Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

MKI67 (marker of proliferation Ki-67)

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Published in Atlas Database: May 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/MKI67ID41369ch10q26.html
DOI: 10.4267/2042/56295

Abstract

Review on MKI67, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: KIA, MIB-1

HGNC (Hugo): MKI67

Location: 10q26.2

Local order
CLRN3, PTPRE, **MKI67**, LINC01163, MGMT.

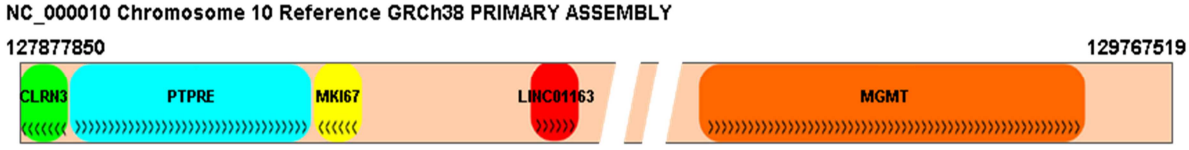
Note
MKI67 is the human homologue of the product recognized by the monoclonal antibody Ki67, which is used as a tumor proliferation marker.

DNA/RNA

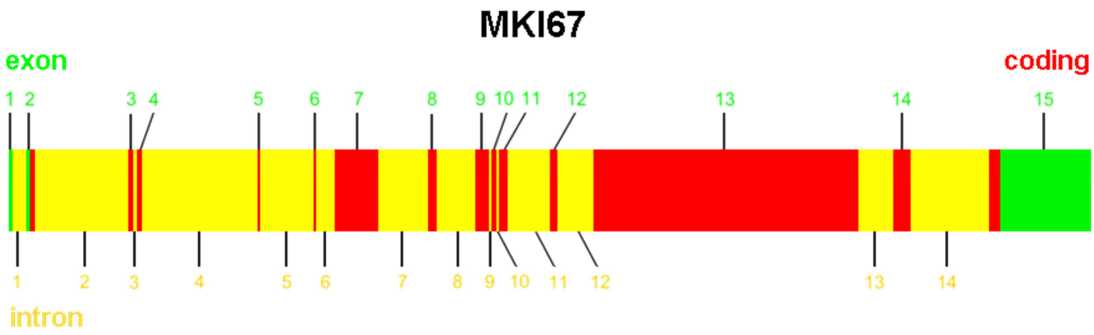
Note
MKI67 is located on chromosome 10 at locus 10q26.2, starting at 128096659 and ending at 128126204 bp from pter (according to GRCh38 Primary Assembly). The gene size is 29,545 bp consisting of 15 exons and 14 introns. The gene has a minus strand orientation.

Description

Promoter: The promoter of MKI67 is located upstream of the transcription start site. Several studies have shown that the 5' flanking region of the gene has promoter activity via reporter gene expression assays and deletion analysis (Zambon, 2010; Pei et al., 2012). The promoter region was shown to contain a TATA-less, GC rich region with several putative Sp1 binding sites and two evolutionary conserved E2F transcription factor binding sites (Zambon, 2010; Pei et al., 2012).
Gene: The gene consists of 15 exons and 14 introns. The first exon and a part of the second form the 5' Untranslated Region (5' UTR) of the mRNA transcript (Duchrow et al., 1996; Schlüter et al., 1993).



The local order of genes around MKI67. The MKI67 gene is surrounded by the genes CLRN3 (clarin 3), PTPRE (protein tyrosine phospatase receptor type E), MGMT (O-6-methylguanine-DNA methyltransferase).



Exons	Length	Coding/ UTR	Introns	Length
1	106	UTR	1	342
2	181	UTR/ 92	2	2406
3	79	79	3	94
4	116	116	4	3561
5	67	67	5	2716
6	46	46	6	483
7	1080	1080	7	1325
8	176	176	8	981
9	313	313	9	87
10	119	119	10	110
11	172	172	11	1111
12	156	156	12	954
13	6845	6845	13	877
14	444	444	14	2002
15	2597	66/ UTR		

MKI67 gene structure. The UTRs are coloured green and the coding regions red. The introns are coloured yellow. MKI67 consists of 15 exons of which the first and a part of the second exon form the 5' UTR. The 3' UTR is formed from a major part of exon 15, which contains only a small coding region. The table at the bottom of the figure shows the length of exons, coding regions and introns according to the information provided by the NM_002417.4 NCBI reference sequence.

