4 transcripts produce two proteins; isoform 1 is 227 amino acids long (RefSeq accession: NP_006521) and isoform 2 is 173 amino acids long (RefSeq accession: NP_001287879). Isoform 1 has two defined structural/functional features: the YEATS domain located between amino acid residue 44 and 123, and a coiled coiled domain (amino acid 168 - ter). The YEATS domain is conserved in YNK7 (Ya9), MLLT1 (ENL), MLLT3 (AF-9) and the TFIIF small subunit. Ya9 in S. cerevisiae is a subunit of the NuA4 histone acetyltransferase complex (Le Masson et al., 2003). Thus, the YEATS domain is thought to be involved in transcriptional regulation. A C-terminal coiled coil domain interacts with several proteins indicated...
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below and is critical for incorporation of YEATS4 into the human TIP60 complex (Park and Roeder 2006). Six chemical modifications have been annotated in the Prosite database on amino acids conserved between human and mouse (Fig. 4), four of which are ubiquitinylation of lysines located in the coiled coil domain (Hornbeck et al., 2014). Fifty five amino acids of the YEATS domain are missing from isoform 2.

![Fig. 4. Location of chemically modified amino acid side chains. Amino acid residues positions are given relative to NP_006521. Key: p- phosphorylation, ac- acetylation, ub- ubiquitination.](image)

**Expression**

Northern blot analysis detects a ubiquitously expressed transcript of approximately 1.7kb, with high expression in brain, heart and skeletal muscle (Harborth et al., 2000). In general, RNA-seq analysis consistently indicates highest expression in the testes, tissues of the immune system (bone marrow, lymph node and thymus) and the brain, specifically the cerebellum (Fagerberg et al., 2013; Duff et al., 2015; GTEx Portal 2017).

**Localisation**

Several articles indicate that YEATS4 is located in punctate structures in the nucleoplasm of the interphase nucleus of the majority of tested cells, including glioblastoma cell lines (Harborth et al., 2000; Munnia et al., 2001; Debernardi et al., 2002; Lauffart et al., 2002). However, YEATS4 is localized to nucleoli in the neuroblastoma cell lines SK-N-SH, Neuro 2a, and NS20 (Munnia et al., 2001), suggesting a possible functional differentiation for YEATS4 in tumors of the peripheral compared to central nervous system.

**Function**

Based on its homology with Yaf 9 (by what is now called the YEATS domain [Fig. 1]), YEATS4 was predicted to be a subunit of the human homologue of the NuA4 histone acetyltransferase complex, the Tip60 complex. This complex is involved in gene regulation and the repair of double-stranded DNA breaks. This multisubunit complex has histone H4/H2A acetyltransferase activity, is capable of ATP-dependent H2AZ -H2B histone dimer exchange, and has DNA helicase activity (Auger et al., 2008). YEATS4 is also a subunit of the SNIP2-related CBP activator protein (SRCAP) complex, which is a distinct complex also involved in the exchange of Histone H2A for H2Z in chromatin, although the complex functions without acetyltransferase activity (Auger et al., 2008). YEATS4 also directly interacts with SWI/SNF component SMARCB1 (BAF47 or INI1) (Debernardi et al., 2002), MLLT10, which is a histone lysine methyltransferase DOT1L cofactor (Debernardi et al., 2002), the KDM1A demethylase (Piccinni et al., 2011), and the TFIIF component GTF2F2 (RAP30) (Heisel et al., 2010). It has been suggested that the YEATS domain acts as an evolutionarily conserved chromatin modification reader, and possibly directly binds to histones (Schulze et al., 2010).

