

Gene Section

Review

PIWIL2 (piwi-like RNA-mediated gene silencing 2)

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Abstract

Review on PIWIL2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CT80, HILI, PIWIL1L, mili

HGNC (Hugo): PIWIL2

Location: 8p21.3

Local order: POLR3D-LOC100507071-PIWIL2-SLC39A14-PPP3CC

Note

Human PIWIL2 or HiLi gene belongs to an evolutionarily conserved PIWI clades of Argonaute gene family that comprises four members of Argonaute genes (AGO1, AGO2, AGO3 and AGO4) and four members of PIWI genes (PIWIL1/HIWI, PIWIL2/HILI, PIWIL3 and PIWIL4/HIWI2) (Sasaki et al., 2003).

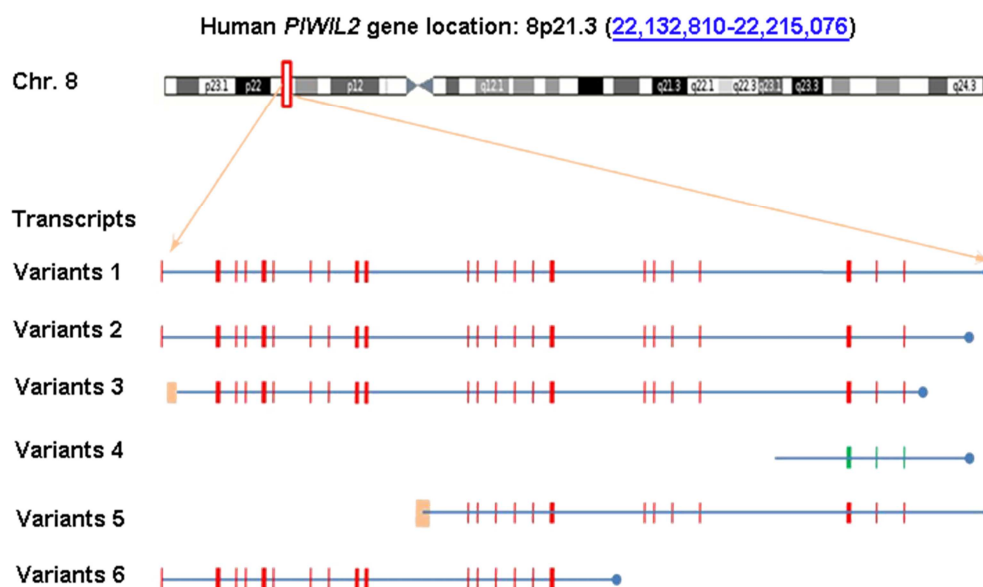


Figure 1. Diagram of Location of PIWIL2/HILI gene and its transcript variants. PIWIL2 is located in chromosome 8 at locus 8p21.3. Six transcript variants are shown.

While the PIWI family genes are exclusively expressed in the testis, the AGO family genes are ubiquitously expressed in adult tissues (Sasaki et al., 2003). All Argonaute family genes contain a central PAZ motif and a C-terminal PIWI motif (Sasaki et al., 2003). They form a RNA-induced silencing complex (RISC) to regulate a variety of biological functions through binding small RNAs (Hutvagner and Simard, 2008). PIWI genes are required for the functions in development and maintenance of germline stem cells (Cox et al., 2000).

DNA/RNA

Note

The ortholog of *Drosophila* PIWI gene was identified as PIWIL1/HIWI in a human testis cDNA library (Qiao et al., 2002), which is required for self-renewing and asymmetry division of germline stem cells (Lin and Spradling, 1997). PIWIL2/HILI was cloned by polymerase chain reaction (PCR) of a testis cDNA library while searching databases for homologs of PIWIL1/HIWI (Sasaki et al., 2003). Normally the transcripts (mRNAs) of PIWIL2 were exclusively found expressed in testis (Sasaki et al., 2003), but it was widely identified in various types of tumor cell lines (Lee et al., 2006; Ye et al., 2010) and stressed somatic cells with DNA damages (Yin et al., 2011b). PIWIL2/MILI was also cloned in mouse and its transcripts were only detected in the testis and spermatogonia (Wang et al., 2001).