The second exon contains the start codon (Schlüter et al., 1993), with the open reading frame extending to the 15th exon, which consists of a short coding sequences, the stop codon and the 3' UTR (Duchrow et al., 1996; Schlüter et al., 1993).
The 1080 bp 7th exon is not present in the alternatively spliced "short type" mRNA transcript. The 6845 bp 13th exon contains the characteristic sixteen homologous "Ki67 repeats", each of them having length of 366 bp. Within Ki67 repeats there is a highly conserved new motif of 66 bp named the "Ki67 motif" (Schlüter et al., 1993).
The introns, vary in size from 87 to 3561 bp. Three introns contain recognized homologue copies of "Alu-repeats". All the intron-exon transitions contain a potential branch site with the exception of the introns flanking exon 7 where there is not any donor-acceptor splicing signal (Durchow et al., 1996).

Transcription

There are two mRNA splice variants of MKI67, that are shown to be processed through translation. These two mRNA variants are named as "long type" and "short type" since they differ only by the presence or absence of exon 7 (Schlüter et al., 1993).
The "long type" mRNA splice variant consists of 15 exons and its total annotated spliced exon length is 12497 bp (NCBI Reference Sequence: NM_002417.4). The "short type" mRNA splice variant consists of 14 exons lacking the 7th exon and its annotated spliced exon length is 11417 bp (NCBI Reference Sequence: NM_001145966.1).

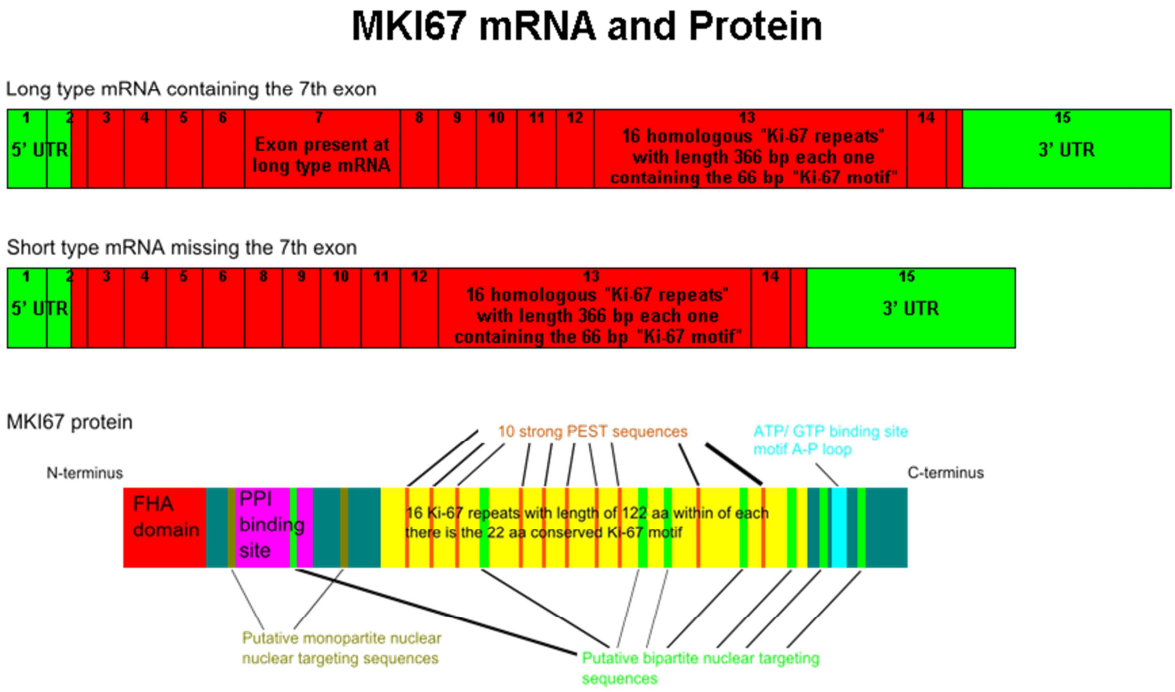
Pseudogene

There is one related pseudogene of MKI67 on chromosome X, named MKI67P1 (marker of proliferation Ki-67 pseudogene 1) with Gene ID 100271918. The MKI67P1 pseudogene is located on chromosomal locus Xp11. It has 1449 bp length and NCBI Reference Sequence: NG_011647.1.

Protein

Note

The MKI67 protein can be found in two complete isoforms, the heavy isoform produced from the "long type" mRNA and the light isoform translated from the "short type" mRNA, lacking the 7th exon. The heavy isoform, referred as Antigen Ki67 isoform 1 with NCBI Reference Sequence: NP_002408.3, consists of 3256 aminoacids (aa) and weights approximately 395 kDa. The light isoform, referred as Antigen Ki67 isoform 2 with NCBI Reference Sequence: NP_001139438.1, consists of 2896 aa lacking the 360 aa encoded by exon 7 and has a molecular weight of about 345 kDa.