Further evidence for a function of YEATS4 in transcription has come from direct interactions with transcription factor TFAP2A (AP-2) (Ding et al., 2006), and the C-terminal region of the myc family members MYCN and MYC (Piccinni et al., 2011), identified by affinity capture techniques such as yeast two-hybrid analysis, GST-pull down and coimmunoprecipitation. The β-catenin gene (CTNNB1) is regulated by binding of YEATS4 to its promoter, either via these transcription factors, or in combination with the chromatin modeling complexes discussed above (Ji et al., 2017; Jixiang et al., 2017). Downstream targets of β-catenin such as CCND1 (Cyclin D1), CDK4, CDK6 and c-Myc, and the apoptotic proteins BCL2 and BAX also respond to overexpression and decreased expression of YEATS4 in gastric cancer and pancreatic cancer (Ji et al., 2017; Jixiang et al., 2017).

As noted above, the TIP60 and SCRAP complex play roles in double-stranded DNA repair. However, YEATS4 is involved in the regulation of DNA repair independent of these complexes. YEATS4 overexpression results in destabilization of TP53, with downregulation of YEATS4 leading to stabilization of p53 with concomitant upregulation of p53 target genes such as CDKN1A (p21), and induction of senescence and apoptosis (Llanos et al., 2006; Park et al., 2006; Pikor et al., 2013; Tao et al., 2015). Furthermore, overexpression of YEATS4 increases resistance of normal bronchial epithelial cells to the platinum drug cisplatin and p53- MDM2 interaction inhibitor, nutlin (Pikor et al., 2013). Mechanistically, YEATS4 acts with PP2Cβ to dephosphorylate ser-366 on p53, and can decrease cell death due to UV-induced DNA damage (Park et al., 2011). Thus, overexpression of YEATS4 may contribute to the cancers described below in part by overcoming the tumor suppressor properties of p53.

Additional functions of YEATS4 in nuclear architecture and regulation of mitotic spindle

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assembly were uncovered shortly after its discovery. Harborth et al., (2000) performed yeast two-hybrid analysis to identify proteins that bind to the C-terminus (amino acids 1048-2115) of NUMA1 (NuMA). Further mapping indicated that YEATS4 bound via its coiled coil domain to the C-terminal region of the coiled-coil rod domain of NuMA (amino acids 1048-1700). This interaction was confirmed independently by co-immunoprecipitation, Dot Overlay Assays, Surface Plasmon Resonance, and by a separate study (Munnia et al., 2001). Later studies showed that interaction between NuMA and YEATS4 was cell-cycle regulated with the interaction being low in G1 to S, increasing in S phase and being maximal at G2/M (Schmitt et al., 2012). NuMA is a nuclear matrix protein that relocalizes to and anchors microtubules to the spindle poles (reviewed in Haren et al., 2009). Manipulation of the expression of YEATS4 and NuMA via expression plasmids and siRNA results in an increased rate of spindle defects leading to multipolar spindles and misaligned chromosomes (Schmitt et al., 2012). Additional interactions of YEATS4 with CEP162 (Munnia et al., 2001), and TACC1 - TACC2 - TACC3 (Lauffart et al., 2002; Lauffart et al., 2003), proteins with known roles in centrosomal dynamics during mitosis (Gergley et al., 2000a,b; Leon et al., 2006), have also been identified. However, even these YEATS4-interacting proteins have been implicated in transcriptional regulation. For instance, during interphase NuMA binds to and acts as a transcriptional coregulator of p53 upon DNA-damage (Endo et al., 2013; Ohata et al., 2013); CEP162 associates with predominantly nuclear localized KAT14 lysine acetyltransferase (Gupta et al., 2015; Wang et al., 2008); and the TACC proteins bind to nuclear localized histone acetyltransferases (Gangisetty et al., 2004), nuclear hormone receptors (Vettaikkorumakanakauv et al., 2008; Guyot et al., 2010; Hein et al., 2015; Huttlin et al., 2017) and other transcription factors (Sadek et al., 2000; Simpson et al., 2004); Bargo et al., 2010), and coregulate their transcriptional targets. YEATS4 has been found in complexes with a further 108 proteins by high-throughput analysis via affinity purification-mass spectrometry (Li et al., 2015; Huttlin et al., 2015; Huttlin et al., 2017). Many of these interactions support the proposed functions of YEATS4 in the TIP60 and SCRAP complexes, transcriptional regulation, and mitotic regulation. For instance, additional transcription factors of relevance to cancer, such as FOS, Fox family members, and the myc partner MAX have been identified as YEATS4-binding factors (Li et al., 2015).

