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Gene Section
Review

TWIST1 (twist homolog 1 (Drosophila))

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Identity

Other names: ACS3; BPES2; BPES3; H-twist; SCS; TWIST; bHLHa38

HGNC (Hugo): TWIST1

Location: 7p21.1

DNA/RNA

Description

This gene can be found on chromosome 7 at location 7p21.2, position 19,121,616-19,123,820 reverse strand.

Transcription

The DNA sequence contains 2 exons and the transcript length is 1,669 bp translated to a 202 residues protein.

Protein

Description

The 20.9 kDa protein encoded by TWIST1 gene is a highly conserved transcription factor that belongs to the family of basic helix-loop-helix (bHLH) proteins. In vertebrates, it is involved in embryonic development through the regulation of epithelial-mesenchymal transitions (EMT) during neural crest migration, also it regulates mesoderm determination, myogenesis, and morphogenesis (Hebrok et al., 1994; Chen et al., 1995). Additionally, TWIST1 is involved in the negative regulation of cellular determination and in the differentiation of several lineages including myogenesis, osteogenesis (Bialek et al., 2004), and neurogenesis (Soo et al., 2002). Inhibits myogenesis by sequestrating E proteins, avoiding trans-activation by MEF2, and inhibiting DNA-binding by MYOD1 through physical interaction. Also represses expression of proinflammatory cytokines such as TNFA and IL1B (Barnes et al., 2009).

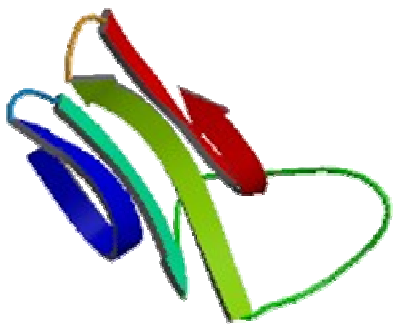
Mutations in this gene have been found in patients with Saethre-Chotzen syndrome (Howard et al., 1997).

TWIST1 has been suggested to be oncogenic, contributing to metastasis through its involvement in EMT regulation (Yang et al., 2004). In addition, TWIST1 is overexpressed in multiple tumor types, and it is usually associated with poor prognosis.

In mammals, there are two Twist-like proteins, TWIST1 and TWIST2 that share high structural homology (Li et al., 1995; Wolf et al., 1991). It is thought that during osteoblast development TWIST2 or Dermo1 may inhibit osteoblast maturation and maintain cells in a preosteoblast phenotype [provided by RefSeq]. Interestingly, TWIST2 has a pro-oncogenic role in human cancer (Ansieau et al., 2008).

Structure

TWIST1 protein contains a helix-loop-helix DNA-binding domain. Efficient DNA binding requires dimerization with another bHLH protein.



(Mod Base provided)

Expression

The strongest expression of the mRNA is in placental tissue. In adults, mesoderm-derived tissues express TWIST1 mRNA preferentially.

Localisation

Nucleus.

Function

Role in embryonic development

The Twist gene was originally identified as being required for mesoderm induction in Drosophila (Thisse et al., 1987; Leptin et al., 1990) which expression is induced by an interleukin-1-like TOLL receptor through nuclear factor kappaB activation (Furlong et al., 2001).

In vertebrates, Twist is predominantly expressed in neural crest cell where is essential for correct patterning of the neural tube (Chen and Behringer, 1995; Soo et al., 2002). However, the nuclear factor kappaB pathway is not involved in mesoderm formation or neural crest development in vertebrates. Instead, BMP-, Wnt-, and fibroblast growth factor-activated pathways are known to modulate vertebrate neural crest development (Meulemans et al., 2004).

During mesoderm formation in Drosophila, Twist induces the expression of the transcription factor Snail to allow invagination and mesoderm differentiation (Leptin and Grunewald, 1990). During neural crest development in vertebrates, expression of Snail and Slug occurs at the neural plate border where Twist is also expressed, and all three transcription factors play critical roles in neural crest formation (Meulemans and Bronner-Fraser, 2004).