Description

HILI is located in chromosome 8p21.3, starting from 22132810 and ending at 22215076 bp (ENSG00000197181), encompasses 82266 bp of DNA and consists of 23 exons (Figure 1).

Transcription

There are at least six transcript variants of human PIWIL2 (Figure 2). The exon 1 of variants 1 and 3 is different in size and non-coding, but they have identical open reading frame (ORF), generating identical peptides. The variant 2 has the exon 1 with the same size as variant 1 but is lack of exon 22. The variant 4 is considered to be a retained intron. The variant 5 coding Piwil2-like (PL2L) proteins 60 (PL2L60) was found in the testis or tumors, which is a product of PIWIL2 alternatively activated by a putative intragenic promoter (Ye et al., 2010). The variant 6 is predicted by computer analysis and probably associated with multiple polyadenylation sites.

The variant 1 (PIWIL2-001; ENST00000356766) is a canonical one, mapping to chromosome 8: 22132810-22215076 with 82.27 kb, containing 23 exons with transcript length of 5128 bps. Twenty

two exons are coding one with translation length of 973 residues.

The variant 2 (PIWIL2-002; ENST00000521356) has 22 exons containing 21 coding exons, mapping to chromosome 8: 22132850-22213584 with 80.73 kb. The transcript length is 3488 bps with translation length of 937 residues.

The variant 3 (PIWIL2-003; ENST00000454009) has 23 exons with transcript length of 3442 bps, mapping to chromosome 8: 22133080-22213029 with 79.95 kb. Twenty two coding exons are translated into 973 residues, same as the variant 1.

The variant 4 (PIWIL2-004; ENST00000519884) has 3 non-coding exons (intron retention), mapping to chromosome 8: 22210312-22213601 with 3.29 kb. Transcript length is 1262 bps.

The variant 5 [PIWIL2-like proteins 60 (PL2L60); AK027497] has 13 exons with transcript length of 2272 bps, mapping to chromosome 8: 22161569-22213584 with 52.015 kb. The transcript is transcribed by a predicted promoter up-stream of the exon 11, and the translation length is 530 residues (Ota et al., 2004; Ye et al., 2010).

The variant 6 [PREDICTED: Homo sapiens piwi-like RNA-mediated gene silencing 2 (PIWIL2), transcript variant X2, mRNA] has 20 exons with transcript length of 2677 bps, mapping to chromosome 8: 22132829-22179503 with 46.674 kb. The translation length is 804 residues (NCBI Reference Sequence: XM_005273551.1).

In addition to the defined transcripts listed above, there are several potentially alternatively transcribed transcripts resulted from intragenic activation of promoters of PIWIL2, such as PL2L50 and PL2L42 (Ye et al., 2010).

Pseudogene

No pseudogene has been found so far.

Protein

Note

HILI proteins are the products of HILI gene, belonging to the PIWI subfamily of Argonaute family proteins. The Argonaute family proteins contain two evolutionarily conserved motifs: PAZ and PIWI domains (Carmell et al., 2002). The PAZ domain is named after the proteins Piwi Argonaut and Zwillig, composing of two subdomains. One subdomain is similar to the OB fold, which is well known as a single-stranded nucleic acid binding fold. The second subdomain is composed of a beta-hairpin followed by an alpha-helix. The 3' ends of single-stranded regions of RNA binds in low-affinity in the cleft between the two subdomains. Although PAZ may not be a primary nucleic acid binding site in Dicer or RISC, it may contribute to the specific and productive incorporation of siRNAs and miRNAs into the RNAi pathway.



Figure 2. Diagram of PIWIL2/HILI protein. The protein structure of PIWIL2 consists of PAZ and PIWI domains. A third functional domain of PIWI proteins, MID domain (not shown) that lies between PAZ and PIWI domains, binds to the 5' phosphates of small RNAs and thus anchors small RNAs onto the PIWI protein, has not been clearly defined in PIWIL2.