**Homology**

The YEATS domain is highly conserved within eukaryotes and defines a family of proteins involved in key functions including transcriptional regulation and chromatin structure (see above). Four YEATS family members are found in humans (MLLT1 [ENL], MLLT3 [AF9], YEATS2, and YEATS4). A BLASTp search of the protein database can identify a defined YEATS4 protein in metazoan eukaryotes representing fungi, arthropods, cnidarians, and chordates, but not plants. In S. cerevisiae, Yaf9 has been proposed to be the closest functional homolog to YEATS4, containing both the YEATS domain and the C-terminal coiled coil region (Le Masson et al., 2003). The Yaf9 protein shows 33% amino acid identity and 57% homology to human YEATS4. The N-terminal YEATS domain of YEATS4 is able to functionally interchange with that of Yaf9 (Piccinni et al., 2011).

**Mutations**

**Somatic**

A total of 39 somatic sequence variations involving the coding region of YEATS4 are recorded in COSMIC v81, released 09-May-17, at http://cancer.sanger.ac.uk/cosmic (Bamford et al., 2004; Forbes et al., 2017). Of those, seven are silent, twenty-seven are missense, four are frameshifts, and one is a nonsense mutation. Each sequence variant has been found in a single case, except for G75D which was detected in 3 colon cancer cell lines HCT8, HCT15, DLD1. c.63C>T, c.66T>G, c.333T>C, c.475C>T, c.498T>C, c.680_681insA are noted as single nucleotide polymorphisms in the dSNP database (https://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusld=8089).

| Position (AA) | Mutation (CDS) | Mutation (Amino Acid) | Mutation Type | Cancer type |
|--------------|----------------|-----------------------|---------------|-------------|
| 2            | c.6C>G         | p.F2L                 | s.m.          | Rectal adenocarcinoma |
| #  | c.227>T>C | p.F8L     | s.m.       | Hepatocellular carcinoma |
|----|-----------|-----------|------------|--------------------------|
| 10 | c.28C>T   | p.P105    | s.m.       | Stomach adenocarcinoma   |
| 21 | c.63C>T#  | p.I21I    | s.s        | Malignant melanoma       |
| 22 | c.66T>G#  | p.V22V    | s.s        | Clear cell renal cell carcinoma |
| 35 | c.103G>A  | p.G35R    | s.m.       | Thyroid carcinoma        |
| 43 | c.127C>T  | p.H43Y    | s.m.       | Malignant melanoma       |
| 43 | c.124delG | p.H43fs*9 | d.fs.      | Lung adenocarcinoma      |
| 52 | c.156A>G  | p.K52K    | s.s        | Stomach adenocarcinoma   |
| 58 | c.172G>C  | p.D58H    | s.m.       | Lung adenocarcinoma      |
| 75 | c.224G>A  | p.G75D    | s.m.       | Colon                    |
| 78 | c.234A>G  | p.L78L    | s.s        | Lung carcinoma           |
| 93 | c.279G>T  | p.W93C    | s.m.       | Primitive neuroectodermal tumour - medulloblastoma |
| 95 | c.284A>C  | p.E95A    | s.m.       | Papillary renal cell carcinoma |
| 97 | c.289G>A  | p.E97K    | s.m.       | Rectal Adenocarcinoma    |
| 100| c.300C>G  | p.I100M   | s.m.       | Pancreatic ductal carcinoma |
| 110| c.328A>G  | p.R110G   | s.m.       | Malignant melanoma       |
| 111| c.333T>C# | p.P111P   | s.s        | Adenocarcinoma of Large intestine |
| 125| c.375C>A  | p.T125T   | s.s        | Malignant melanoma       |
| 133| c.398C>G  | p.T133R   | s.m.       | Clear cell renal cell carcinoma |
| 136| c.407C>T  | p.S136L   | s.m.       | Malignant melanoma       |
| 141| c.421G>T  | p.E141*   | s.n.       | Endometrioid carcinoma   |
| 147| c.438delC | p.P147fs*4| d.fs.      | Breast Ductal carcinoma  |
| 150| c.449T>C  | p.M150T   | s.m.       | Pancreas Ductal carcinoma |
| 151| c.453G>A  | p.M151I   | s.m.       | Liver neoplasm           |
| 154| c.461T>C  | p.L154S   | s.m.       | Head neck Squamous cell carcinoma |
| 159| c.475C>T# | p.R159C   | s.m.       | Malignant melanoma       |
| 162| c.485C>T  | p.T162I   | s.m.       | Papillary renal cell carcinoma |
| 163| c.489A>C  | p.L163F   | s.m.       | Breast Carcinoma          |
Table 1: Sequence variations tabulated from COSMIC v81 (accessed 7/25/2017). KEY: d.fs. - deletion leading to frameshift; i.fs. - insertion leading to frameshift; s.m. - missense substitutions; s.s. - silent substitution; s.n. - nonsense substitution; # variants recorded as single nucleotide polymorphisms. Cells in green denote variations located in the YEATS domain, and cells in blue denote variations located in the C-terminal coiled coil domain.

