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Review

CHFR (Checkpoint with fork-head associated and ring finger)

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Abstract

Growing evidence in mice, primary human tumors, and mammalian cell culture models indicate that CHFR may function as a potent tumor suppressor. CHFR functions as part of an early G2/M checkpoint, more specifically in antephase. Antephase refers to late G2 when chromosome condensation starts. This early mitotic checkpoint causes a delay in chromosome condensation in response to mitotic stresses. The human CHFR gene was originally identified during a search for novel cell cycle checkpoint proteins that have fork-head associated domains. Initial analysis indicated that the CHFR-associated G2/M checkpoint was inactivated in a subset of cancers as demonstrated by high mitotic indices (a high percentage of cells that have condensed chromosomes) in response to exposure to the microtubule poison, nocodazole, due to lack of CHFR expression or CHFR mutations in various cancers. Many other studies showed promoter hypermethylation leading to low/no expression of CHFR.

Keywords
CHFR, cell cycle, checkpoint, antephase

Identity

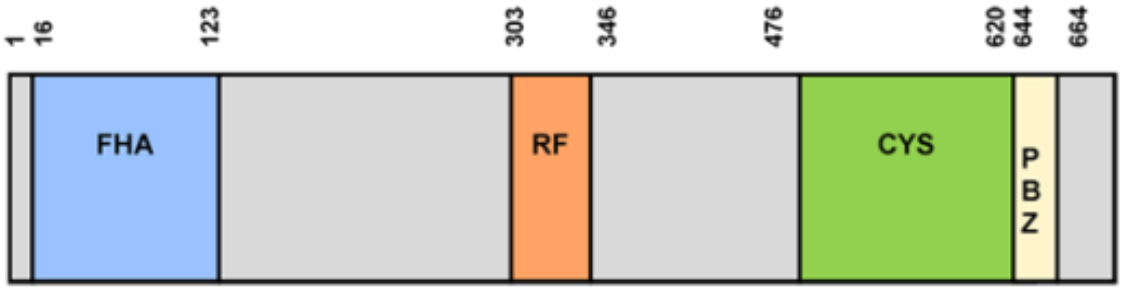
HGNC (Hugo): CHFR

Location: 12q24.33

Other names: FLJ10796

Local order
Genes flanking CHFR in centromere to telomere direction on 12q24.33:
Peroxisomal membrane protein 2 gene (PXMP2) --- Hypothetical protein gene (MGC5352) --- Golgi autoantigen, golgin subfamily a3 gene (GOLGA3) --- **Checkpoint with FHA and RING finger gene (CHFR)** --- Hypothetical gene (GeneID: 90462) --- Zinc finger protein 26 gene (ZNF26)

Note
CHFR functions as part of an early G2/M checkpoint, more specifically in antephase. Antephase refers to late G2 when chromosome condensation starts.
This early mitotic checkpoint causes a delay in chromosome condensation in response to mitotic stresses. The human CHFR gene was originally identified during a search for novel cell cycle checkpoint proteins that have fork-head associated domains. Initial analysis indicated that the CHFR-associated G2/M checkpoint was inactivated in a subset of cancers as demonstrated by high mitotic indices (a high percentage of cells that have condensed chromosomes) in response to exposure to the microtubule poison, nocodazole, due to lack of CHFR expression or CHFR mutations in a neuroblastoma, an osteosarcoma and 2 colon cancer cell lines (4 of 8 different cancer cell lines) (Scolnick and Halazonetis, 2000).



Domains of CHFR. The forkhead-associated domain of CHFR is located at the N-terminus. RING-finger domain with the ubiquitination activity is located through 303-346 amino acids. Poly-ADP-ribose binding zinc finger motif overlaps with the cystein-rich region near the C-terminus.

Various further studies demonstrated loss of or low CHFR expression in various types of cancer cells including those from colon, esophageal, gastric, lung and breast cancers.
Over time, CHFR has been identified as an inactivated tumor suppressor protein in a diverse group of solid tumor malignancies, mostly as demonstrated by promoter CpG island methylation.

DNA/RNA

Description

The CHFR gene spans approximately 47 kb and has at least 18 exons (BC012072 vs. NT_024477) as predicted according to Spidey (http://www.ncbi.nlm.nih.gov/spidey/) http://www.ncbi.nlm.nih.gov/spidey/). While multiple splice forms have been demonstrated (Toyota et al, 2003), the genomic structure has not been experimentally confirmed.