The PIWI domain is named after the *Drosophila* protein PIWI (P-element induced wimpy testis), which is essential for gametogenesis and maintenance of asymmetry division of germline stem cells (Cox et al., 1998; Cox et al., 2000; Deng and Lin, 2001; Lin and Spradling, 1997). The function of this domain is the dsRNA guided hydrolysis of ssRNA. Crystal structural analysis of Argonaute reveals that PIWI is an RNase H domain, and identifies Argonaute as Slicer, the enzyme that cleaves mRNA in the RNAi RISC complex (Song et al., 2004). The PIWI domain core has a tertiary structure belonging to the RNase H family of enzymes. By analogy to RNase H enzymes which cleave single-stranded RNA guided by the DNA strand in an RNA/DNA hybrid, the PIWI domain can be inferred to cleave single-stranded RNA, for example mRNA, guided by double stranded siRNA (Letunic et al., 2012; Schultz et al., 1998).

The Argonaute family proteins can be categorized into AGO and PIWI subfamily (Carmell et al., 2002). Both AGO and PIWI proteins can form transcriptional complexes with small RNAs to regulate gene expression. Normally AGO subfamily proteins are ubiquitously expressed in adult tissues to regulate various cell functions through binding exogenous 20-25 nucleotide (nt) small interfering RNAs (siRNAs) or endogenous 22-nt microRNAs (Carmell et al., 2002); whereas PIWI proteins are exclusively expressed in embryonic developmental stages and/or testis to regulate germline development through binding 24-31 nt piwi-interacting RNAs (piRNAs) (Lim et al., 2013b). Like all other Argonaute family members, HILI contains a central PAZ motif and a C-terminal PIWI motif (Figure 2). Aberrant or ectopic expression of HILI proteins in adult tissues is likely associated with tumorigenesis (Peng and Lin, 2013; Suzuki et al., 2012).

Description

Six HILI isoforms of transcripts have been described (Figure 1). The HILI protein contains two characteristic domains: a PAZ domain (aa 390-524) and a PIWI domain (aa 668-956). Transcripts PIWIL2-001 (5128 bp), PIWIL2-002 (3488 bp), PIWIL2-003 (3442 bp) and PL2L-60 (2288 bp) encodes three variants of PIWIL2 proteins.

Transcripts PIWIL2-001 and PIWIL2-003 have identical open reading frame (ORF) and encode an identical peptide of 973 amino acids (109.8 kDa). Transcript PIWIL2-002 encodes a variant of 937 residues (105.8 kDa) with a complete PAZ domain (aa 390-524) and a spliced PIWI domain (aa 668-887). PL2L-60 mRNA encodes a variant of 530 residues (59.85 kDa) with a truncated PAZ domain (aa 1-61) and a complete PIWI domain (aa 69-514). PIWIL2-004 does not encode protein product.

There are at least four putative PL2L proteins including PL2L60, PL2L50, PL2L40 and PL2L40, which are the products of intragenic promoter activation of PIWIL2 and truncated at various N terminal sites of PIWIL2. Human PL2L60 has been identified and characterized (Ye et al., 2010).

Argonaute proteins contain amino-terminal (N), PAZ (PIWI-ARGONAUTE-ZWILLE), MID (middle) and PIWI (P-element induced wimpy testis) domains. N domain assists the loading of small RNA and unwinding of the RNA duplex (Kwak and Tomari, 2012). PAZ domain and M domain anchors 3'-end and 5'-end of the small RNA, respectively, by providing a specific binding pocket (Jinek and Doudna, 2009). PAZ domain can bind small regulatory RNAs such as miRNAs to AGO subfamily proteins and piRNAs to PIWI subfamily proteins, whereas PIWI domain bound by mRNA contains RNase H fold, probably functioning as endonuclease to cleave the bound mRNA that is complementary to the bound small RNA (Carmell et al., 2002; Jinek and Doudna, 2009; Parker and Barford, 2006; Song et al., 2003).

Expression

Normally, HILI is exclusively expressed in the spermatogonia and spermatocytes of the testis (Sasaki et al., 2003) and in the female oocytes and supporting cells of human (Lim et al., 2013b). However, it can be temporarily activated in somatic cells in responding to DNA damages and in the primary cancers, and its intragenically activated products such as PL2L60 are expressed in various types of tumor cell lines (Ye et al., 2010; Yin et al., 2011b).

