APAF1 (Apoptotic protease activating factor 1)

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Identity

Other names: KIAA0413; Apaf-1
HGNC (Hugo): APAF1
Location: 12q23
Local order: solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3 12q23; IKK interacting protein 12q23.1; APAF1 12q23; E2a-Pbx1-associated protein/EB1 12q23.1-q23.2

DNA/RNA

Description
The APAF1 gene is comprised of 27 exons, with the coding region spanning 26 exons (the ATG is in the second exon).

Transcription
Five isoforms of APAF1 cDNA have been identified in Homo sapiens:
The original APAF1 (also called Apaf-1S) is 3585 bp long (it contains 12 WD40 repeats);
The APAF1-1M isoform (3618 bp) contains an insertion of 33 nt after position 295 of the first published sequence (11 aa insertion GKDVSQITSY between aa 98 and 99; it also contains 12 WD40 repeats);
The APAF1XS isoform (3516 bp) contains the same insertion of Apaf-1M form, lacks the base pairs from 3171 to 3296 of the Apaf-1S form (the deletion is in WD40 domain) but has an insertion of 24 nt at position 1725
The APAF1L (3714 bp) contains an insertion of 129 nt at position 2466 (contains 13 WD40 repeats);
The APAF1XL (3747 bp) isoform contains the same insertion of APAF1M form, plus an additional insertion of 129 bp (43 aa between aa 811-812; Apaf-1XL also contains 13 WD40 repeats).

Pseudogene
Not known.

Protein

Description
The protein can be divided into three domains: the N-terminal is a CARD domain and is necessary for APAF1 function; alternatively, it can bind the WD40 domain or cytochrome C. The ced-4-like domain is responsible for APAF1 conformational changes. The C-terminal WD40 domain is a negative regulator element composed of 12 or 13 WD40 repeats: it can bind the CARD domain but it can probably interact with other apoptotic regulator proteins as well.

Expression
APAF1 promoter can interact with E2F1 (also E2F2-3) and p53 which can in turn regulate its expression.

Localisation
Cytosolic.
**Function**

APAF1 is the structural core of the apoptosome. When the mitochondrial pathway of apoptosis is activated, cytochrome c is released from mitochondria to cytosol, and then binds to APAF1 CARD domain changing its conformation. A further binding of ATP molecules mediates a second conformational change which leads to open APAF1 conformation. By means of the CARD domain, seven APAF1 molecules bind to each other and to seven molecules of initiator Caspase-9 forming the apoptosome and causing the activation of effector caspases. The formation of apoptosome and the activation of caspases are regulated by numerous interacting proteins.

**Homology**

CED-4 (C. elegans); DARK (D. melanogaster); CARD proteins.

**Mutations**

**Germinal**

Not known in H. sapiens.

**Somatic**

Not known in H. sapiens.

**Implicated in**

**Skin cancers (melanoma, basal cell carcinoma, squamous cell carcinoma)**

**Cytogenetics**

Frequent LOH in 12q22-23 locus (primary melanomas: 20-25% metastatic melanomas 35-40%).

**Oncogenesis**

The silencing of Apaf1 expression is often found in
Melanomas. Two main mechanisms have been posited for APAF1 diminution, either the allelic LOH in 12q22-23 locus and/or a transcriptional silencing by promoter methylation. The inactivation was not found in Nevi but it increased significantly in the later stages of carcinogenesis, when primary melanomas are fully developed (1-3mm of diameter). Very often such inactivation was associated with metastatic melanomas. Moreover, the APAF1 level is correlated with chemosensitivity to different agents; different studies demonstrate that overexpressing or restoring a normal APAF1 level could sensitize chemoresistant melanoma cell lines, in vitro. Recently, APAF1 LOH determination on blood serum DNA has been proposed as a marker for selecting appropriate chemotherapy in stage IV melanoma patients.

**Brain tumors (neural tumors, glial tumors)**

**Cytogenetics**

Frequent LOH in 12q22-23 locus in glioblastomas (40%).

**Oncogenesis**

APAF1 seems to be downregulated or absent in Glioblastomas at mRNA and protein level. In addition, the co-overexpression of APAF1 and Caspase-9 sensitizes glioma cell lines (U-251 and U-373 MG) to p53-dependent apoptosis. Other modulations of the apoptosome-related apoptosis have been successfully conducted in order to induce apoptosis in glioma resistant lines. By contrast, APAF1 seems to be active in Neuroblastomas while there are no studies about a putative APAF1 role in other glial tumors (such as ependimoma, astrocytoma, ganglioglioma).

**Head and neck cancers and odontogenic tumors**

**Oncogenesis**

There is no direct evidence of APAF1’s role in the oncogenesis of these types of cancer even though Apaf1 loss has been correlated with gain of Cisplatin Chemoresistance in HSC-2CR cells (derived from HSC-2 head squamous carcinoma cells).