| #  | c.             | p.             | s.          | Tumor Type                          |
|----|----------------|----------------|-------------|-------------------------------------|
| 166| c.498T>C#      | p.Y166Y        | s.s.        | Head neck Squamous cell carcinoma   |
| 170| c.509C>G       | p.T170R        | s.m.        | Basal (triple-negative) carcinoma   |
| 174| c.521A>C       | p.E174A        | s.m.        | Breast Phyllodes tumour             |
| 180| c.539G>C       | p.R180T        | s.m.        | Lung Adenocarcinoma                |
| 192| c.575T>C       | p.F192S        | s.m.        | Stomach Intestinal adenocarcinoma   |
| 207| c.619A>T       | p.T207S        | s.m.        | Central nervous system Oligodendroglioma |
| 207| c.619delA      | p.T207fs*2     | d.fs.       | Endometrium Serous carcinoma        |
| 208| c.624A>G       | p.I208M        | s.m.        | Hepatocellular carcinoma            |
| 224| c.671C>T       | p.A224V        | s.m.        | Breast Ductal carcinoma             |
| 228| c.680_681insA# | p.*228fs?      | i.fs.       | Breast Carcinoma                    |

Implicated in

The YEATS4 gene is located in a region of Chromosome 12 that is subject to genomic instability and amplification in several different cancers. 117 of 508 human cancer cell lines (23%) exhibited copy number gains of YEATS4 (Pikor et al., 2015). Fusion genes have been identified by RNA-seq analysis of the samples in the Cancer Genome Atlas, as well as in other tumor samples. As many rearrangements resulting in fusions between YEATS4 and other coding genes are found in the same region of the long arm of chromosome 12 that is also subject to amplification, they may be the result of intrachromosomal inversions or deletions. However, as the mechanism of the rearrangements is unclear, the genomic alterations will be designated as translocations for the purpose of this review.

Bladder urothelial carcinoma

RNA-seq analysis of 414 bladder urothelial carcinomas, detected one rearrangement, t(12;12)(q15;q15), fusing exon 4 of YEATS4 out-of-frame to exon 2 of the human lysozyme (LYZ) gene (Yoshihara et al., 2015). Presumably non-sense mediated decay would prevent significant protein product accumulating.
**Fig. 5.** Hybrid gene and protein produced by t(12;12)(q15;q15). With a breakpoint located in intron 4 of YEATS4 and intron 1 of LYZ, RNA-seq detected an out-of-frame fusion gene that could only produce a significantly truncated YEATS4 protein.

