Gene Section

Review

TFAP2C (transcription factor AP-2 gamma (activating enhancer binding protein 2 gamma))

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Abstract

Review on TFAP2C, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: AP2-GAMMA, ERF1, TFAP2G, hAP-2g
HGNC (Hugo): TFAP2C
Location: 20q13.31
Note: TFAP2C is a member of the retinoic acid-inducible, developmentally regulated family of AP-2 factors. TFAP2C regulates cell growth and differentiation during ectodermal development (Qiao et al., 2012; Hoffman et al., 2007).
It plays a critical role in establishing the luminal phenotype of normal mammary cells during their differentiation process.
TFAP2C was shown to be involved in regulation of ESR1 and luminal - associated genes in breast cancer (Woodfield et al., 2010).
TFAP2C maintains breast cancer luminal phenotype through the induction of luminal-associated genes and repression of genes characteristic of the basal subtype.

DNA/RNA

Description

TFAP2C consists of 7 encoding exons. The open reading frame of the coding region is 1353 bp. TFAP2C cDNA was isolated in 1996 (Williamson et al., 1996) and predicted protein was conserved with TFAP2A DNA-binding and dimerization domains, and differs in the N-terminal activation domain.
The promoter lacks canonical binding sites for basal transcription factors such as TATA and CCAAT boxes, but contains a cluster of CpG islands and may rely on an initiator element for transcription (Li et al., 2002). A potential trophoblast cell-specific regulatory element located approximately 6 kb upstream of the murine Tfap2c gene transcription start site (Li and Kellems, 2003).

Transcription

3 splice variants are described (Ensembl).

Pseudogene

No pseudogenes are reported.

TFAP2C human gene including promoter, 7 exons (blue rectangles) and 6 introns. Modified from Entrez Gene (Genomic DNA).
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Protein

Note
Active TFAP2C forms consist of homo - and heterodimers and play an important role in activation of retinoic acid-mediated differentiation including development of the eyes, face, body wall, limbs, neural tube (Hoffman et al., 2007; Li and Cornell, 2007).
Placental defect and embryonic death were reported as results of TFAP2C total knockdown.
TFAP2C protein was purified in 1997 (McPherson et al., 1997) from ESR1 - positive cell line, was designed as ERF1. TFAP2C, 450-aa protein, has 48 kDa molecular mass.
TFAP2C has 65% sequence homology to TFAP2A overall and 76% identity in C-terminal part.
The consensus site from the ChIP-seq data, SCCTSRGGS (S=G/C, R=A/G), is consistent with the optimal binding site, GCCTGAGGG, which was determined by in vitro PCR-assisted binding site selection (Woodfield et al., 2010).
Estrogen receptor-alpha (ESR1) and HER2/c-erbB2 genes are regulated by TFAP2C (Bosher et al., 1995; McPherson et al., 1997; Delacroix et al., 2005; Woodfield et al., 2007) along with genes associated with luminal phenotype of breast cancer (Woodfield et al., 2010).
Activity of TFAP2C at specific target genes depends upon epigenetic chromatin structure.
The combination of increasing chromatin accessibility and inducing TFAP2C provides a more robust activation of the ESR1 gene in ESR1-negative breast cancer cells (Woodfield et al., 2009).
TFAP2C repressed CD44 expression in basal-derived breast cancer (Spanheimer et al., 2013a).
TFAP2C regulates the expression of GPX1, which influences the redox state and sensitivity to oxidative stress induced by peroxides (Kulak et al., 2013).
Wwox tumor suppressor protein inhibits TFAP2C oncogenic activity by sequestering it in the cytoplasm (Aqeilan et al., 2004).
Reporter and chromatin immunoprecipitation assays demonstrated a direct, functional interaction by TFAP2C at the CDKN1A proximal promoter. TFAP2C silencing coincided with acquisition of an active chromatin conformation at the CDKN1A locus and increased gene expression (Gee et al., 2009).
TFAP2C SUMOylation modification was described in mammalian cells and SUMO site was mapped to conserved lysine 10 (Eloranta and Hurst, 2002).
Epithelial hyperplasia and impaired differentiation were reported in Tap2c overexpressing transgenic mice (Jäger et al., 2003).

Description
A helixloop-helix motif in the DNA binding domain binds to GC-rich consensus site, SCCTSRGGS (S=G/C, R=A/G) (Woodfield et al., 2010), in the promoters of target genes and mediates TFAP2C specific transcriptional activity.

Expression
TFAP2C is widely expressed within secondary outgrowths in the human mammary gland by 19 weeks gestation.
In the adult mammary gland TFAP2C expression can be found in epithelial and myoepithelial compartments.
TFAP2C expression was reported in 16-40 weeks placenta, 5-10 weeks decidu and chorion (Li et al., 2002).
TFAP2C is expressed in gonocytes at weeks 12-37 of gestation, indicating a role of this transcription factor in fetal germ cell development.
TFAP2C and c-KIT, a known target of AP-2 transcription factors, were coexpressed in gonocytes, making a direct regulation possible. With increasing differentiation of fetal testis, gradual downregulation of TFAP2C from the 12th to 37th week of gestation was observed. Furthermore, TFAP2C was expressed abundantly in 25/25 IGCNUs, 52/53 testicular seminomas, 10/10 metastatic seminomas, 9/9 extragonadal seminomas and 5/5 dysgerminomas (Pauls et al., 2005).
Normal tissues with TFAP2C expression: colon, lymph node, brain, heart, kidney, liver, lung, thyroid, adrenal gland, ovary, prostate, testis.