Transcription

CHFR mRNA is 3189 bp (BC012072).
Transcripts that lack exon 2, exon 5 and exon 6 have been detected in various tissues including bone marrow, small intestine, lung, heart, testis, kidney, stomach and lympocytes as well as some cancer cell lines by RT-PCR. Northern blot transcript analysis suggests that limited if any alternative splicing is present in most fetal and adult tissues where CHFR is expressed a prominent 3.2 kb is observed. CHFR mRNA is detected in heart, brain, placenta, lung, liver, muscle, kidney, pancreas by Northern blot analysis (Scolnick and Halazonetis, 2000).
Alternative mRNA transcripts lacking specific exons (2, 5, and/or 6) have been described for CHFR (Toyota et al. 2003) The isoform that lacks exon 2 happens to lack the FHA domain and was also found to be highly expressed in cancer cells when compared to normal samples .

Pseudogene

No known pseudogene has been reported

Protein

Description

CHFR encodes a 652 amino acid protein (according to BC012072 nucleotide sequence) with FHA (forkhead associated), RING (really interesting new gene) finger and cysteine rich domains. Cysteine rich region further harbors a PBZ domain. No alternative isoforms have been described to date.
Domains:
- FHA domains (16-123) are present in cell cycle checkpoint genes, transcription factors, protein kinases and have roles in protein-protein interactions with specificity for phosphorylated targets.
The three dimensional structure of CHFR suggests that CHFR may be able to recognize as of yet unidentified phosphorylated targets targets (Stavridi et al., 2002; Tsai 2002)..
- RING finger domains are found in ubiquitin ligases.
Ubiquitin ligases attach ubiquitin to target proteins during a cascade of enzymatic reactions. RING finger domains are present in a variety of proteins (e.g. Anaphase promoting complex, APC, Cbl family proteins, MDM2) implicated in cancer.
- Cys: Cystein-rich region (476-641)
- PBZ: poly-ADP-ribose binding zinc finger motif (620-644) is at the C terminus. PBZ domain allows CHFR to bind to poly (ADP-ribose). This domain is generally required for the activity of checkpoint response proteins (Ahel et al., 2008)

Expression

CHFR is ubiquitiously expressed in normal fetal and adult human tissues.
Protein levels are predicted to fluctuate during the cell cycle possibly through auto-ubiquitination based on overexpression studies in cancer cell lines (Chaturverdi et al., 2002; Kim et al., 2011).
Upon mitotic stresses, CHFR protein levels are thought to be stabilized and reaching the highest levels at G2/M.

Localisation

Various lines of evidence suggest different cellular localizations for CHFR. Endogenous and low ectopic expression of CHFR showed cytoplasm and

spindle localization patterns during mitosis. Higher expression of ectopic CHFR correlated with a shift in the localization to the nucleus (Burgess et al., 2008). Later on, nuclear presence of CHFR was explained via a short lysine-rich stretch (KKK) at amino acid residues 257-259 (Kwon et al., 2009).
Egeberg et al., 2012 suggested a centrosome/primary cilium axis localization of CHFR. CHFR was also shown to localize to the mitotic spindle by an interaction with TCTP, a protein involved in microtubule stabilization and a-tubulin (Kim, 2011)