**Brain cancer**

YEATS4 was identified as an amplified sequence (GAS41) in glioblastoma multiforme (GBM) cell line TX3868, with amplification subsequently noted at higher frequency in lower grade astrocytoma grades I and II. (Fischer et al., 1997). In a larger study by Schmitt et al. (2012) of 258 glioblastoma samples from the Cancer Genome Atlas, 9 glioblastomas had high level of YEATS4 amplification. However, 26.1% of the samples exhibited reduced expression.

Four genomic rearrangements involving YEATS4 have been noted in glioblastoma. Frattini et al. (2013) performed RNA-sequencing of 161 primary GBM and 24 short-term glioma sphere cultures. These authors detected a single rearrangement t(12;12)(q14.1;q15), resulting in a fusion between YEATS4 and XRCC6BP1 (X-ray repair cross-complementation group 6 binding protein 1). XRCC6BP1 (AKA ATP23) is involved in double-stranded DNA break repair (Fischer et al., 2013) and, based on homology via its metalloprotease domain, is suggested to be important in the biosynthesis of mitochondrial ATPase (Zeng et al., 2007). The detected transcript indicates that the fusion protein contains the YEATS domain fused to the majority of the peptidase M76 domain of XRCC6BP1 (missing 20 amino acids at the N-terminus) (Fig. 6).

**Fig. 6.** Hybrid gene and protein produced by t(12;12)(q14.1;q15) that fuses YEATS4 exon 6 to exon 3 of XRCC6BP1. The Mitelman database contains records generated from paired-end whole genome-sequencing of
42 paired TCGA glioblastoma tumors and matching normal samples (Zheng et al., 2013, Yoshihara et al., 2015).

A translocation t(12;12)(q15;q24) resulting in an in-frame fusion between YEATS4 exon 4 and exon 33 of EP400 (Fig. 7) was reported in the Mitelman database, however this fusion is absent from the TUMOR FUSION GENE DATA PORTAL developed by the same authors (http://54.84.12.177/PanCanFusV2/), and may not have survived further validation. The YEATS4-EP400 hybrid protein would contain contains 111 amino acids of YEATS4, containing part of the YEATS domain fused to the C-terminal 1811 amino acids of EP400, containing the SNF2 family domain and DNA_pol3_delta2 super family domain (cl26247). Yoshihara et al (2015) detected one case of a t(12;12)(q13.3;q15), generating an out-of-frame fusion of YEATS4 exon 6 to methionyl-tRNA synthetase (MARS) exon 12 (Fig. 8). If the fusion protein is produced from the initiator methionine of YEATS4, the protein would be 187 amino acids long and contain the YEATS domain. However, one might predict that nonsense-mediated decay may reduce the accumulation of the fusion mRNA, and subsequent protein. A larger RNA-seq analysis followed by sequencing of 185 GBM samples from TCGA and Ivy center cohort also detected a fusion between YEATS4 (exon 1) and exon 4 of SLC35E3 located 601kb centromeric (Shah et al., 2013). While the fusion RNA detected would be driven from the YEATS4 promoter, the 106 amino acid fusion protein would only contain part of the triose phosphate transporter domain of SLC35E3 (Fig. 9). While it is possible that the fusion could inhibit the function of any normal YEATS4 or SLC35E3 protein in the tumor cell, it would seem more likely that the reciprocal product, if produced, would be of functional significance. However, the reciprocal SLC35E3-YEATS4 fusion transcript was not recorded.

Fig. 7. Fusion between exon 4 of YEATS4 and exon 33 of EP400 (numbering based on NM_015409 and protein NP_056224). The fusion protein is 1922 amino acids long. Domain Key: Y: YEATS domain; cc: Coiled coil domain; EP400_N: pfam15790, E1A-binding protein p400, N-terminal domain is characterized by low-complexity but its function is unknown; Atroph: Atrophin-1 super family domain, a polyglutamine stretch may interact with histone acetyltransferase CBP; HSA: domain found in helicases and associated with SANT domains; SNF2_N: SNF2 family N-terminal domain; SNF: SNF2 family domain; DN: DNA_pol3_delta2 super family domain (cl26247).

