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Gene Section
Review

TGFBR2 (Transforming Growth Factor, Beta Receptor II (70/80kDa))

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Abstract

Review on TGFBR2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: AAT3, FAA3, LDS1B, LDS2B, MFS2, RIIC, TAAD2, TGFR-2, TGFbeta-RII

HGNC (Hugo): TGFBR2

Location: 3p24.1

Note
Ensembl version: ENSG00000163513
SwissProt ID: P37173
ENZYME entry: EC=2.7.11.30

DNA/RNA

Description

Length of TGFBR2 gene is 87641 bases. TGFBR2 gene encodes 8 exons. Orientation: plus strand.

Transcription

The TGFBR2 gene encodes two well-known protein coding transcripts:
- TGFBR2-001 (Ensembl version ENST00000295754.5): Encoded by 7 exons; mRNA length: 4621 bps; Translation length: 567 amino acid residues;
- TGFBR2-002 (Ensembl version ENST00000359013.4): Encoded by 8 exons; mRNA length: 4605 bps; Translation length: 592 amino acid residues.

Protein

Description

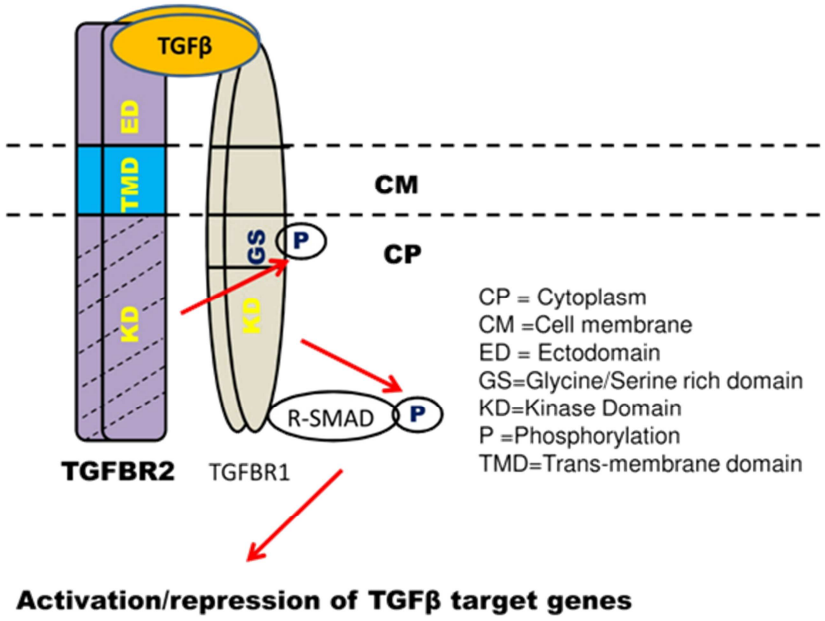
The TGFBR2 gene encodes two proteins through alternative splicing (592 aa and 567 aa long respectively); both can convey TGFβ signals. TGFBR2 is a transmembrane Serine/Threonine kinase. It has a molecular weight of 70/80kD. TGFBR2 consist of an N-terminal extra-cellular ligand binding ectodomain, a transmembrane region, and a C-terminal serine/threonine kinase domain. The ectodomain is formed by nine beta-strands and a single helix stabilised by a network of six intra strand disulphide bonds (Hart et al., 2002).

Expression

This protein is ubiquitously expressed in all cell types. Loss of TGFBR2 expression is linked with many pathological conditions involving cancer. The level of expression may vary depending up on cell-type.

Localisation

Primarily, it is a transmembrane protein, involved in extra-cellular TGFβ ligand binding. However, ligand binding can trigger internalization of both ligand and receptors. Receptors internalized in endosomes can either be targeted to lysosomes for degradation or be recycled back to the cell surface for re-use (Chen et al., 2009).



Structure and the mechanism of TGFBR2 activation: The TGFBR2 consists of an N-terminal extra-cellular ligand binding domain, a transmembrane region, and a cytoplasmic, C-terminal serine/threonine kinase domain. On TGFβ ligand mediated activation, TGFBR2 forms hetero tetramers with TGFBR1 and triggers TGFBR1 kinase activity by phosphorylating the GS domain. The activated TGFBR1 kinase can phosphorylate downstream SMAD transcription factors and there by mediate the expression of TGFβ-responsive genes.