The MKI67 mRNA and protein. The two types of mRNA transcripts, shown to be translated to protein, are depicted in the first part of the figure. The long type mRNA differs from the short type by the presence of the 7th exon which is alternatively spliced in the short type. The UTRs are coloured green and the coding regions red. At the second part of the figure, it is depicted the protein product of the long type mRNA which contains all the putative domains of this protein. The major protein domains are the FHA domain coloured red, the PPI binding site coloured purple, the Ki67 repeats coloured yellow and the ATP/ GTP binding site motif A-P loop coloured blue. There are other putative functional regions within these major domains, which are highlighted in different colours.

Description

Starting from the N-terminus:

Major domains:

- Forkhead associated domain (FHA): 8-98 aa.

This domain is characterized as a modular phosphopeptide recognition domain with specificity to phosphothreonine containing sequences (Hammet et al., 2003; Durocher et al., 1999). The MKI67 FHA domain is shown to lie at the N-terminus of the protein. According to computer alignment, the core domain is found within 27-76 amino acids but the functional domain is believed to expand from 8 to 98 residue. So far, two proteins have been identified to interact with MKI67 FHA domain, the hNIFK (human nucleolar protein interacting with the FHA domain of pKi-67) and the Hklp2 (human kinesin-like protein 2).

- Protein phosphatase 1 binding site: 502-563 aa.

The Protein Phosphatase 1 (PPI) is a Ser/Thr phosphatase which belongs to the PPP family of phosphatases, and it is believed to dephosphorylate its substrates in large complexes consisting of regulatory as well as target proteins (Moorhead et al., 2008). In MKI67 protein there is a docking site of PPI at the N-terminal part of the protein within residues 502 to 563.

- Ki67 Repeats:

1) 1002-1113 aa, 2) 1124-1235 aa, 3) 1246-1357 aa, 4) 1368-1478 aa, 5) 1489-1599 aa, 6) 1610-1721 aa, 7) 1732-1843 aa, 8) 1854-1965 aa, 9) 1976-2087 aa, 10) 2098-2204 aa, 11) 2216-2327 aa, 12) 2337-2448 aa, 13) 2459-2570 aa, 14) 2582-2690 aa, 15) 2701-2806 aa, 16) 2820-2929 aa.

The Ki67 repeat is a cluster of 122 residues repeated 16 times within the 13th exon of the molecule with identity ranging from 43 to 62% to the consensus sequence.

Within the Ki67 repeat there is a highly conserved motif of 22 amino acids named "the Ki67 motif" which has 72-100% identity to the consensus sequence and includes the F-K-E-L epitope recognized by the prototype Ki67 antibody (Schlüter et al., 1993).

So far, their function remains an enigma.

- ATP/ GTP binding site motif A-P loop: 3034-3041 aa.

A-P-R-A-R-G-K-S

At the C-terminus of the protein there is a sequence resembling the predictive nucleotide binding site of Walker A motif.

This well-known motif is a nucleotide binding fold recognized by Walker et al. (1982) and it is found in many nucleotide binding proteins.

Minor domains:

- PEST sequences:

The cDNA sequences show 40 weak and 10 strong PEST sites.

These sites are named as PEST due to the fact that they are rich in proline, glutamic acid (E), serine and threonine and to a lesser extent aspartic acid. They are found in several proteins with diverse functions such as key metabolic enzymes, transcription factors, protein kinases, phosphatases and cyclins. The regulation of proteins based on PEST sequences is characterized by strict expression, high susceptibility to proteolysis and short half-life, especially in those proteins participating in cell cycle and mitosis regulation. In MKI67 protein, the 10 strongest PEST sequences are located within exon 13, surrounding the conserved cysteine residues at position 8 of the Ki67 repeats (Ross and Hall, 1995). PEST sequences seem to be functional in the MKI67 protein, based on its biological behavior with susceptibility to proteases, short half-life and rapid loss of the protein after mitosis (Ross and Hall, 1995; Schlüter et al., 1993).

- Putative Monopartite Nuclear Targeting Sequences: 502-505 and 687-690 aa.

The MKI67 protein has two putative monopartite nuclear targeting sequences at the N-terminal part of the protein, which could function as nuclear localization signals (NLS) through the classical importin a/b nuclear import mechanism.