Colorectal carcinoma
In a study of 86 colorectal carcinoma patients, increased expression (> 4th quartile) of YEATS4 correlated with decreased survival HR = 1.910, 95% CI: 1.005-3.632, P = 0.048 (Tao et al., 2015).

One rearrangement involving YEATS4 was detected in a study of 95 rectal adenocarcinomas by RNA-seq analysis and recorded in the TUMOR FUSION
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GENE DATA PORTAL. The rearrangement is identical to that observed in hepatocellular adenocarcinoma, fusing YEATS4 exon 6 to the final (noncoding exon) of CPSF6 (Fig. 11). Thus, the predicted fusion protein contains a truncated YEATS4 coding sequence contain the YEATS domain, but lacking the C-terminal coiled coil domain.

**Gastric Cancer**

Quantitative real time reverse transcriptase PCR analysis of 30 Gastric cancers by Ji et al. (2017) detected increased expression of the YEATS4 transcript compared to normal adjacent tissue. 13% of samples showed decreased expression. Overexpression of YEATS4 mRNA and protein was associated with cancer stage, with highest expression observed in Stage III gastric cancer. Overall survival and disease-free survival was decreased with high expression of YEATS4 (Ji et al., 2017). The authors detected increased occupancy of the beta-catenin promoter by the YEATS4 protein, leading to histone acetylation and increased transcription of the beta-catenin gene.

One case of a t(12;12)(q15;q15) fusing exon 6 of YEATS4 to exon 2 of the human lysozyme gene (LYZ) was identified from 414 cases in the Tumor Fusion Gene Data Portal. The resulting fusion protein contains the YEATS domain and the hydrolytic catalytic cleft of lysozyme. This rearrangement is identical to that detected in liver hepatocarcinoma cancer (see Fig. 10).

**Hypertension**

The SNP rs7297610, located between YEATS4 and FRS2, was associated with antihypertensive response to hydrochlorothiazide. Specifically, the C/C genotypes was associated with significant improvement in blood pressure in treated African Americans. Baseline YEATS4 expression was increased in peripheral blood of C/C genotype individuals, but decreased upon treatment with hydrochlorothiazide (Duarte et al., 2013).

**Liver hepatocellular carcinoma**

Two rearrangements involving YEATS4 have been detected in a study of 374 hepatocellular carcinomas by RNA-seq analysis and recorded in the TUMOR FUSION GENE DATA PORTAL (2017). One case of a t(12;12)(q15;q15) fusing exon 6 of YEATS4 to exon 2 of the human lysozyme gene (LYZ) was identified. The resulting fusion protein contains the YEATS domain and the hydrolytic catalytic cleft of lysozyme (Fig. 10). This rearrangement is identical to that detected in stomach cancer (see below). The second rearrangement involves CPSF6 (cleavage and polyadenylation specific factor 6), located 101kb centromeric to YEATS4 (Fig. 1), and fuses exon 6 to the final, noncoding, exon of CPSF6 (Fig. 11). Thus, the fusion protein would be a truncated YEATS4 coding sequence containing the YEATS domain, but lacking the C-terminal coiled coil domain. The rearrangement is identical to that detected in rectal adenocarcinoma (see below).
Fig. 10. Fusion between YEATS4 and LYZ, with a breakpoint located in intron 6 of YEATS4 and intron 2 of LYZ. The resulting fusion gene produces a fusion protein containing the YEATS domain and the Lysozyme catalytic cleft (LCC).

Fig. 11. The CPSF6 protein (NP_0008938) is coded by the first 9 exons of the CPSF6 transcript (NM_007007). CPSF6 has one conserved domain (RRM_CFIm68) defined as a 'RNA recognition motif of pre-mRNA cleavage factor Im 68 kDa subunit (CFIm68 or CPSF6) and similar protein'. The 4846 base pair tenth exon is untranslated, thus the fused hybrid gene produces a truncated YEATS4 protein.