Localisation

HILI and its variants can be found in cytoplasm, nucleus or both of germline stem cells and tumor

cells (Lee et al., 2010; Liu et al., 2010; Ye et al., 2010). They may present in chromatoid body, a probable component of the meiotic nuage, also named P granule, a germ-cell-specific organelle required to repress transposon during meiosis (Lim et al., 2013a; Wang et al., 2009). The significance of HILI expression in cytoplasm versus in nucleus remains to be elucidated.

Function

PIWIL2 has multiple functions in germline development and tumorigenesis. The functions of PIWIL2 are mainly mediated by two motifs: PAZ and PIWI domains, which are highly conserved evolutionarily. PIWIL2 is associated with ribonuclease type III (DICER 1), an important component of RISC complexes (Sasaki et al., 2003).

PIWIL2 plays critical roles in the PIWI/PIWI-interacting RNA (piRNA) pathway, which is essential for spermatogenesis and transposon repression. The associated factors of the PIWI-piRNA pathway may include VASA, MAELSTROM, and TUDOR domain proteins. In coordination with the associated factors, PIWIL2 mediates piRNA biosynthesis, transcriptional silencing (Li et al., 2012), translational regulation (Unhavaithaya et al., 2009), and DNA methylation of transposons (Kuramochi-Miyagawa et al., 2008). In a mouse model, piRNA was required for de novo methylation of the differentially methylated region (DMR) of the imprinted mouse *Rasgrf1* locus, but not other paternally imprinted loci, suggesting that piRNAs and a target RNA direct the sequence-specific methylation of *Rasgrf1* (Watanabe et al., 2011). PIWIL2 also participate posttranslational modification through interaction with Tudor domain-containing protein TDRD1. Arginine methylation of *Piwil2* proteins by PRMT5 is required for its interaction with *Tdrd1* and subsequent localization to the meiotic nuage, also named P granule (Vagin et al., 2009).

In germline development, PIWIL2 may regulate the self-renewal of germline stem cells (Unhavaithaya et al., 2009) and maintain genomic integrity through interacting with piRNA to suppress the mobility of transposons, such as long interspersed nuclear elements-1 (L1, also known as LINE-1) (Marchetto et al., 2013). The piRNAs are 26 to 31 nucleotides in length and thus clearly distinct from the 21 to 23 nucleotides of microRNAs (miRNAs) or short interfering RNAs (siRNAs). PIWIL2 mediates spermatogenesis in mouse and human. DNA methylation of retrotransposons was controlled and regulated by *Piwil2* partnered with piRNA (Aravin et al., 2006; Aravin et al., 2007; Kuramochi-Miyagawa et al., 2008; Xu et al., 2008). In human, male infertility is associated with inactivation of PIWI pathway caused by the

promoter hypermethylation of PIWIL2 and TDRD1. The epigenetic inactivation of PIWI gene pathway resulted in a defective production of piRNAs and a hypomethylation of the LINE-1 repetitive sequence in the affected patients (Heyn et al., 2012). In mouse testis piRNAs accumulated at the onset of meiosis (Aravin et al., 2006), silencing L1 in meiotic pachytene cells (Di Giacomo et al., 2013). PIWIL2/MILI deficient mice were infertile (Kuramochi-Miyagawa et al., 2004). Mili-mediated secondary piRNA biogenesis fuels piRNA amplification that is absolutely required for LINE-1 silencing (De Fazio et al., 2011).

In tumor development, PIWIL2 may play multiple functions, probably depending on its activating status (Ye et al., 2010). At the beginning of tumorigenesis, PIWIL2 could temporally respond to environmental stresses, such as ionizing radiation, ultraviolet radiation and genotoxic agents, mediating chromatin relaxation to promote DNA repair and thus playing a protective role (Yin et al., 2011b). PIWIL2 expression was enhanced in testicular seminomas, but not in testicular nonseminomatous tumors (Lee et al., 2006). PIWIL2 was also expressed in human and mouse tumors of various tissues (Lee et al., 2006; Ye et al., 2010).