Function

Initially, CHFR was described to induce an early G2/M checkpoint in response to mitotic stress (Scolnick and Halozenetis, 2000). Cell lines expressing wild-type CHFR exhibit low mitotic index (percentage of cells with condensed chromosomes) and delayed entry into metaphase when centrosome separation is inhibited by mitotic stress. In contrast, cancer cell lines lacking CHFR function enter metaphase without delay and demonstrate higher mitotic indices compared to the CHFR expressing cell lines. (Erson and Petty, 2004).
In vitro studies suggest that the RING finger domain in CHFR also facilitates ubiquitin ligase function and that it is essential for checkpoint function of CHFR (Chaturved et al., 2002).. In vitro Xenopus extract experiments suggested that CHFR specifically targets PLK1 (polo-like kinase 1) for degradation when extracts are supplemented with high ubiquitin concentrations (Kang, 2002). Thus, according to this in vitro model, CHFR is able to halt cell cycle progression early in mitosis by degrading PLK1, a major player for the activation of mitosis promoting factor. In addition, AURORA A is known to phosphorylate and activate PLK1 as well as CDC25B eventually driving CYCLIN B/CDK1 activation. Interestingly, CHFR was also found to bind via its cysteine rich C-region and ubiquitinate AURORA A, leading to its degradation (Yu et al., 2005). The auto-ubiquitylation ability of CHFR at G2 Phase was proposed to be required for the accumulation of Plk1 and mitotic entry in mammalian cells (Kim et al., 2011). Earlier, Oh et al., showed deubiquitination of Chfr, by USP7/HAUSP (deubiquitinating enzyme) also to regulate its own stability and activity (Oh et al,. 2007).
On the contrary, Summers et al. suggested PLK1 and AURORA A levels not to change when CHFR was expressed in HCT116 cells treated with Nocodazole (Summers et al., 2005).
More recently, other proteins including TOPK and PTEN have been shown to play a role in the CHFR related mitotic spindle checkpoing (Shinde et al. 2013)
Furthermore, Bothos et al., showed that CHFR was able to activate the p38 stress kinase pathway, which reverses chromosome condensation and induces a mitotic arrest and suggested that the ubiquitin ligase function of CHFR may be different than the current in vitro model and that instead of Lys48 ubiquitination, CHFR may link ubiquitin to target protein or proteins via Ly63 due to its interaction with the heteromeric ubiquitin conjugating enzyme complex, Ubc13-Mms2 (Bothos et al., 2003).
In the canonical ubiquitin/proteasome pathway, Lys48 is a signal for degradation of target proteins whereas Lys63 ubiquitination functions as a non-proteolytic tag for protein targets. Lys63 ubiquitination is thought to be involved in DNA repair mechanisms. Indeed, CHFR appears to have important roles in DNA damage response (Shtivelman et al., 2003). CHFR and RNF8 (A ubiquin ligase) ubiquitinate histones (H2A and H2B) upon ioinizing radiation (Al-Hakim et al., 2010; Wu et al., 2011).
These ubiquitinations seem to be important for the eventual activation of the key DNA damage checkpoint effector, ATM (Derks et al., 2006; Lavin and Kozlov, 2007).
Recently, CHFR was reported to interact with MAD2, an important component of the spindle assembly checkpoint. CHFR knockdown resulted in mislocalization of MAD2 and disruption of the MAD2/CDC20 interaction.
The cysteine-rich region of CHFR appears to be the essential domain for the CHFR/MAD2 interaction and for promoting interaction between MAD2 and CDC20 to inhibit the anaphase-promoting complex (Privette et al., 2008; Keller and Petty, 2011).

Homology

M.musculus 5730484M20Rik RIKEN cDNA 5730484M20 gene, R.norvegicus LOC288734 similar to RIKEN cDNA 5730484M20, budding yeast proteins, Dma1 and Dma2 are 58% identical to each other and are possible homologs of human CHFR. Dma1 and Dma2 have roles in spindle formation and formation of septin ring during cytokinesis (Fraschini et al., 2004).

Mutations

Germinal

No germline mutations have been reported yet.

Somatic

A panel of 53 lung carcinomas has been screened with matching normal tissue and 3 mutations were found, one of which was associated with loss of heterozygosity. Mutations found in patient samples were: C587T, G695C (both between the FHA and RING domains) and T1697C (in the C-terminal cysteine rich region of CHFR). However, no correlation was found with a specific diagnosis or stage of the disease in the patients (Mariatos et al.,

2003). No clear pathogenic mutations in the CHFR coding sequence have been observed in the analysis of tumors (Privette and Petty, 2008).

Epigenetics

Hypermethylation of the CHFR promoter has been the most commonly reported mechanism lowering CHFR expression observed in tumors (Privitte and Petty, 2008).

Implicated in

Gastric cancer

In gastric cancer, methylation of CHFR promoter is highly recurrent (Hu et al., 2011; Li et al., 2014; Satoh et al., 2003). Decreased CHFR expression has been shown in 20% of gastric cell lines and 39% of primary gastric cancers tested (Satoh et al., 2003). In a study with 102 paraffin-embedded gastric cancer samples, 34% of samples showed methylation. No association was found between methylation of CHFR promoter with gender, age, tumor size, tumor differentiation, and lymph node metastasis. According to Cox proportional hazards model in docetaxel-treated gastric cancer patients, resistance to docetaxel was found in CHFR unmethylated patients. CHFR methylation may serve as a docetaxel-sensitive marker in human gastric cancer (Li et al., 2014).