Localisation
Nuclear.
**Function**

It plays a role in the development of the eyes, face, body wall, limbs, and neural tube (Hoffman et al., 2007; Li and Cornell, 2007).

Deletion of Tcfap2c during development resulted in a specific reduction of upper layer neurons in the occipital cortex (Pinto et al., 2009).

Conditional ablation of Tcfap2c results in a delay in skin development and abnormal expression of p63, K14, K1, filaggrin, repetin and secreted Ly6/Plaur domain containing 1, key genes required for epidermal development and differentiation (Guttormsen et al., 2008). Heterozygous Tcap2c-knockout mice were detected to have decreased body size while homozygous mice died at 7-9 days of embryonic development due to failure of proliferation of extraembryonic trophodermal cells (Werling and Schorle, 2002). TFAP2C is also implicated in the regulation of the adenosine deaminase (ADA) gene, a gene involved in purine metabolism found expressed at the maternal-fetal interface (Werling and Schorle, 2002).

**Homology**

Mouse, Tcap2c (Mus musculus: NP_033361.2) (NCBI).

Predicted homology: chicken (Gallus gallus: XM_417497.4), zebrafish (Danio rerio: NM_001008576.1) (NCBI).

**Mutations**

**Germinal**

2 patients with deletions of chromosome 20q13.2-q13.3 were reported to have feeding difficulties, microcephaly, facial dysmorphism with high forehead, broad nasal bridge, small chin and malformed ears, mild psychomotor retardation, and hypotonia (Geneviève et al., 2005).

**Somatic**

39 mutations were detected after analysis of 8164 samples (COSMIC: gene overview for TFAP2C) without direct links to certain diseases pathogenesis.

Deletion analyses of the promoter and chloramphenicol acetyl transferase reporter gene assays indicate that the sequence between -746 and -575 is important for its expression in mammary carcinoma cell lines (Li et al., 2002).

Combined mutation of the three putative Sp sites reduced promoter activity by 80% in trophoblast and nontrophoblast cells, demonstrating the functional importance of these sites in regulating TFAP2C gene expression (Li and Kellems, 2003).

**Implicated in**

**Breast cancer**

**Note**

TFAP2C plays a critical role in maintaining the luminal subtype of breast cancer. TFAP2C directly binds to promoters and activates ESR1 along with luminal-associated genes (Woodfield et al., 2010).

TFAP2C repressed CD44 expression in basal-derived breast cancer (Spanheimer et al., 2013a).

Regulation of Ret by TFAP2C occurs independently of ESR1 expression in breast carcinoma (Spanheimer et al., 2013b). TFAP2C regulates the expression of GPX1, which influences the redox state and sensitivity to oxidative stress induced by peroxides (Kulak et al., 2013).

**Prognosis**

Resistance to Tamoxifen treatment and reduction of survival rate had correlation with TFAP2C overexpression (Guler et al., 2007). ERBB2-negative/AP-2-positive expression patients had a better prognosis than patients with ERBB2-positive/AP-2-positive tumors (Gee et al., 2009).

In primary breast cancer specimens, high TFAP2C and low CD44 expression were associated with pCR after neoadjuvant chemotherapy and could be predictive of tumors that have improved response to neoadjuvant chemotherapy (Spanheimer et al., 2013a).

Elevated expression levels of TFAP2C in breast tumors were reported as predictors of poor prognosis (Zhao et al., 2003) and advancing clinical grade (Sotiriou et al., 2006).

**Seminomatous germ cell tumors**

**Note**

Immunohistochemistry marker to the detection of germ cell tumors (Pauls et al., 2005).

**Melanoma**

**Note**

AP-2γ expression is lower in thick melanomas, it is associated with unfavourable histo-pathological parameters (increased vascularity, vascular invasion and mitoses) (Osella-Abate et al., 2012).

**Pre-eclampsia**

**Note**

Elevated TFAP2C concentrations are associated with human placental defects such as pre-eclampsia and intrauterine growth restriction (Kuckenber et al., 2012).
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TFAP2C target genes. Analysis was done by Ingenuity Systems. Red tone indicates genes repressed by TFAP2C and green indicates genes induced by TFAP2C. Insert: TFAP2C target genes RXR, RAR, and CRABP2 are involved in the retinoic acid signaling pathway (Woodfield et al., 2010).

Breakpoints

See figure above.

References


McPherson LA, Baichwal VR, Weigel RJ. Identification of ERF-1 as a member of the AP2 transcription factor family. Proc Natl Acad Sci U S A. 1997 Apr 29;94(9):4342-7


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An increased rate of pathologic complete response following neoadjuvant chemotherapy in breast cancer. J Surg Res. 2013a Sep;184(1):519-25


Williams CM, Scibetta AG, Friedrich JK, Canosa M, Berlato C, Moss CH, Hurst HC. AP-2gamma promotes proliferation in breast tumour cells by direct repression of the CDKN1A gene. EMBO J. 2009 Nov 18;28(22):3591-601


Li W, Cornell RA. Redundant activities of Tcfap2a and Tcfap2c are required for neural crest induction and development of other non-neural ectoderm derivatives in zebrafish embryos. Dev Biol. 2007 Apr 1;304(1):338-54

Woodfield GW, Horan AD, Chen Y, Weigel RJ. TFAP2C controls hormone response in breast cancer cells through multiple pathways of estrogen signaling. Cancer Res. 2007 Sep 15;67(18):8439-43


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