Lee et al. showed that overexpression of PIWIL2 in a murine fibroblast cell line or human breast cancer stem cells resulted in inhibiting apoptosis and promoting proliferation and cell transformation via a signal transducer and activator of transcription 3 (STAT3)/BCLXL signaling pathway (Lee et al., 2010; Lee et al., 2006). Chen et al. demonstrated that *Piwil2* transcripts was constitutively and stably expressed in murine precancerous stem cells (pCSCs) and overexpression of *Piwil2* resulted in hematopoietic stem cell proliferation and transformation (Chen et al., 2007). Overexpression or ectopic expression of PIWIL2 in normal cells appeared to be associated with cell transformation and tumor initiation (Shahali et al., 2013). However, whole length of PIWIL2 was only detected in apoptotic cancer cells of primary cancers (Ye et al., 2010). PIWIL2 variants might determine the fate of a cancer cells. Ye et al. demonstrated that PIWIL2 gene could be activated via intragenic promoters, leading to expression of PIWIL2-like (PL2L) proteins, such as PL2L60, which may promote tumor survival and growth through regulating NF- κ B translocation to nucleus (Ye et al., 2010). The alienation activation of PIWIL2 appeared to be associated with tumor malignancy, because PL2L proteins were mainly detected in proliferating cancer cells and cancer cell lines as well as metastatic cancer cells (Ye et al., 2010). Elucidation of the roles of PIWIL2 variants in tumorigenesis is critical for understanding complex functions of PIWIL2.

The PIWIL2 appears to be involved in various signaling transduction pathways. In TGF- β mediated signaling pathway, it suppressed TGF- β signaling pathway by physically associating with Hsp90, preventing formation of Hsp90-T β R heteromeric complexes and improving ubiquitination and degradation of T β Rs in a manner depending on the ubiquitin E3 ligase Smurf2 (Zhang et al., 2012). In p53 signaling pathway, the PIWIL2 repressed the tumor suppressor P53 in human cancer cells. Its PAZ domain directly associated with STAT3 protein to form a PIWIL2/STAT3/c-Src triple proteins complex, which resulted in STAT3 phosphorylation by c-Src and translocation to nucleus, then binding to P53 promoter and repressing its transcription (Lu et al., 2012). In colon cancer cell lines, the PIWIL2 could modulate matrix metalloproteinase 9 (MMP9) transcriptional activities (Li et al., 2012). In addition, silencing PIWIL2 suppressed the expression of STAT3, down-regulating Bcl-X(L) and cyclin D1, leading to a reduction of cell proliferation and survival (Lee et al., 2010).

PIWIL2 may also play important roles in maintaining genomic integrity by suppressing retrotransposons, stabilizing heterochromatin structure, and regulating target genes during meiosis and mitosis. In the murine mesenchymal stem cells (MSC), Piwil2 is expressed in the cytoplasm of metaphase. In contrasting to promoting cell proliferation (Lee et al., 2010a; Lee et al., 2006; Lu et al., 2012; Zhang et al., 2012), Piwil2 did not do so in the MSCs, because knockdown of Piwil2 with a specific siRNA enhanced cell proliferation, significantly increased the number of cells in G1/S and G2/M cell cycle phases and was associated with increased expression of cell cycle genes CCND1, CDK8, microtubule regulation genes, and decreased expression of tumor suppressors Cables 1, LATS, and Cxxc4 (Wu et al., 2010).

Along with piRNAs PIWIL2 could suppress LINE1 in tumor cells. A set of piRNAs and other repeat-associated small RNAs were observed in HeLa cells. By using in situ hybridization, piR-49322 was localized in the nucleolus and around the periphery of nuclear membrane in HeLa cells. Following the overexpression of HILI, the retrotransposon element LINE1 was significantly repressed, while LINE1-associated small RNAs decreased in abundance (Wu et al., 2013).

PIWIL2 might contribute to great ape evolution. Comparative gene expression analysis of human and nonhuman primate iPS cells revealed that levels of L1-restricting factors or DNA cytosine deaminase APOBEC3B (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3B) and PIWIL2 inversely correlated with L1 mobility and endogenous L1 mRNA levels. The increased copy

numbers of species-specific L1 elements in the genome of chimpanzees compared to humans suggests that differences in L1 mobility may have differentially shaped the genomes of humans and nonhuman primates (Burns et al., 2013; Marchetto et al., 2013).

In addition, PIWIL2 was upregulated in the TGF- β induced EMT-type breast cancer stem cells (CD44⁺CD24⁻), forming a complex with piR-923 and promoting Latexin (LXN) promoter methylation (Zhang et al., 2013).