**Lung cancer**

Pikor et al., (2015) performed gene expression and copy number analysis of 261 non-small cell lung cancers (NSCLC) relative to matched normal tissues. The 432 kb region encompassing LYZ to BEST3 (Fig. 1) (and RAB3IP located telomeric to BEST3) was amplified in 20% of the samples tested. Of the 7 genes within the amplicon, only YEATS4 was both gained/amplified and concomitantly overexpressed in lung tumors with YEATS4 amplified in 18% (47/261) and overexpressed in 31% (15/48) of tumor samples originally tested. YEATS4 copy gain/amplification was detected in an additional 43/128 (33.6%) lung cancer cell lines. YEATS4 was overexpressed in 18% (15/83) of the Early Detection Research Network samples and 33% (14/42) from the Cancer Genome Atlas. 3/83 tumors showed higher amplification of YEATS4 compared to the MDM2 protooncogene, that is the main suspected driver of 12q15 amplification, suggesting that YEATS4 can provide an independent advantage over MDM2 in some lung cancers. The study validated overexpression of the YEATS4 protein in 15/59 (25.4%) tumors and 8/18 (44.4%) NSCLC cell lines. Knockdown of YEATS4 in cell lines containing YEATS4 amplification induced senescence and apoptosis in a p53/p21 mediated manner. Overexpression of YEATS4 increased resistance of normal bronchial epithelial cells to the platinum drug cisplatin and p53-MDM2 interaction inhibitor, nutlin (Pikor et al., 2015).

The TUMOR FUSION GENE DATA PORTAL (2017) reports one case of a t(12;12)(q15;q15) from 541 Lung adenocarcinomas, involving YEATS4 and SLC35E3. The rearrangement fuses YEATS4 (exon 4) to exon 4 of SLC35E3 resulting in part of the YEATS domain to 65 amino acids of the triose phosphate transporter domain (Fig. 12).
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**Fig. 12.** In-frame fusion between YEATS4 and SLC35E3. SLC35E3 encodes a protein of 313 amino acids (NP_061126) and is identified as a member of the triose-phosphate transporter (TPT) family based upon a central 278 amino acid domain. The YEATS4-SLC35E3 fusion protein contains 111 amino acids of YEATS4 fused to 88 amino acids of the SLC35E3 protein containing the C-terminal 65 amino acids of the triose phosphate transporter domain.

**Müllerian adenosarcomas of the uterus**

In an analysis of 15 uterine and one ovarian Müllerian adenosarcomas, five cases showed amplification of a 900kb region stretching from SLC35E3 to BEST3, and thereby encompassing the YEATS4 locus on 12q15 (Lee et al., 2016).

**Pancreatic cancer**

YEATS4 transcript overexpression was noted in 31 pancreatic cancer samples relative to adjacent non-cancerous tissues (Jixiang et al., 2017). An expansion of this study to 93 pancreatic samples in the ONCOMINE database (Rhodes et al., 2004) further indicated clinical significance of YEATS4 expression in pancreatic cancer. Introduction of YEATS4 into a normal pancreatic epithelial cell lines promote growth invasion and motility. These effects were mediated, at least in part, by activation of the Wnt pathway and direct interaction with beta catenin (Jixiang et al., 2017).

**Soft tissue Sarcomas (unclassified)**

Five translocations were identified by Verhaak and colleagues from 263 Sarcomas and reported in the TUMOR FUSION GENE DATA PORTAL (2017). The adult sarcomas are unclassified in the National Cancer Institute Genomic Data Commons Data Portal. Each translocation fuses YEATS4 3' prime to its fusion partner.

One case t(1;12)(q21.3;q15) fuses the exon 4 of KCNN3 (potassium calcium-activated channel subfamily N member 3)(based on transcript NM_002249) in-frame to exon 2 of YEATS4. The fusion protein would be 740 amino acids long and contain the calcium-activated SK potassium channel domain and part of the ion channel domain (pfam03530 and pfam07885) from KCNN3 and the YEATS4 YEATS domain and coiled coil domain (Fig. 13).