Lung cancer

Loss of detectable CHRF levels has been linked to aberrant hypermethylation in lung cancer (Mizuno et al., 2002). Apart from hypermethylation, inactivation of CHFR gene by missense mutations is reported for lung carcinomas (Mariatos et al., 2003). In a study with 165 lung carcinomas, 10% were found to have hypermethylated CHFR promoter. In addition,

Prognosis

CHFR hypermethylation was significantly correlated with poor prognosis of lung carcinomas, suggesting a therapeutic potential for CHFR targeted approaches (Koga et al., 2013).

Cytogenetics

A lung cancer patient sample demonstrates loss of heterozygosity for a CA repeat located on a BAC that contains the CHFR gene. Several other cancers demonstrate allelic imbalance involving chromosome band 12q24 but specific analysis of CHFR in these samples has not been investigated.

Breast cancer

An initial screening resulted with 50% of 24 breast cancer cell lines to have CHFR expression (Erson and Petty, 2004). CHFR protein levels were also low in 36% of breast cancer patients. Lack of CHFR expression in primary cancers was associated with increased tumor size and estrogen receptor negativity (Privette et al., 2007). In another study, 110 primary breast cancers were investigated for methylation status, only 0.9% showed hypermethylation of CHFR promoter (Tokunaga et al., 2006). Although hypermethylation of CHFR promoter is common in various cancers, this study showed it to be a rare event in primary breast carcinomas. Moreover, an interaction between CHFR and PARP-1 was shown to have an important role in cell cycle regulation. CHFR, by its E3 ubiquitin ligase function, caused degradation of PARP-1, which lead to cell cycle arrest in prophase. These findings suggested a novel potential therapeutic approach for combinational chemotherapy with PARP inhibitors for breast cancer cells (Kashima et al., 2012).

Leukemia

Methylation of CHFR promoter was detected in 39% of leukemia patients. CHFR hypermethylation incidence was shown to be unchanged between acute myelocytic leukemia and acute lymphocytic leukemia (Gong et al., 2005).

Esophageal cancer

When expression level of CHFR was investigated, 4 out of 15 esophageal cancer cell lines (26.7%) and 7 out of 43 (16.3%) primary esophageal cancers showed loss of CHFR expression due to hypermethylation of promoter (Shibata et al., 2002). In another study, CHFR transcript was found to be downregulated in 79% of esophageal adenocarcinomas (44 of 56 samples) compared to 41 normal samples. Immunohistochemical analysis also correlated with expression analysis, 75% (56 of 75) of samples showed either weak or no immunostaining. Hypermethylation of promoter correlated with low CHFR expression in esophageal cancer patients; 31% of samples (18 of 58) displayed significant hypermethylation (Soutto et al., 2010). Another recent study used 40 esophageal squamous cell carcinoma patient samples for RT-qPCR analysis of CHFR expression. Aberrant hypermethylation of the CHFR promoter was observed in 13 of 29 primary esophageal cancers. The CHFR expression levels of the methylated samples was significantly lower than that of the unmethylated samples (Suzuki et al., 2014)

Hepatocellular carcinoma

Aberrant methylation was detected in 22 of 65 (35%) primary hepatocellular carcinomas (HCC), compared to noncancerous liver cells (Sakai et al., 2005). Also, methylation of CHFR was found to be significantly correlated with advanced disease stage ($p=0.037$) and an infiltrated growth pattern ($p=0.047$). In another study with 70 HCC samples, methylation frequency of CHFR was 43% (30 out of 70) (Li et al., 2012). 5-aza-2'-deoxycytidine (5-aza-

dC) treatment of HCC cell lines restored expression of CHFR.

Prostate cancer

In a genome profiling study, blood and bone-marrow samples of prostate cancer patients were investigated using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) (Schwarzenbach et al., 2011). MS-MLPA detected genetic and epigenetic aberrations of 37 tumor suppressor genes including CHFR.

Head and neck cancer

19% of 126 head and neck cancer patients showed methylation of a group of tumor suppressors. CHFR was one of the most frequently methylated genes in tumor tissue compared to normal (Yalniz et al., 2011).

Cervical cancer

Out of 14 cervical adenocarcinoma specimens tested by methylation-specific PCR, 2 of them (12.3%) showed aberrant methylation of CHFR (Banno et al., 2007). When six cell lines derived from human cervical carcinoma were analyzed, hypermethylaton of CHFR was observed in HeLa and SKG-IIIb cells. In another study, sequential methylation of eight genes including CHFR was linked to HPV-induced cervical carcinogenesis (Henken et al., 2007).

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