- Putative Bipartite Nuclear Targeting Sequences: 1) 536-550 aa, 2) 1516-1530 aa, 3) 2244-2258 aa, 4) 2365-2379 aa, 5) 2651-2665 aa, 6) 2890-2904 aa, 7) 2997-3011 aa, 8) 3141-3155 aa.

There are other classical nuclear targeting sequences within this molecule, which could mediate nuclear localization with importin a/b pathway as well. These bipartite sequences are characterized by two clusters of basic residues separated by a 10 to 12 aa linker that is tolerant to residue substitution (Kosugi et al., 2009).

- Post-translational modifications:

The predicted post-translational modifications of MKI67 protein comprise 19 N-myristoylation, 3 amidation and over 200 phosphorylation sites (143 PKC, 89 casein kinase II, 2 tyrosine kinase sites and 8 consensus sites for Cdc2 kinase) (Schlüter et al., 1993).

- MKI67 protein interactions:

The MKI67 protein has been found to interact directly with four proteins. The HP1 proteins, which are small non-histone chromosomal proteins found in several chromatin complexes, interact with its C-terminal region (Kametaka et al., 2002). The Hklp2, a kinesin-like motor, interacts with the N-terminal FHA domain of MKI67 protein (Sueishi et al., 2000). Another protein shown to interact with the N-terminal FHA domain of MKI67 protein is a putative RNA-binding protein with length of 293 residues, named hNIFK (Takagi et al., 2001). MKI67 protein was found to be a candidate protein for interacting with the HiNF-P transcription factor in a yeast two-hybrid screen (Miele et al., 2007).

Finally, several studies have shown that MKI67 protein interacts with DNA and more specifically with the heterochromatin (Kreitz et al., 2000; Bridger et al., 1998).

Expression

The expression profile of MKI67 is much more related to the proliferating state of a cell rather than to the histological background of that cell. Through immunostaining experiments Gerdes et al. (1983) showed that this gene is present in proliferating normal cells such as germinal centers of cortical follicles, cortical thymocytes, neck cells of gastrointestinal mucosa and other cell lines but absent in resting differentiated cells such as lymphocytes, monocytes, hepatocytes, renal, brain, or parietal cells and many others.

A very important finding was that the expression of MKI67 was triggered in differentiated cells after proliferative stimulation and disappeared after differentiation of proliferating cells (Gerdes et al., 1983).

During cell cycle this gene is always detectable through G1, S, G2 and M phase at continuously proliferating cells but totally absent in resting cells at G0 phase (Gerdes et al., 1984).

Localisation

Distribution of MKI67 protein during cell cycle:

1. Interphase:

a. Early G1 phase: Accumulates in several foci within the nucleoplasm (Gerdes et al., 1983; Kill, 1996).

b. Late G1, S, G2 phase: Localizes predominantly within nucleoli at the dense fibrillar component but also there is diffuse nucleoplasmic staining (Gerdes et al., 1983; Kill, 1996).

2. Mitosis: Coats chromosome surface (Gerdes et al., 1983).

a. Metaphase: a reticulate but uniform network of fibrils around chromosomes, at the perichromosomal layer (Ross and Hall, 1995).

b. Anaphase: a reticulate more granular network of fibrils around chromosomes with the highest density of staining (Ross and Hall, 1995).

c. Telophase: the staining moves from the perichromosomal layer and becomes speckled at the nucleoplasm and subsequently concentrates at the newly reformed nucleoli (Ross and Hall, 1995).

Function

The function of MKI67 protein during cell cycle is still unknown. However, experiments with anti-sense oligonucleotides and antibodies against MKI67 revealed a decreased rate of cell division, indicating the important role of this protein in cell cycle (Schlüter et al., 1993; Starborg et al., 1996).

More details for MKI67 function are unavailable, although there are some assumptions based on localization and protein-protein interactions experimental data.
Models:
1. Nucleolar localization of MKI67 protein is believed to be related to:
a. Structural modulation of the nucleolus in order to enhance the high rates of ribosomal synthesis during cell proliferation, since its expression is related to high rates of protein synthesis (Plaat et al., 1999; Scholzen et al., 2002).
b. Sequestration of MKI67 protein within nucleoli until the mitosis starts again. During mitosis the nucleolar structures are dispersed and the MKI67 protein is free to interact with nuclear components (Scholzen et al., 2002).
2. Localization of MKI67 to the surfaces of chromosomes during mitosis (prometaphase to anaphase) is believed to be related to:
a. Protection of chromosomal surface during mitosis (Verheijen et al., 1989; Yasuda and Maul, 1990).
3. DNA interaction:
a. It was believed that the central part of the MKI67 protein and especially the "Ki67 repeat" region has the ability to bind DNA through its Thr-Pro-X-X motif (Schlüter et al., 1993).
b. The LR domain has the ability to bind DNA in order to compact chromatin (Kametaka et al., 2002).