**Gastro-intestinal tract cancers**

*Oesophagus cancer, gastric cancer, gallbladder cancer, ampulla of vater cancer, peritoneum cancer, vermiform appendix cancer, colon cancer, cancer of the anus*

**Oncogenesis**

A low frequency of mutations (10-15 % of cases) is found in colorectal and gastric cancer. These mutations are due to the genetics of microsatellite instability and appear to be heterozygous. No evidences of APAF1 involvement have been found in the pathogenesis of the other tumors mentioned.

**Exocrine pancreas cancers (various stages of the pancreas ductal adenocarcinoma - PDAC)**

**Cytogenetics**

12q locus deletions could be considered among the most frequent deletions in PDAC.

**Oncogenesis**

There is no direct evidence of APAF1 mutations in the progression of the PDAC (some even deny its possible role completely). There are many studies, however, which point out the 12q22-23 locus LOH or mutation in PDAC. Most of the mutated genes involved (such as K-Ras, p53, p16INK4a, p19ARF) can control the APAF1 level directly or indirectly through the action of p53 and E2F-1 which both have active binding boxes to the APAF1 promoter.

**Liver cancer and liver metastases**

**Oncogenesis**

Methylation is a common feature in hepatocellular carcinoma (HCC) regulation. While the analysis of promoters methylation in HCC samples showed that the APAF1 gene is not hypermethylated, the HepG2 cells exposed to a demethylating agent (DEM, diethyl maleate) showed an increased level of Apaf1 and of some caspases which lead to G2 phase arrest and apoptosis.

**Lung cancer**

**Oncogenesis**

There is no direct evidence for abrogation of APAF1 function in lung cancer. However, the APAF1/Caspase-9 upregulation seem to be a protective mechanism in some NSCLC (non small cell lung carcinoma) cell lines, while in other NSCLC lines (such as the NCI-H460) an indirect APAF1 loss of function is mediated by the upregulation of XIAP (an inhibitor of Apoptosome assembly). Furthermore, a driven expression of APAF1/Caspase-9 (through the Inibition of XIAP in NCI-H460 cells or with low dose lung cancer cell lines) seems to augument sensitivity to death.

**Tumors of the female reproductive organs**

*Ovarian carcinoma, neoplasms of Fallopian tube, endometrium, cervix, vulva and vagina*

**Oncogenesis**

In ovarian carcinoma, the APAF1 gene seems to be active. However, dysfunction in the apoptosome assembly process has been correlated with chemoresistance. In contrast, loss of heterozygosity was found in the apaf1 locus in malignant ovarian germ cell tumors. There is no information about the reproductive tract.

**Tumors of the male reproductive organs**

*Seminoma, nonseminomatous germ
cell tumors, sex cord-stromal tumors, other testis cancers, neoplasms of prostate, tumor of the penis)

Cytogenetics
Frequent deletions in Chromosome 12 long and short arm in germ line tumors; LOH in 12q22-23 is present in seminomas, non-seminomatous tumors and in mixed teratomas with various reported percentage (20-45%).

Oncogenesis
In Germ line tumors the APAF1 locus is often deleted; however it seems that APAF1 level was normal in various analyzed lines. Interestingly, Cisplatin treatment of an embryonal carcinoma cell line, TTSC-3 lead to the differentiation of the carcinoma through the up-regulation of pro-differentiation and pro-apoptotic genes (such as APAF1, Caspase-8 and TNFR1). In Prostatic Tumor there is no evidence of APAF1 involvement; however some studies have been conducted demonstrating an increase of Apaf1 at transcription level as a cellular response to chemotherapeutic agents.

Urinary tract tumors (renal cell carcinoma, neoplasms of the renal pelvis, ureter, bladder, urethra)

Oncogenesis
The apoptosome function seems to be active in primary samples and in a few cell lines of renal cell carcinoma. There are no informations about the urinary tract.

Hematopoietic system tumors

Oncogenesis
It's not clear if APAF1 gene is corrupted in leukaemias and lymphomas. However, while the methylation of the promoter was demonstrated in different kinds of leukaemia, the protein level does not correlate with the messenger level, suggesting a multistep regulation in APAF1 expression. Furthermore, it has been demonstrated that the APAF1 overexpression, conducted by in vitro transfection or by chemoadiuvants, could overcome the resistance to chemo-radiotherapeutic agents.

Bone and soft tissue cancers (osteoma, sarcoma, fibroma, osteosarcoma)

Oncogenesis
There is no direct evidence of APAF1 role in the oncogenesis of these types of cancer even though in Ewing's sarcoma cell lines the Apaf1 low level found in two different lines (STA-ET-2.1 and STA-ET-2.2) was correlated with chemoresistance to p53-dependent death stimuli compared with lines with normal APAF1 level. APAF1 was also absent and correlated with chemoresistance in the HT-1080 fibrosacroma cell line.

Various tumors (eye tumor, heart and great vessels tumors, neoplasm of the endocrine glands and of the diffuse endocrine system, tumor of the mesotheliums)

Oncogenesis
At present, there is no direct evidence of APAF1 involvement in the carcinogenesis of these neoplasms.

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