Function

TGFBR2 is an important member of the Transforming Growth Factor Beta (TGFβ) signaling pathway. The TGFβ signaling controls important cellular activities like cytostasis, apoptosis, epithelial to mesenchymal transition (EMT), migration, etc. in a context dependent manner (Massague et al., 2005; Feng and Derynck, 2005). These pleiotropic cytokines are encoded by 42 open reading frames in human. They are divided into two subfamilies, the TGFβ/Activin/Nodal subfamily and the BMP(bone morphogenetic protein)/GDF(growth and differentiation factor)/MIS(Muellerian inhibiting substance) subfamily, as defined by sequence similarity and the specific signaling pathways that they activate (Shi and Massague, 2003). These cytokines are known to convey cellular signals through the serine/threonine kinase family receptors - 7 type I and 5 type II receptors - that are dedicated to TGFβ signaling (Manning et al., 2002). TGFBR2 is the most important and well-characterized type II receptor of TGFβ family.

The TGFβ-SMAD signaling cascade gets activated when TGFβ ligand binds to the TGFBR2 (Massague, 1998; Shi and Massague, 2003). The TGFβ ligand is secreted as latent complex in which the TGFβ dimer is bound to the latency-associated peptide (LAP) (Young and Murphy-Ullrich, 2004). Many latent TGFβ binding proteins (LTBPs) can bind to and sequester this latent complex to extra cellular matrix (ECM) (Derynck et al., 2001). The latent TGFβ is activated by plasmins and MMP2 and MMP9 through proteolytic processing that leads to removal of LAP. The active form of TGF-β is a 25 KDa disulphide linked homodimer. (Derynck et al., 2001; Padua and Massague, 2009). TGFBR2 is a constitutively active kinase that occurs as homodimer (Hart et al., 2002; Shi and Massague, 2003). On ligand binding mediated activation, TGFBR2 forms heteromeric complex with type I TGFβ receptor (TGFBR1) (Luo and Lodish, 1997).

TGFBR2 kinase mediated phosphorylation of Glycine/Serine-rich GS domain of TGFBR1 leads to activation of type I receptor kinase. Activated TGFBR1 then phosphorylates downstream SMAD transcription factors.

The pathway restricted SMADs-SMAD2 and SMAD3- are involved in signaling through TGFBR2/TGFBR1 receptor complexes. They are commonly called receptor regulated SMADs or R-SMADs. They bind directly to TGFBR1 and are phosphorylated at a C-terminal SSXS motif, that is exclusive and conserved for R-SMADs (Feng and Derynck, 2005; Schmierer and Hill, 2007). SMAD4 lacks a C-terminal SSXS motif and does not interact directly with TGFBR1. SMAD4 is commonly referred to as co-SMAD and serves as a common partner for all R-SMADs (Shi and Massague, 2003).

The binding of the R-SMAD to the type I receptor is mediated by adaptor proteins like SARA (SMAD anchor for receptor activation), a zinc double finger FYVE domain containing protein.
They restrict SMAD2/3 proteins to the plasma membrane and early endosomes and thus facilitate the interaction of SMAD2/3 proteins with activated TGFBR1 (Panopoulou et al., 2002; Chen, 2009).
The phosphorylated R-SMADs can form heteromeric complex with the common mediator SMAD (Co-SMAD, SMAD4) and this enables the nuclear translocation of the complex (Wrighton et al., 2009).
In the nucleus, the SMAD transcription factors orchestrate the expression of various target genes; depending on the DNA binding partners they associate (Massague, 2008).
The DNA binding partners are responsible for the context dependency exhibited by TGFβ signaling (Inman, 2005). Many protein phosphatases are responsible for switching off TGFβ signaling through R-SMAD dephosphorylation and dictate the strength and duration of TGFβ signaling (Wrighton et al., 2009).
The inhibitory SMADs (SMAD 6 and SMAD 7) are responsible for feedback repression of this signaling pathway (Xu, 2006). SMAD7 acts through competition for receptor mediated phosphorylation, and through the recruitment of SMAD ubiquitination regulatory Factors1 or 2 (Smurf1/Smurf2) to R- SMADs (Lönn et al., 2009).
In addition to the canonical signaling through the SMADs, TGFBR2 can activate many non-SMAD pathways like PI3K-Akt, JNK, p38MAPK, ROCK, PKC, PP2A, Ras, Erk1/Erk2 and Rho-like GTPases including RhoA, Rac and Cdc42 (Zhang, 2009). These non-SMAD signaling pathways add greatly towards the context-dependent nature of TGFβ signaling.
Many studies consider TGFβ alterations as a key reason for tumorigenesis (Derynck et al., 2001; Seoane, 2006).
These alterations arise at genetic as well as at epigenetic level.
While mutations are responsible for major share of genomic level TGFβ aberrations, the microRNA alterations contribute towards a fair share of the epigenetic alterations (Sivadas and Kannan, 2013). Besides, loss of integration of TGFβ signaling with other important pathways such as p53 signaling is an important reason for tumorigenesis (Massague, 2008).