Homology

The MKI67 gene has homologous genes in several organisms such as chimpanzee, rhesus monkey, dog, cattle, mouse and rat.
Additionally, through genome annotation studies, 53 other organisms have been found to carry an MKI67 orthologue. However, the most interesting case is a similar but not homologous gene, found in the long-nosed rat Kangaroo, named chmadrin (Takagi et al., 1999). The chmadrin protein has primary structural similarities with the MKI67 protein. The N-terminal region of the chmadrin protein has a nucleotide binding motif which is similar to a putative one found in MKI67 at the C-terminal region (Takagi et al., 1999). The central region of chmadrin contains a repetitive sequence domain, named the "chmadrin repeat domain" which resembles the "Ki67 repeat domain" (Takagi et al., 1999). Finally, both of these proteins have LR domains with conserved functionality but different amino acid sequence (Takagi et al., 1999).

Mutations

Note
MKI67 is used as a tumor proliferation marker with an unknown function. The contribution of this gene in tumor development is unknown. In 2003, Buban et al. found eight different point mutations in four tumor cell lines (HeLa, CXF94, SW480, A549) indicating that MKI67 might provide a genetic background in tumor development. These mutations include a deletion in position 1496 resulting in a truncated product, a base exchange silent mutation in position 433 (A433T) and six other exchange mutations resulting in residue changes (Buban et al., 2004).

Implicated in

Several cancers

Note
Although the MKI67 gene is not associated with any type of human cancer as a causative factor, it is implicated in many of them as a prognostic factor based on the expression profile of this gene at tumor cells. Additionally, a new application of MKI67 expression is the implication in diagnosis of certain diseases such as lymphoma. The prognostic value of MKI67 expression in malignancy was categorized by Brown and Gatter (2002) into three classes:
1. Group of malignancies where >75% of the studies shown significant prognostic value: breast cancer, soft tissue tumors, lung cancer, astrocytoma and meningioma.
2. Group of malignancies where 25-75% of the studies shown significant prognostic value: cervical cancer, prostate cancer.
3. Group of malignancies where <25% of the studies shown significant prognostic value: colorectal cancer.

Breast cancer

Note
In breast cancer, most of the studies show significant correlation between MKI67 expression in tumor cells and clinical outcomes both in univariate and multivariate analysis (Brown and Gatter, 2002; Kontzoglou et al., 2013). The prognostic value of MKI67 expression in breast cancer is comprised in the following conclusions:
1. MKI67 expression is associated with common histopathological parameters and the strongest correlation is established with tumor grading (Inwald et al., 2013).
2. MKI67 expression is an independent prognostic parameter of overall and disease-free survival (Inwald et al., 2013).
3. MKI67 expression is associated with earlier central nervous system metastases (Ishihara et al., 2013).
4. In triple negative breast cancer (TNBC) MKI67 expression could be used to classify TNBC into two subtypes with different prognosis (Keam et al., 2011).

5. In node-negative breast cancer, which is treated with surgery and subsequent radiation but not with adjuvant systemic therapy, MKI67 expression and hormone receptor status is a significant prognostic parameter of survival (Pathmanathan et al., 2014).
6. The expression of MKI67 gene after neoadjuvant chemotherapy is prognostic of disease relapse and death (von Minckwitz et al., 2013; Tanei et al., 2011).
7. The prognostic value of MKI67 expression is available in samples of breast tumors acquired via fine needle aspirate with accuracy comparable to histological evaluation (Konofaos et al., 2013).
8. Breast cancer patients with Grade 3 tumors positive for MS110, Lys27H3, VIM (vimentin) and MKI67 expression are at high risk of carrying BRCA1 mutations and therefore could be screened for such mutations (Hassanein et al., 2013).
Additionally, another diagnostic use of MKI67 expression in breast cancer addresses two specific subtypes of this malignancy:
1. In Phyllodes tymor the expression of MKI67 and TP53 mRNA is associated with the grade of this tumor and could help in distinguishing the benign from the malignant form (Kucuk et al., 2013).
2. The expression profile of the estrogen receptor, ERBB2 (c-erbB2) and MKI67 mRNA could help in distinguishing between Toker cells, which are normal components of nipple epidermis, and cells of Paget's disease (Park and Suh, 2009).