Homology

The PIWIL2 gene is conserved in zebrafish, mouse, rat, dog, cow and chimpanzee.

Mutations

Note

Numerous mutations of PIWIL2/HILI have been detected in various types of primary cancers, including the cancers of breast, lung, liver, kidney, ovary, pancreas and large intestine. Copy number variation (CNV) has also been observed in the cancers of breast, large intestine, kidney, lung, ovary, pancreas, endometrium, central nervous system, hematopoietic and lymphoid, and skin (CONAN).

Implicated in

Various cancers

Note

Although PIWIL2 is exclusively expressed in the testis of human and animals, it has been detected in the stressing cells (Yin et al., 2011b) and almost all the various types of cancer cell lines tested of human and animals (Chen et al., 2007a; Lee et al., 2006; Ye et al., 2010) as well as in various primary cancers, including leukemia, breast tumor, medulloblastoma, rhabdomyosarcoma, colon cancer, cervical cancer and papillary thyroid carcinoma (He et al., 2010; Lee et al., 2006; Li et al., 2010; Yin et al., 2011a). Interestingly, PIWIL2 transcripts or proteins were enriched in precancerous stem cells, and cancer stem cells isolated from breast cancer and cervical cancer (Chen et al., 2007; Feng et al., 2009; Lee et al., 2010). The intragenic promoter activation resulted in alienation products of PIWIL2, such as PL2L60 protein, promoting tumor cell growth and metastasis, while full length of PIWIL2 was mainly detected in the apoptosing cancer cells of primary cancers (Ye et al., 2010). It should be noted that the failure to detect PIWIL2 transcripts in some cancers such as bladder cancers is likely associated with false negativity from RT-PCR analysis in which the primers used did not complement the alternatively transcribed mRNA (Ye et al., 2010).

Seminoma

Note

Testicular germ cell tumors can be categorized as seminoma and non-seminoma. PIWIL2 was detected in human seminoma but not in non-seminomatous tumors (Lee et al., 2006).

However, a recent report showed that in addition to testicular germ cell tumor cell lines, PIWIL1, PIWIL2, PIWIL4, and TDRD1 in primary seminoma and non-seminoma testicular tumors were silenced by promoter CpG island hypermethylation. Importantly, these epigenetic lesions were associated with piRNA downregulation and loss of DNA methylation of the LINE-1 repetitive sequences (Ferreira et al., 2014).

Bladder cancer

Note

The PIWIL2 transcripts were reportedly not detected by qRT-PCR in bladder cancer cell lines and primary bladder cancers (Nikpour et al., 2009). However, a recent report showed that the PIWIL2 mRNA was detectable by qRT-PCR in 76.08% (35/46) patients with the bladder urothelial carcinoma (Cao et al., 2012).

The conflicting results may be caused by the primers used, a pair of which did not complement the truncated transcripts of PIWIL2 in tumors (Ye et al., 2010).

Cervical cancer

Note

The PIWIL2 can be detected by immunohistochemical staining (IHS) in various stages of human cervical squamous cell carcinomas and adenocarcinomas.

It was also detected in some metaplastic epithelial cells as well as histologically "normal" appearing tissues adjacent to malignant lesions. In Papanicolaou (Pap) test, PIWIL2 was also detected by immunocytological staining (ICS) in atypical glandular cells (AGC), low-grade (LSIL) and high-grade squamous intraepithelial lesions (HSIL). PIWIL2 is a more sensitive biomarker than p16, which was not always concomitantly detected in the same specimens (He et al., 2010).

Especially, a subpopulation of cancer cells with stem-like properties expressed higher level of PIWIL2 (Feng et al., 2009).

Colon cancer

Note

The PIWIL2 and PIWIL4 were detected by immunohistochemistry (IHC) in colon cancers.

The former was detected at the occurrence of colon cancers, while the later was associated with distant metastasis of the cancers (Li et al., 2010).

In another report, the PIWIL2 was detected by IHC

in primary colon cancer tissue and lymph node metastasis (LNM) lesions and significantly correlated with clinicopathological invasiveness, poorer five-year metastasis-free survival and poorer overall survival (Li et al., 2012; Oh et al., 2012). In addition, PIWIL2 expression was associated with poor differentiation, aggressive invasion, and perineural invasion in colorectal carcinomas (Oh et al., 2012).