Additional evidence supports the key role of Twist in development, since Twist mutation in mice causes failure in cranial neural tube closure, indicating its role in proper migration and differentiation of neural crest and head mesenchymal cells (Chen and Behringer, 1995; Soo et al., 2002).

Role in myogenesis

TWIST1 functionally inhibits muscle development by sequestrating E proteins from forming functional myogenic complexes with the skeletal muscle specific bHLH factor, MyoD. The mechanism of action is through the block of both cis- and trans- MyoD elements, and inhibiting transactivation of Mef2 (Barnes and Firulli, 2009).

Role in EMT

EMT is a process whereby epithelial cell layers lose polarity and cell-cell contacts and undergo a dramatic remodelling of the cytoskeleton. EMT is essential for the morphogenic movements underlying gastrulation and the subsequent formation of various tissues and organs such as the neural crest, heart, musculoskeletal system, craniofacial structures, and peripheral nervous system, and is also implicated in tissue repair in the adult.

TWIST1 induces EMT through repression of E-cadherin (Yang et al., 2004). Cells undergoing EMT acquire expression of mesenchymal components and manifest a migratory phenotype. TWIST1 triggers the acquisition of invasive properties through induction of pro-migratory molecules, such as the cell adhesion protein N-cadherin (Alexander et al., 2006) and RhoC, as consequence of inducing the microRNA molecule miR-10b (Ma et al., 2007).

Role in control of apoptosis

Twist, as a basic helix-loop-helix transcription factor, may activate or suppress diverse downstream targets, including apoptosis genes. Two studies reported that the expression of Twist could inhibit Myc-induced apoptosis in mouse embryo fibroblasts (Maestro et al., 1999) and neuroblastoma cells (Valsesia-Wittmann et al., 2004). This transcriptional control is relevant during EMT, since Twist may need to activate antiapoptotic programs in order to allow epithelial cells to convert to a mesenchymal fate while avoiding cell death due to loss of cell-cell adhesions by epithelial cells.

Role in cancer

TWIST1 has a key role during cancer development and progression in multiple tumour types. There are four main different malignant processes where this transcription factor is involved: EMT (Vernon et al., 2004), resistance to apoptosis by cytotoxic drugs (Wang et al., 2004) and pro-survival signalling (Puisieux et al., 2006) and hypoxia (Yang et al., 2008).

Mutations

Note

Germline mutations in the coding region of TWIST1 gene in humans cause Saethre-Chotzen syndrome (SCS), an autosomal-dominant hereditary disorder characterized by limb abnormalities, facial dysmorphisms, and premature fusion of cranial sutures (Howard et al., 1997). This disease is also known as acrocephalosyndactyly type 3 (ACS3).

A frameshift mutation in TWIST1 that produce defects of this protein is the cause of Robinow-Sorauf syndrome (RSS); also known as craniosynostosis-bifid hallux syndrome. RSS is an autosomal dominant defect characterized by minor skull and limb anomalies which is very similar to Saethre-Chotzen syndrome (Kunz et al., 1999).

Missense mutations in the TWIST1 have been found in a significant number of patients of craniosynostosis type 1 (CRS1). Craniosynostosis consists of premature fusion of one or more cranial sutures, resulting in an abnormal head shape (Seto et al., 2007).

Implicated in

Breast cancer

Oncogenesis

In human breast cancer, TWIST1 is overexpressed at protein and mRNA levels (Watanabe et al., 2004; Yang et al., 2004; Martin et al., 2005). This upregulation has been usually associated with malignant features of the tumour: invasive lobular carcinoma, a highly infiltrating tumor type (Yang et al., 2004; Vesuna et al., 2008); the increasing nodal involvement (tumor-node-metastasis status); and the poor prognosis of the patients (Martin et al., 2005). TWIST1 overexpression, as a marker of EMT, has been also associated with the metastasis process. Circulating tumour cells of metastactic breast cancer patients showed an increased in EMT and tumor stem markers, included TWIST1 (Aktas et al., 2009); In addition, micrometastatic cells detected in the bone marrow which have prognostic significance in breast cancer displayed a specific expression of TWIST1 (Watson et al., 2007).