In a different tumor, another in-frame fusion occurs between exon 2 of MARCH9 on 12q14.1 and exon 2 of YEATS4 (Fig. 14). MARCH9 is a member of the MARC family of membrane-bound E3 ubiquitin ligases. The fusion protein product is 380 amino acids long, containing the C4HC3 zinc-finger like RING domain and the YEATS4 YEATS domain and coiled coil domain.

The other three translocations observed fuse YEATS4 exon 7 out of frame 3-prime to its fusion partner, suggesting that these rearrangements produce a truncated protein lacking any YEATS4 components. One case of t(1;12)(q24.2;q15) fuses exon 16 of a coactivator of ligand-dependent nuclear receptors, DCAF6, to exon 7 of YEATS4 (Fig. 15). A truncated protein would contain the WD40 and cl26247 (DNA polymerase III, delta subunit) domains involved in transcriptional regulation, but miss the final 200 amino acids of the coactivator. A single t(12;12)(q21.1;q15) fuses exon 1 of the THAP domain containing, apoptosis associated protein 2 (THAP2) out-of-frame to exon 7 of YEATS4. The "fusion" protein would also be truncated, and only contain the first 24 amino acids of the THAP2 protein, and 5 amino acids encoded out of frame from exon 7 of YEATS4 (Fig. 16). The last case noted was an out of frame fusion between exon 10 of TMTC1 and exon 7 of YEATS4 t(12;12)(p11.22;q15). If the truncated 564 amino acid 'fusion' protein is produced, it would lack the C-terminal tetratricopeptide repeats of TMTC1 (Fig. 17).
**Fig. 13.** In-frame fusion between KCNN3 and YEATS4. Exon numbering for KCNN3 is based upon transcript NM_002249 that codes for isoform a (NP_002240). Key: Y: YEATS domain; CC: coiled coil domain; SK_C: calcium-activated SK potassium channel domain; I_T2: Ion Transporter_2 (ion channel) domain; CM: Calmodulin binding domain; Grey box: Prefoldin super family domain structure.

**Fig. 14.** The MARCH9 gene contains 4 exons and encodes a transcript (NM_138396) of 2985 nucleotides, with a 5’ untranslated region of 431 nucleotides and a 3’ untranslated region of 1517 nucleotides. The full length MARCH9 protein is 346 amino acids long (NP_612405). The fusion between exon 2 of MARCH9 and exon 2 of YEATS4 could produce a fusion peptide of 380 amino acids.

**Fig. 15.** The DCAF6 gene contains 22 exons and encodes multiple alternatively splice transcripts. Protein Isoform b (NP_001017977) was selected as the canonical form by UniProtKB, coded by a transcript 2 (NM_001017977) of 3360 nucleotides, with a 5’ untranslated region of 353 nucleotides and a 3’ untranslated region of 1064 nucleotides. This transcript is missing exon 11, 12, and 17. W: WDR11 repeat region.
YEATS4 (YEATS domain containing 4)

Fig. 16. The THAP2 gene contains 3 exons and encodes a transcript of 4840 nucleotides, with a 5' untranslated region of 613 nucleotides and a 3' untranslated region of 3959 nucleotides. The full length THAP2 protein is 228 amino acids long (NP_113623), containing the DNA binding THAP domain. The fusion between exon 1 of THAP2 and exon 7 of YEATS could produce a fusion peptide of only 29 amino acids in size.

Fig. 17. The TMTC1 mRNA is encoded by 18 exons and is 8.75kb long with a 3' untranslated region of 6.2kb. The full length TMTC1 protein (NP_001180380) is 882 amino acid long and contains two domains: the DUF1736 (D) and the TPR-11 domain. The TMTC1-YEATS4 fusion gene would produce a 2468 nucleotide mRNA encoding 559 amino acids of TMTC1, missing the C-terminal 323 amino acid region containing most of the tetratricopeptide repeats of the TPR-11 domain.

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