Homology

The TGFBR2 gene is conserved in human, chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken and zebra fish. Notably, TGFBR2 of human beings and chimpanzee shows 100% and 99.6% identity, at protein and DNA level respectively. Furthermore, 72 organisms have orthologs with human gene TGFBR2.

Mutations

Note

Somatic mutations of TGFBR2 is a common event in various cancers (Seoane, 2006), Loeys-Dietz syndrome, Marfan syndrome, etc. (Loeys et al., 2006; Singh et al., 2006; Stheneur et al., 2008). Deletion of the chromosomal region 3p, that carries TGFBR2 is reported in many solid tumors (Kok et al., 1997).

Implicated in

Lung cancer

Disease

Lung cancer is the leading cancer in terms of incidence and death world-wide.
The most important subtype of lung cancer is non-small cell lung cancer (NSCLC), which accounts for ~ 87%, of all lung cancers.

Prognosis

The five year survival rate (~15%) is very poor for lung cancer. In the case of advanced lung cancers, the 5-year survival rate is as low as 2%. Moreover, no effective screening strategy is available.

Cytogenetics

Cytogenetic abnormalities to chromosomes 3p, 5q, 13q, and 17p are particularly common in small-cell lung carcinoma (Salgia and Skarin, 1998).

Oncogenesis

TGFBR2 is regarded as an important tumor suppressor that is altered in lung cancers. Microdeletions in the TGFBR2 gene are reported in non-small cell lung carcinoma (Wang et al., 2007). Further, studies showed decreased expression of TGFBR2, which is associated with the histopathological grading of NSCLCs (Xu et al., 2007).
Furthermore, reduced TGFBR2 expression in human NSCLC was found to be associated with smoking, reduced differentiation, increased tumor stage, increased nodal metastasis, and most importantly, reduced survival (Malkoski et al., 2012). These results suggest that loss of this tumor suppressor is an important event in lung tumorigenesis.

Breast cancer

Disease

Breast cancer is the second leading cancer in terms of incidence and is at fifth position with regards to cancer-associated mortality.
The important sub-types of breast cancer are ductal carcinoma in situ (DCIS), lobular carcinoma in situ

(LCIS), and invasive or infiltrating ductal carcinoma (IDC).

Prognosis

There is a good five year survival rate (>80%) for breast cancer. This scenario is primarily due to world-wide awareness programmes and improvement of early screening strategies.

Cytogenetics

The most consistent chromosomal regions that show gain are on 1q, 20q and 8q, while the most common regions of loss are on 3p and 6q.

These chromosomal changes were more frequently found in high grade ductal breast carcinomas with overexpression of c-erbB-2 oncoprotein (Malamou-Mitsi et al., 1999). Notably, gain of 3q is reported to be a stronger predictor of recurrence than grade, mitotic activity index (MAI) and other features in invasive breast cancers (Janssen et al., 2003).

Oncogenesis

The TGFβ signaling shows a dual role in breast cancers. Even though it is tumor suppressor initially, this signaling cascade can trigger lung metastasis of advanced breast cancers by inducing angiopoietin-like 4 (Padua et al., 2008).