There are a wide number a molecular mechanisms described to explain the oncogenic role of TWIST1 in breast cancer progression. One of the most common is through the inhibition of expression of the epithelial marker E-cadherin (Yang et al., 2004; Vesuna et al., 2008). Recently, it has been reported that the microRNA, miR10b, is transcriptionally regulated by TWIST further leading to the activation of the pro-metastasic gene product RHOC promoting tumor invasion and migration in breast cancer (Ma et al., 2007). TWIST1 prosurvival and proinvasive functions are also mediated by the transcriptional up-regulation of AKT2 (Cheng et al., 2007). Moreover, there is a correlation between Wnt signalling and TWIST1 (Howe et al., 2003), which were included in a poor prognosis gene signature during metastasis to lung (DiMeo et al., 2009). In addition, TWIST1 is able to increased vascular endothelial growth factor (VEGF) synthesis in MCF7 cells inducing angiogenesis and chromosomal instability (Mironchik et al., 2005; Vesuna et al., 2006).

TWIST1 expression is also associated with multidrug resistance since its depletion completely blocked the mesenchymal transformation, partially reversed multidrug resistant and greatly abolished invasion induced by Adriamycin treatment in MCF7 cells (Li et al., 2009). Moreover, TWIST1 specific expression is found in therapy resistant cell populations (Watson et al., 2007; Aktas et al., 2009). Thus, therapy based on interference of TWIST1 might be a successful strategy for chemotherapy resistant breast tumours.

Interestingly, an increase of the grade of methylation at TWIST1 promoter has been shown in breast tumours where this feature was correlated with malignant phenotypes (Fackler et al., 2003; Mehrotra et al., 2004). Despite of these findings are opposite to the oncogene behaviour of TWIST1 gene that had been addressed by other authors, no correlation has been found between TWIST1 promoter methylation and TWIST1 protein or RNA expression (Gort et al., 2008).

Rhabdomyosarcomas

Oncogenesis

High protein levels of TWIST1 have been observed in 50% of rhabdomyosarcomas. TWIST1 might play multiple roles in the formation of rhabdomyosarcomas, halting terminal differentiation, inhibiting apoptosis, and interfering with the p53 tumor-suppressor pathway (Maestro et al., 1999). Villavicencio and collaborators suggest that TWIST1 could have such oncogenic role at least in part through the activation of GLI1 which is a critical transcription factor of sonic hedgehog signalling able to prevent the exit of the cell cycle and trapping cells in proliferating myoblast pool (Villavicencio et al., 2002).

Gastric carcinomas

Oncogenesis

TWIST1 mRNA and protein up-regulation is found with different incidences in both Laurén's classification for gastric carcinomas, with an increase of 40-60% in diffuse type and 25% in intestinal type (Rosivatz et al., 2002; Yan-Qi et al., 2007).

Furthermore, TWIST1 expression is correlated with lymph node metastasis, suggesting an association with the neoplastic transformation and subsequent development of gastric cancer (Yan-Qi et al., 2007).

In diffuse type gastric carcinomas overexpression of TWIST1 is significantly associated with the increased of expression of N-cadherin (Rosivatz et al., 2002).

This bHLH transcription factor is able to regulate the expression of several genes involved in the differentiation, adhesion, migration, invasion and proliferation of several gastric cancer cells (Feng et al., 2009). One of the most important pathways altered in this cancer cell lines is the Wnt/Tcf-4 signalling (Luo et al., 2008).

Neuroblastomas

Oncogenesis

TWIST1 is overexpressed in N-Myc-amplified neuroblastoma tumors and cell lines. This oncogenic cooperation of two key regulators of embryogenesis causes cell transformation and malignant outgrowth. While N-Myc induces cell proliferation, TWIST1 inhibits the ARF/p53 pathway involved in the Myc-dependent apoptotic response (Valsesia-Wittmann et al., 2004).