Endometrial cancer

Note

Although in endometrial cancer MKI67 expression is used as a proliferation marker associated with specific characteristics of this tumor, there is not yet any validated prognostic or diagnostic connection as there is for breast cancer. More specifically:
1. High MKI67 expression is associated with endometrial cancer and the overexpression of MKI67 and TP53 genes indicates a more malignant phenotype with poor differentiation of the tumor cells (Markova et al., 2010).
2. High MKI67 expression is correlated with poorly differentiated carcinomas, invasion of the myometrium and stage III tumor (Stoian et al., 2011). There is also a significant correlation with the degree of differentiation, the stage of tumor and vascular invasion (Stoian et al., 2011).
3. MKI67 expression is higher in high-grade endometrial carcinomas and complete negative in atrophic endometrium (Mourtzikou et al., 2012).
4. High MKI67 expression correlates with morphologic features of aggressiveness and high grade of endometrial cancer (Konstantinos et al., 2013).
5. Although previous studies associated MKI67 expression with survival, recent ones correlate survival with estrogen and progesterone receptors expression rather than MKI67 gene (Li et al., 2014; Salvesen et al., 1999; Gassel et al., 1998).

Cervical cancer

Note

In cervical cancer MKI67 expression is used as a proliferation index marker of malignant cells, associated with specific characteristics of the tumor but not as a prognostic factor of survival or disease relapse.
Additionally, it is suggested that under certain circumstances MKI67 expression could be used in low-grade lesion triage for referral colposcopy. More specifically:
1. There is no significant correlation between MKI67 expression and classical prognostic factors (Ancuta et al., 2009).
2. MKI67 and CDKN2A (P16) gene is expressed in cervical intraepithelial neoplasia (CIN) and the intensity of positive expression is significantly correlated with CIN grade (Shi et al., 2007). In another study these two markers were shown to increase linearly from control cases to more dysplastic lesion to squamous cell carcinoma (Gatta et al., 2011). This indicates that CDKN2A and MKI67 gene could be useful markers in diagnosis and staging of CIN lesions (Shi et al., 2007).
3. Expression of CDKN2A, MKI67 gene and ProxEX C (a cocktail of monoclonal antibodies against proteins associated with aberrant S phase cell cycle induction) are most associated with the severity of cervical dysplasia and related to HPV-16 infection (Conesa-Zamora et al., 2009).
4. MKI67 expression is enhanced in high grade CIN lesions and cervical squamous cell carcinoma (Looi et al., 2008). TP63 and MKI67 expression is correlated better with cancer progress than TP53 expression (Vasilescu et al., 2009).
5. CDKN2A/MKI67 expression increases according to histologic severity and could be used to predict high-grade lesion better than HPV DNA testing since it is more accurate in patients with atypical squamous cells (Koo et al., 2013). Additionally, they could be used for low-grade squamous intraepithelial lesions triage better than HPV DNA testing and reduce referral colposcopy to almost the half by detecting the more severe cases of CIN3 (Wentzensen et al., 2012).

Ovarian cancer

Note

In ovarian cancer MKI67 expression is associated with several histopathological characteristics of the malignancy and in some subtypes with the overall survival. However, more studies are needed in order to validate such correlations. More specifically:
1. PIK3CA amplifications and MKI67 expression are strong predictors of an early tumor-associated death (Woenckhaus et al., 2007).

2. The combined evaluation of CDKN1B (P27KIP1) and MKI67 expression in ovarian carcinomas is an independent and more accurate prognostic marker of overall survival than each marker alone (Korkolopoulou et al., 2002).
3. In stage III ovarian carcinomas, MKI67 expression is an independent prognostic marker where high expression of this gene is significantly associated with shorter survival (Khouja et al., 2007).
4. The expression of MKI67 gene is higher in malignant ovarian tissues than control ones and within the malignant tissues it is enhanced in low differential carcinoma and stage III-IV (Wang et al., 2010b).
5. The expression of MKI67 gene is higher in primary ovarian tumors than in metastatic cells (Wang et al., 2010b).
6. The high-grade ovarian carcinomas have significantly higher expression of MKI67 gene than the low-grade, but there is little correlation between this expression and overall or disease-free survival (Shen et al., 2011).
7. The MKI67 expression is associated with higher cancer stage and histological grade and a worse outcome for patients (Heeran et al., 2013).
8. The MKI67 expression was found to be associated with poorer overall survival in ovarian cancer patients (Kucukgoz Gulec et al., 2014).