Breast cancer

Note

The PIWIL2 was detected, though variable in levels, by IHS in almost all of the breast cancer samples at premalignant and malignant stages. It was detected in cytoplasm (Cyt), nucleus (N) or both cytoplasm and nucleus (C-N).

The N pattern was less observed in precancerous lesions, whereas all the three patterns were observed in invasive and metastatic cancers. While the Cyt pattern correlated with ER expression; N pattern correlated with Ki67 expression.

The shift of Cyt --> C-N --> N patterns were associated with the reduction of ER expression and an increase of Ki67 expressions (Liu et al., 2010). In primary breast cancers, full length of PIWIL2 was mainly expressed in apoptotizing cells while PL2L proteins, the products of PIWIL2 that was alternatively activated by intragenic promoters, appeared to be expressed in proliferating cancer cells and metastatic cancer cells (Ye et al., 2010).

Like observed in cervical cancers, PIWIL2 was predominantly expressed in the breast cancer stem cells (Lee et al., 2010a; Zhang et al., 2013). Up to 90% of invasive carcinomas and 81% of carcinomas in situ expressed highest level of PIWIL2 (Lee et al., 2010).

Thyroid cancer

Note

Piwil2 proteins and mRNAs were detected by IHS and in situ hybridization (ISH) in 88.3% and 88.5% papillary thyroid carcinoma (PTC), respectively. The level of PIWIL2 expression was associated with the invasiveness and metastasis of PTC (Yin et al., 2011a).

Gastric cancer

Note

The expression of PIWIL2 detected by IHS was significantly higher in the gastric tumor tissue than that in adjacent non-tumor tissue.

Expression level of PIWIL2 was positively correlated with the T stage, lymph node metastasis and clinical TNM (cTNM).

Moreover, elevated PIWIL2 expression in cancer tissue predicted poorer overall survival (OS) compared with the group of lower expression (Wang et al., 2012).

Sarcoma

Note

PIWIL2 expression in 125 soft tissue sarcoma (STS) samples together with PIWIL3 and PIWIL4 expressions were measured by real-time PCR (qPCR). Low PIWIL2 or PIWIL4 mRNA expressions were significantly associated with a poor prognosis. Low expression of both genes was associated with a 2.58-fold increased risk of tumor-related death. PIWIL4 and the combined PIWIL2 and PIWIL4 mRNA levels correlated significantly with prognosis only for female but not for male patients. However, the combined low PIWIL 2 and PIWIL3 transcript levels were associated with worse survival for male patients (Greither et al., 2012).

Prostate cancer

Note

The PIWIL2 was detected using Whole Human Genome Oligo Microarrays in prostate cancer. Compared to peripheral zone, PIWIL2 was down-regulated in poorly differentiated tumors but not in moderately differentiated tumors (Shaikhibrahim et al., 2013).

Leukemia

Note

PIWIL2 expression in acute myeloid leukemia (AML) was analyzed by real-time PCR and differed in expression pattern in a gender-dependent manner (Shaikhibrahim et al., 2013).

Ovarian cancer

Note

The PIWIL2 was detected by IHS in the primary ovarian cancer and metastatic tissues from the patients with stage III epithelial ovarian cancer (EOC). Other PIWI proteins such as PIWIL1, PIWIL3, and PIWIL4 were also detected in the primary tumor and metastatic tissues (Chen et al., 2013).

Male infertility

Note

Defective PIWIL2 expression is associated with male infertility in mouse and human (Heyn et al., 2012; Kuramochi-Miyagawa et al., 2004). In human, the disorder was likely associated with the promoter hypermethylation of PIWIL2 and its associated factor TDRD1, which resulted in a defective production of piRNAs and a hypomethylation of the LINE-1 repetitive sequence in the affected patients (Heyn et al., 2012). The presence of PIWIL2 in oocytes or ovary also suggests that it may participate in similar functions during oogenesis in females (Lim et al., 2013b; Olesen et al., 2007). The link of PIWIL2/HILI single nucleotide polymorphisms (SNPs) with

spermatogenic failure has not been established (Gu et al., 2010).

To be noted

Note

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