Gliomas

Oncogenesis

TWIST1 expression in human gliomas is increased comparing with normal brain at mRNA and protein levels. The mRNA levels are associated with the highest grade gliomas, and increased TWIST1 expression accompanies transition from low to high

grade in vivo, suggesting a role in promoting malignant progression in gliomas (Elias et al., 2005).

Oesophageal squamous cell carcinoma

Oncogenesis

Upregulation of TWIST1 has been found in oesophageal squamous cell carcinoma (SCC), and this high level of TWIST1 was significantly associated with a greater risk for developing distant metastasis within 1 year of oesophagectomy (Yuen et al., 2007). TWIST1 has been proposed as a prognostic marker for predicting the development of distant metastasis in oesophageal SCC (Yuen et al., 2007).

The ectopic expression of TWIST1 drives to the suppression of TIMP1, a specific inhibitor of matrix metalloproteinases, promoting tumour invasion the human epithelial-like osteosarcoma cell line Saos-2 (Okamura et al., 2009).

Pancreatic cancer

Oncogenesis

Decreased or only weak expression of TWIST1 is observed in malignant pancreatic epithelium (Hotz et al., 2007; Cates et al., 2009). However, the different expression levels of TWIST1 in pancreatic juice may be useful to differentiate pancreatic cancer from nonmalignant neoplasms, since Twist expression differed significantly between cancer and intraductal papillary mucinous neoplasm bulk tissues (Ohuchida et al., 2007). Additionally, TWIST1 could be also used as a diagnostic marker in chronic pancreatitis because decreased expression is also seen (Cates et al., 2009).

Despite of the weak expression in pancreatic cancer, it has been demonstrated that TWIST1 is activated after exposure to hypoxia in several pancreatic cancer cell lines, suggesting an important role in the invasive behavior of pancreatic tumors (Hotz et al., 2007). Several signaling molecules have been reported to be able to activate TWIST1 resulting in EMT during tumour progression in this tumour type: Axl receptor tyrosine kinase (Koorstra et al., 2009); MSX2 (Satoh et al., 2008) and VEGFR-1 (Yang et al., 2006).

Melanoma

Oncogenesis

Increased TWIST1 expression and altered expression of additional transcriptional regulators implicated in embryonic development and epidermal/mesenchymal transition has been reported in melanoma cells lines and tissues. Overexpression of TWIST1 in these tumours is associated with worse outcome suggesting its use in assessing prognosis, staging, and therapy of melanoma patients (Hoek et al., 2004).

The induction of expression of TWIST1 through MFG-E8 secreted protein from tumor microenviroment has been suggested as one of the mechanisms of regulation of this bHLH transcription factor to promote progression of the disease (Jinushi et al., 2008).

Prostate cancer

Oncogenesis

TWIST1 is highly expressed in the majority of prostate cancer tissues. Its expression levels are positively correlated with high-grade prostatic cancer and metastasis (Kwok et al., 2005; Yuen et al., 2007). Furthermore, TWIST1 is able to specifically promote metastasis to bone regulating the expression of DKK-1 via RUNX2 (Wang et al., 2006). Over-expression of TWIST results in down-regulation of p14 (ARF), which leads to the impairment of DNA damage checkpoint in response to genotoxic stress. This negative effect of TWIST on DNA damage response facilitates uncontrolled cell proliferation with genomic instability and tumorigenesis in non-malignant immortalized human prostate epithelial cell lines (Kwok et al., 2007).

TWIST1 expression has also been associated with chemotherapy and castration resistance prostate tumours through different mechanisms such as the downregulation of Y-box binding protein-1 and androgen receptor signaling respectively (Kwok et al., 2005; Shiota et al., 2009a; 2009b).