Vulvar cancer

Note

The vulvar carcinomas, mainly represented by squamous cell carcinoma (SCC) and non-invasive lesion of vulvar intraepithelial neoplasias (VINs), are associated with MKI67 expression in several studies.

The general idea is that the expression of this gene is associated with dysplastic lesions and it is more intense in more malignant lesions. More specifically:

1. The expression of MKI67 and CDKN2A are statistically positively related with HPV-associated dysplastic lesions (Gincheva et al., 2009).
2. There is an increase in MKI67 and TOP2A (topoisomerase IIa) expression in VIN lesions and SCC comparing to normal vulvar epithelia, indicating these two genes as markers of proliferation in vulvar epithelial tissues (Brustmann and Naude, 2002).
3. In differentiated VIN lesions the MKI67 expression is confined in the basal and parabasal layers.

However, in usual VIN lesions associated with high-risk HPV virus infection, MKI67 is highly expressed (Hoevenaars et al., 2008; Ding et al., 2012).

Bladder cancer

Note

In bladder cancer MKI67 expression is examined in several studies classifying this gene as a common marker used in diagnosis and staging of this malignancy. The expression of this gene is correlated with the grade and the stage of the malignancy and it is higher in females (Wang et al., 2013).

Gliomas: astrocytomas, oligodendrogliomas

Note

In these brain tumors the MKI67 gene has great potential as a marker of cell proliferation, survival, therapy response and even discrimination between subtypes of gliomas. High expression of this gene is related with shorter overall survival of patients (Liu et al., 2013b). Additionally, MKI67 expression was shown to be correlated with survival of patients with a specific subtype of gliomas in univariable analysis, indicating the prognostic potential of this gene in glioma tumors (Preusser et al., 2012). The MKI67 expression could also be associated with post-treatment results, such as in adjuvant radiotherapy of gliomas where high expression is correlated with worse response to the therapy (Horbinski et al., 2012). Another interesting study showed that MKI67 might have differential expression between subtypes of gliomas indicating a role in diagnosis of these subtypes in accordance to other promising molecular markers (Huang et al., 2011).

Meningiomas

Note

MKI67 is believed to have some influence in meningioma development and progression since there is significant correlation between its expression and tumor grade, certain subtypes, tumor recurrence and size (Pavelin et al., 2013; Wang et al., 2010a). Another interesting correlation was proposed by Uzum and Ataoglu (2008) in which the tumor grade is the most important prognostic factor of meningiomas, which in turn is significantly correlated with MKI67 expression. Terzi et al. (2008) proposed that MKI67 and TP53 expression could be useful additional markers for grade classification in borderline cases.

Pituitary adenomas

Note

The MKI67 expression is correlated with neoplasm recurrence and visual field defect (Paek et al., 2005). Additionally, it is believed to be an independent predictor of pituitary adenomas' progression after surgery (Gejman et al., 2008).

In general MKI67 is a useful marker in predicting tumor recurrence or invasiveness in accordance to other factors (de Aguiar et al., 2010).

Gastric cancer

Note

In gastric cancer the relation of MKI67 with the characteristics of this malignancy are not well established. Expression of MKI67 and PCNA are correlated with high grade of gastric cancer (Czyzewska et al., 2004). The overexpression of TSPAN1 and MKI67 genes are negatively correlated with carcinoma differentiation (Chen et al., 2008). Additionally, MKI67 expression is shown to be related to tumor size (Giaginis et al., 2011).

Gastrointestinal stromal tumor

Note

MKI67 expression is higher in the malignant gastrointestinal stromal tumors than in benign ones, indicating a role in predicting malignant potential of GIST in accordance with other tumor markers such as TP53 and KIT (c-kit) (Aoyagi et al., 2009). Addditionally, MKI67 expression was correlated with GIST recurrence and patient survival (Belev et al., 2013; Liu et al., 2013a).

Colorectal cancer

Note

In colorectal cancer, the MKI67 gene is associated with several characteristics of this malignancy. Additionally, there is a strong correlation of gene expression with the response of this cancer to potential therapeutic approaches. More specifically:

1. MKI67 in addition to other tumor markers such as CD34, KRT19 (CK19), KRT20 (CK20) are highly expressed in colorectal cancer compared to normal tissues. Additionally, expression of CD34 and MKI67 are significantly correlated with tumor stage, differentiation and low survival (Ma et al., 2010).
2. MKI67 and BMI1 overexpression in colorectal cancer is significantly related to tumorigenesis, metastasis and prognosis (Lin et al., 2008).
3. MKI67 expression is a reliable marker for predicting metastatic potential of rectal carcinoid (Hotta et al., 2006).
4. The expression of MKI67, PDPN (podoplanin) and cytokeratin are correlated with increased lympangiogenesis but not with poorer prognosis (Omachi et al., 2007).
5. Decreased expression of MKI67, HIF1A and BCL2 markers were found after chemoradiotherapy of rectal cancer (Havelund et al., 2013).
6. Rectal tumors with lower MKI67 expression were more sensitive to neoadjuvant therapy and the gene expression was decreased after the therapy (Jiang et al., 2008).
7. High MKI67 expression in colon cancer is associated with better relapse-free survival in patients who underwent surgery and adjuvant chemotherapy (Fluge et al., 2009).
8. MKI67 expression and the inflammation marker, C-reactive protein are correlated with poorer survival in patients undergoing surgery for colorectal cancer (Canna et al., 2008).

Lung cancer

Note

The MKI67 gene is not a validated prognostic marker in non-small cell lung cancer and more studies with standardized methodology are required to elucidate the role of this marker in this lung cancer subtype (Jakobsen and Sorensen, 2013).

Lymphoma

Note

In lymphoma malignancies, MKI67 is considered as a powerful tool in distinguishing benign from malignant cases (Bryant et al., 2006). Additionally, MKI67 can be used as a prognostic factor of survival, with highly expressing tumors being correlated with worse overall survival (Kim et al., 2007). However, in specific subtypes such as diffuse large B-cell lymphoma low expression of MKI67 is an adverse prognostic factor (Hasselblom et al., 2008). Another use of MKI67 expression is the evaluation of prognosis after therapy in specific lymphoma subtypes (Determann et al., 2008).

Neuroendocrine tumors

Note

In neuroendocrine tumors, MKI67 expression is the sole strong independent risk factor for poor outcome and it is considered as predictor marker of disease progression and it is significantly associated with patients' overall survival (Panzuto et al., 2012). The use of MKI67 expression is believed to be a better prognostic marker than mitotic count in these malignancies (Khan et al., 2013). This gene is incorporated in the grading of neuroendocrine neoplasms into two major categories: a) well differentiated neuroendocrine tumors (grade 1 and 2) and b) poorly differentiated endocrine carcinomas (grade 3) (Fung et al., 2013). In ileal well-differentiated neuroendocrine tumors, MKI67 predicts the progression-free survival (Dhall et al., 2012). However, a differentiation about the prognostic value of this gene is reported for the small cell lung patients where it has no prognostic value (Erler et al., 2011).

Thyroid cancer

Note

In thyroid carcinomas, MKI67 and TP53 are expressed with increasing frequency in progressed stages of this cancer (Saltman et al., 2006).

MKI67 expression and mutational analysis of RET gene could be used as prognostic factors of more aggressive medullary thyroid carcinoma (Mian et al., 2011). MKI67 expression, LGALS3 (Galectin-3) and PTTG1 (pituitary tumor transforming 1) genes could be used not only to distinguish benign from malignant tumors but also to differentiate follicular carcinoma from papillary one (Cui et al., 2012).

Other cancers

Note

Basal cell carcinoma, cutaneous pilar leiomyoma, leiomyosarcoma, embryonal tumors, gallbladder carcinoma, hypopharyngeal-squamous cell carcinoma, squamous cell carcinoma of larynx, malignant fibrous histiocytoma, parathyroid cancer, hepatocellular carcinoma, prostate cancer, penile carcinoma, retinoblastoma and salivary gland tumors are some of the malignancies in which MKI67 expression is considered as proliferation, stage, grade or survival marker. However, more sophisticated studies are needed in order to elucidate the exact correlation of this gene with these tumors.

Other non-malignant diseases

Note

MKI67 is evaluated in several other not malignant diseases, mostly as a proliferation marker, such as hemimegalencephaly, eosinophilic esophagitis, hepatitis, Reinke's edema, problems in placental development, psoriasis, Barret's esophagus, endometriosis, multiple sclerosis, hemangioma, myocardial infarction, Alzheimer disease, Langerhans cell histiocytosis and endometrial polyps.

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Pathmanathan N, Balleine RL, Jayasinghe UW et al.. The prognostic value of Ki67 in systemically untreated patients with node-negative breast cancer. J Clin Pathol. 2014 Mar;67(3):222-8

This article should be referenced as such:

Ntzeros K, Stanier P, Mazis D, Kritikos N, Rozis M, Anesidis E, Antoniou C, Stamatakos M. MKI67 (marker of proliferation Ki-67). Atlas Genet Cytogenet Oncol Haematol. 2015; 19(2):105-116.