However, mutations in the kinase domain of TGFBR2 are reported in recurrent breast cancers. Since no mutations were observed in the primary tumors, TGFBR2 mutations might have a role in breast cancer recurrence (Lucke et al., 2001). Furthermore, TGFBR2 positivity is an independent prognostic factor for good disease-free survival and overall survival in human epidermal growth factor receptor-2 (HER2)-negative patients (Paiva et al., 2010).

Colorectal cancers

Disease

Colon and rectal cancers account for around 9.4% of all cancer cases.

These cancers are at third position in terms of incidence and are at fourth position with regards to cancer-associated mortality.

Prognosis

There is a good five year survival rate (>80%) for stage 1 2 cases. However, the 5-year survival rate is only about 10% in stage IV colorectal cancers.

Cytogenetics

Colorectal cancers show frequent gains at 7p, 7q, 8q, 16p, 20p and 20q, while losses are often at 18q. Interestingly, metastatic tumors show frequent gains at 8q and 20q and loss at 18q, suggesting these chromosomal aberrations are linked to the progression of colorectal cancer (Aragane et al., 2001). DNA copy number loss at 18q12.2, involving BRUNOL4 that encodes a splicing factor, is an independent prognostic indicator for colon cancers (Poulogiannis et al., 2010).

Oncogenesis

Mutations in at least one member of the TGFβ signaling are demonstrated in ~50% colorectal cancers, there by confirming the tumor suppressor activity of this pathway in these cancers (Seoane, 2006).

Mutational inactivation of TGFBR2 in microsatellite unstable colon cancer is a frequent event. Further, in vivo experiments also confirmed the role of TGFBR2 inactivation in the establishment and progression of colorectal cancers (Biswas et al., 2004; Biswas et al., 2008).

Stomach cancers

Disease

Gastric cancer is the fourth most common cancer worldwide, with ~988000 cases per year and second among mortality with ~737000 deaths per year.

Prognosis

The 5-year survival rate of gastric cancer is poor. Even in developed countries like USA, the five-year survival is only 24%.

This is due to the lack of early screening strategies.

Cytogenetics

The recurrent chromosomal abnormalities includes gains at 17q, 20q, 1p, 22q, 17p, 16p, 6p, 20p, 7p, 3q and 13q4 while losses at 18q, 3p, 5q and 9p are common (Wu et al., 2002).

In gastric cancers gain of 1q32.3 has a correlation with lymph node status while loss of 18q22.1 was associated with poor survival (Weiss et al., 2004).

Oncogenesis

Frameshift mutations in the 10bp poly(A) repeat of TGFBR2 coding regions is frequent in gastric cancers with microsatellite instability (MSI).

In contrast, gastric adenomas without MSI seldom exhibit TGFBR2 mutations.

This suggest that TGFBR2 is the main target of genomic instability during the development of MSI(+) gastric cancers (Song et al., 2010).

Prostate cancers

Disease

With ~0.9 million incident cases all over the world, prostate cancers are fifth common cancer in the world. Globally it is the sixth leading cause of cancer-related death in men, but it ranks second in the United States.

Prognosis

The survival rates of prostate cancer vary among region to region; overall the 5-year survival rate is >90%.

Cytogenetics

The most common aberrations are losses in chromosomes 5q, 6q, 8p, 10q, 13q, 16q, 17p, and 18q and gains in 7p/q, 8q, 9p, and Xq.

Moreover, a chromosomal rearrangement in 21q is observed in over 50% of prostate cancers (Saramaki and Visakorpi, 2007). Further, recurrent breakpoints at 5q11, 8p11, and 10q22 were observed in prostate cancer cell lines, suggesting the importance of tumor suppressor/oncogenes in these regions (Pan et al., 2001).

Oncogenesis

The in vivo experiments have demonstrated that the conditional loss of TGFBR2 in prostatic stromal cells can trigger prostate cancer initiation, progression, and invasion (Bhowmick et al., 2004). Silencing of TGFBR2 through CpG methylation at site -140 is a common event in prostate cancers (Zhao et al., 2005). However, TGFβ signaling has been shown to induce vicious cycles of prostate cancer bone metastases by inducing parathyroid hormone-related protein (PTHrP) via Gli2 (Kingsley et al., 2007).

Liver cancers

Disease

Liver cancer is the third leading cause of cancer death after lung and stomach cancers. It causes ~754000 deaths per year. The most common sub-type of liver cancer is hepatocellular carcinoma, which accounts for approximately 75% of all primary liver cancers.