Hepatocellular carcinoma (HCC)

Oncogenesis

TWIST1 mRNA and protein are both increased in HCC as compared to non-cancerous tissues. In addition, patients with high Twist expression have poor prognosis (Lee et al., 2006; Niu et al., 2007). These upregulated levels are associated with invasion and migration as a consequence of EMT induction and also with angiogenesis process (Niu et al., 2007; Matsuo et al., 2009).

Epithelial ovarian carcinoma

Oncogenesis

Positive TWIST1 expression predicts a poorer overall and progression free survival in patients with epithelial ovarian carcinoma (Kajiyama et al., 2006; Hosono et al., 2007). The role of TWIST1 in tumour progression has been suggested to be associated with EMT and also with chronic paclitaxel-resistance (Kajiyama et al., 2007; Yoshida et al., 2009). There is also a significant incidence of promoter hypermethylation of TWIST1 gene promoter that could be important in early clinical diagnosis and in chemotherapeutic management and treatment of the disease (Dhillon et al., 2004).

Endometrial cancer

Oncogenesis

TWIST1 is an independent predictor of patient survival in endometrial cancer and is correlated with E-cadherin silencing (Kyo et al., 2006). Furthermore, ionizing irradiation leads to the increased expression of

TWIST1 in the HEC1A endometrial carcinoma cell line promoting cell invasion, suggesting a crucial role in the enhanced invasion after irradiation (Tsukamoto et al., 2007).

Bladder cancer

Oncogenesis

In bladder cancer, TWIST1 overexpression is correlated with advanced-stage, high-grade tumours, metastatic lesions, negative expression of E-cadherin and positive expression of N-cadherin (Zhang et al., 2007). More importantly, TWIST1 high expression levels are associated with smoking status of the patients and with worse clinical outcome (Fondrevelle et al., 2009).

Cervical cancer

Oncogenesis

Positive TWIST1 expression significantly predicted poorer prognosis in patients with cervical cancer (Shibata et al., 2008). Additionally, the tumour suppressor genes SFRP1 and SFRP2 decrease the invasion abilities of cervical cancer cells through the inhibition of the expression of SLUG, TWIST1 and SNAIL (Chung et al., 2009). However, the promoter methylation status of TWIST1 in combination with RAR-beta and MGMT have also been proposed as markers to distinguish between squamous cell carcinomas and negative squamous intraepithelial lesions from liquid based cytology specimens (Kim et al., 2009).

Head and Neck cancer

Oncogenesis

TWIST1 malignant effect is dependent on different molecules like HIF-1, Fascin, EBV and AKT (Horikawa et al., 2007; Yang et al., 2008; Chen et al., 2009; Hong et al., 2009). Upregulation of TWIST1 in nasopharyngeal carcinoma cells has been associated with resistance to microtubule disrupting agents, especially taxol (Zhang et al., 2007). TWIST1 increased levels are associated with malignant parameters such as lymph node invasion and distant metastasis, and the poor prognosis of nasopharyngeal carcinoma patients (Song et al., 2006).

Colorectal cancer

Oncogenesis

TWIST1 mRNA is upregulated in colorectal cancer patients. High levels of expression are associated with lymph node metastasis suggesting the relevance of TWIST1 in the outcome of the patients (Valdés-Mora et al., 2009). Interestingly, such increased levels are significantly associated with male gender revealing a plausible regulation through sexual hormones (Valdés-Mora et al., 2009).

Lung cancer

Oncogenesis

Overexpression of TWIST1 is associated with poor survival of non-small cell lung cancer (NSCLC) patients (Hung et al., 2009). Again, TWIST1 is an important player in chemotherapy resistance in A549 cell raising the possibility of TWIST1 depletion as a promising approach to lung cancer therapy (Zhuo et al., 2008). Promoter hypermethylation of this gene has been also proposed as a marker of lung adenocarcinoma (Tsou et al., 2007).

Pheochromocytomas

Oncogenesis

TWIST1 expression is found in malignant phechromocytomas and correlates with other EMT markers consolidating the relevant role of EMT in the malignant progression of this tumour type (Waldmann et al., 2008).

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