Prognosis

The 5-year survival rate of liver cancer is just above 50%. This scenario is mainly due to the delay in diagnosis. Because of this delay, less than 40% of individuals with hepatocellular carcinoma are eligible for surgery and transplant.

Cytogenetics

Studies suggest deletions are frequent at chromosomal arms 1p, 4q, 6q, 8p, 9p, 11q, 12q and 13q, whereas gains are common at 1q, 6p, 8q, 11q and 17q in samples positive for Hepatitis B and C virus (Tornillo et al., 2000).

Oncogenesis

In hepatic cancers, TGFBR2 downregulation is reported to be correlated with larger tumor size, poor differentiation, portal vein invasion, intrahepatic metastasis and shorter recurrence-free survival (Mamiya et al., 2010). Further, in vivo experiments revealed that TGFBR2 loss along with TGF-alpha over expression can cooperate in hepatocarcinogenesis (Baek et al., 2010).

Oral cancers

Disease

With an estimated 263000 cases, cancers of the oral cavity account for 2% of the cancer burden worldwide.

But they are the second most common cancer in males and the fourth most common cancer in females in Melanesia and South-Central Asia, accounting for 7% of the total cancers diagnosed in this region.

The most common type of oral cancer is squamous cell carcinoma, which accounts for more than 90% of the cancers of the oral cavity.

Prognosis

The overall 5-year disease-specific survival rate for patients is approximately 50% throughout the world and is unchanged over past two decades.

Cytogenetics

Recurrent loss of chromosomes 9, 13, 18 and Y are reported in oral cancers whereas the most frequent chromosomal imbalances involves deletions at chromosome arms 3p, 7q, 8p, 11q, 17p.

The chromosomal breakpoints in structural rearrangements frequently involve the centromeric regions of chromosomes 1, 3, 8, 14 and 15 as well as bands 1p22, 11q13 and 19p13 (Jin and Mertens, 1993).

Oncogenesis

TGFBR2 mutations are frequent in oral cancers, kinase domain mutations being common.

The loss of TGFBR2 expression in the tumor is associated with significantly reduced overall survival among oral cancer patients (Sivadas et al., 2013). Further, metastatic oral cancers show significantly lower TGFBR2 expression as compared to primary tumour, indicating its anti-metastatic activity in oral cancers (Paterson et al., 2001).

Pancreatic cancer

Disease

Even though pancreatic cancer is at 13th position, contributing only 2% of cancer incidence, it is at 8tth position in terms of mortality and causes 4% of cancer associated deaths. The most common form is pancreatic ductal adenocarcinoma.

Prognosis

Pancreatic cancer shows an extremely poor prognosis. The 5-year relative survival rate is only 6%.

Cytogenetics

The chromosomal region 18q21 that bears SMAD4 gene is homozygously deleted in 30% to 37% pancreatic ductal adenocarcinomas. Other important alterations involve genomic gains of 3q, 8q, 11q, 17q, and frequent loss of chromosome 17p, 6q, and 8p (Hahn et al., 1996; Griffin et al., 2007).

Oncogenesis

Even though mutations in TGFBR2 occur at lower rate, the downstream molecule SMAD4 mutation rates are as high as 50% in pancreatic cancers (Venkatasubbarao et al., 1998; Cowgill and Muscarella, 2003). This signifies the importance of TGFβ-signaling in preventing pancreatic tumorigenesis.

Cervical cancers

Disease

The high-risk Human papillomavirus types 16, 18, 31 and 45 are the cause of ~90% of the cervical cancer globally.

These cancers are at 7th and 8th position in terms of global cancer incidence and deaths respectively.

Prognosis

There is a better 5-year survival rate for cervical cancers. The 5-year survival rate for the early stages of cervical cancer is ~92% while the overall 5-year survival rate is about 72%.

Cytogenetics

Studies have reported abnormalities of chromosome 1 in up to 95% of cervical cancer samples. The main alterations included are the deletions of chromosome 1 at bands q32, p34, q42, p32, and p22.

Further, abnormality of chromosome 4 occurs in 92% cases (Sreekantaiah et al., 1988, Sherwood et al., 2000).

Oncogenesis

Though TGFBR2 mutations happen at lower rate in cervical cancers (Chen et al., 1999), in vivo experiments provided evidence that estrogen and HPV E7 proteins cooperate to silence TGFBR2 expression during the induction and progression of cervical neoplasms (Diaz-Chavez et al., 2008).

Leukemias

Disease

The haematological neoplasms can be broadly classified into four sub-types: Acute lymphoblastic leukemia (ALL), Chronic lymphocytic leukemia (CLL), Acute myelogenous leukemia (AML) and Chronic myelogenous leukemia (CML).

Prognosis

Prognosis varies from subtype to subtype.

Cytogenetics

The well-known chromosomal aberration in CML is a reciprocal translocation between chromosome 9 and 22 designated as t(9;22)(q34;q11). This translocation generates the oncogenic Bcr-Abl fusion protein. Other important translocations involves t(4;11); t(11;14); and t(1;3).

Oncogenesis

Mutations in TGFBR2 associated with microsatellite instability were observed in 20% of cell lines derived from hematologic malignancies. Though alterations of the microsatellite regions in the TGFBR2 are not common in CML, but TGFBR2 downregulation was evident in CML cells as compared with the hematopoietic cells of normal donors.

Furthermore, decreased TGFBR2 expression was also observed in the other haematological neoplasms (Rooke et al., 1999; Kim and Letterio, 2003).

Ovarian cancers

Disease

Majority of ovarian cancers arise in the epithelial surface of the ovary. They comprise ~2% of global cancer incidence and cancer-associated deaths.

Prognosis

Because more than 60% of ovarian cancers are diagnosed at a later stage, ovarian cancer has a relatively poor 5-year survival rate of ~47%.

Cytogenetics

The deletion of chromosome 3p region carrying TGFBR2 is a frequent event in ovarian cancers (Lounis et al., 1998).

Further, abnormalities of chromosomes 1, 3, 6, and 11 were found in metastatic effusions of ovarian cancer (Ioakim-Liossi et al., 1999).

The breakpoints in regions 1p3 and 11p1 are important early events in ovarian cancers. Particularly, the ovarian cancers with breakpoints at 1p1, 3p1 and 11p1 present poor prognosis (Simon et al., 2000).

Oncogenesis

Kinase domain mutations of TGFBR2 in up to 25% of ovarian cancers are reported.

Added, loss of TGFBR2 expression was found in >40% of samples (Lynch et al., 2004).

Epigenetic silencing of TGFBR2 through promoter methylation could be the reason for the loss of TGFBR2 expression, which is a common event in ovarian cancers (Matsumura et al., 2011).

Renal carcinomas

Disease

Kidney cancers are generally originated in the lining of the proximal convoluted tubule. Renal cell carcinoma (RCC) is the most common type of kidney cancer, causing for 80% of cases.

Prognosis

Even though the five year survival rate among stage I patients is around 90%, while the 5-year survival rate is less than 10% for patients presenting with stage IV disease.

Cytogenetics

The deletion of the chromosome 3p region is the hallmark of nonpapillary/clear cell RCC (Siebert et al. 1998).

Oncogenesis

The downregulation of TGFBR3 and TGFBR2 are the important events during renal carcinogenesis and acquisition of metastatic phenotype respectively (Copland et al., 2003). The reason for the loss of TGFBR2 expression could be due to promoter hypermethylation (Zhang et al., 2005).

Glioblastoma multiforme

Disease

Glioblastoma is the most aggressive malignant primary brain tumor in humans, involving glial cells and account for more than 50% of all brain tumor cases.

Prognosis

The survival rates are very poor, most of the patients die within a period of 1-2 years.

Cytogenetics

Loss of heterozygosity (LOH) at 10q involving PTEN is the most common genetic alteration shown by both primary as well as secondary glioblastomas (Ohgaki et al., 2004).

Oncogenesis

p53 mutations are the most common event in glioblastomas. More than 30% of the primary and 65% of the secondary glioblastomas show p53 mutations (Ohgaki et al., 2004). Mutations in the 10 bp poly(A) tract of TGFBR2 are very common (71%) in gliomas with genomic instability. However, TGFBR2 mutation rates are less (3%) in microsatellite stable gliomas (Izumoto et al., 1997).

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