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Gene Section
Review

SNAI1 (snail homolog 1 (Drosophila))

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Identity

Other names: SLUGH2, SNA, SNAH, dJ710H13.1

HGNC (Hugo): SNAI1

Location: 20q13.13

DNA/RNA

Note

Human Snail homolog 1 (SNAI1, SLUGH2, SNA, SNAH, dJ710H13.1), homolog of the Drosophila gene sna, is localized on 20q13.13 (Paznekas et al., 1999; Twigg and Wilkie, 1999). Both publications describe a SNAI1-related pseudogene SNAI1P mapped to chromosome 2q33-37.

Description

SNAI1 has 3 exons (1: 143 bp, 2: 528 bp and 3: 1015 bp size) separated by intron 1-2 (682 bp) and intron 2-3 (3520 bp); spanning an approximately 6 kb region. A CpG island has been described upstream of the coding sequence.

Two silent single nucleotide polymorphisms, a T/C transition at position 783 and a G/A transition at position 1035, have been described (Twigg and Wilkie, 1999).

Transcription

A single transcript of 1686 bp size gives rise to a protein of 264 aa and approximately 29.1 kDa.

Pseudogene

SNAI1P.

Protein

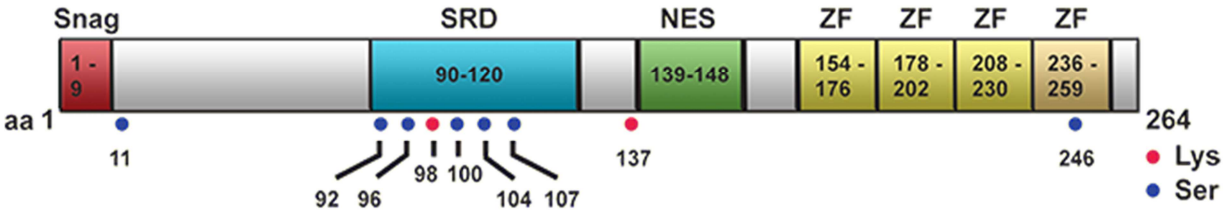
Note

Charge 13.0, isoelectric point 8.7563, molecular weight 29082.97 Da (source: Uswest.Ensembl).

Description

The N-terminal portion (aa 1-150) of the Snail protein contains a SNAG (SNAI1/GFI) domain (aa 1-9) which includes the consensus sequence PRSFLV found in all Snail family members. This motif is highly conserved among species and also found in several other transcription factors where it is associated with repressive functions. A serine-rich domain (SRD: aa 90-120) and a nuclear export sequence (NES: aa 139-148) are involved in the regulation of Snail protein stability and subcellular localization, respectively.

The C-terminal portion (aa 151-264) contains 3 typical (154-176, 178-202, 208-230) and one atypical (236-259) C2H2-type zinc finger (ZF) domains.



Snail protein structure.

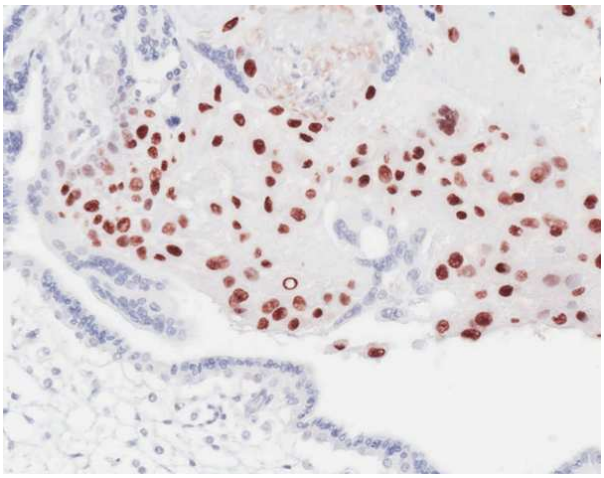
Expression

Nucleus.

Localisation

The human SNAI1 transcript has been detected in placenta, adult heart and lung. Lower levels were reported for adult brain, liver and skeletal muscle (Paznekas et al., 1999). Several human fetal tissues were reported to express the SNAI1 transcript, with the highest levels detected in kidney (Twigg and Wilkie, 1999).

Reliable high protein expression is present in the extravillous trophoblast of the human placenta which can be utilized as positive control (Rosivatz et al., 2006).



Snail protein expression in 1st trimester human placenta. Method and Antibody: Schwock et al., 2010.

Function

Snail protein (SNAI1) is part of a superfamily of transcription factors composed of the SNAI and the SCRATCH family (Nieto, 2002; Barrallo-Gimeno and Nieto, 2009). The SNAI family contains two more members: Slug (SNAI2 (Cohen et al., 1998)) and Smuc (SNAI3 (Katoh, 2003)) on chromosomes 8 and 16, respectively.

The Snail gene in Drosophila (sna), first identified during analysis of dorso-ventral patterning, is a zinc finger gene with repressor function required for mesoderm formation (Boulay et al., 1987; Leptin, 1991). Isolation of other Snail homologues in different species including the human indicated a high degree of conservation in coding sequence and predicted protein pointing towards a conserved role in early morphogenesis (Paznekas et al., 1999).

Snail protein functions as E-cadherin repressor and is essential during early developmental stages (Cano et al., 2000; LaBonne and Bronner-Fraser, 2000). Snail is re-expressed during adult life in tissue repair as well as in neoplasia, and, in the latter, thought to contribute to the acquisition of a metastatic potential in tumor cells (Batlle et al., 2000). The process by which Snail confers increased motility in individual cells is characterized by a down-regulation of epithelial (cell-cell adhesion, apical-basal polarity) and up-regulation of mesenchymal (cell-extracellular matrix interaction, front-back polarity) features associated with respective changes in molecular composition of the cell which include (among others) cell adhesion molecules and intermediate filaments. This process, termed epithelial-mesenchymal transition (EMT) (Hay, 1989; Thiery, 2002; Peinado et al., 2007), has been classified into 3 types: type 1 in the context of developmental processes, type 2 in inflammation, tissue repair and fibrosis, and type 3 in tumor invasion and metastasis (Kalluri and Weinberg, 2009).

To exert its function as repressor, Snail nuclear import is mediated by importins which recognize a nuclear localization signal that consists of basic residues situated in the zinc finger region (Mingot et al., 2009). Inside the nucleus Snail is required to form ternary complexes with co-repressors via the Snag domain. Different ternary complexes have been described which consist of Ajuba as mediator for the interaction with PRC2 (Herranz et al., 2008), 14-3-3 and PRMT5 (Hou et al., 2010), Sin3A for the interaction with HDAC1/HDAC2 (Peinado et al., 2004), and LSD1 for the interaction with CoREST (Lin et al., 2010). Binding to DNA occurs via E-box elements (5'-CACCTG-3') found in the promoter region of different genes including the E-cadherin gene CDH1 (Batlle et al., 2000; Cano et al., 2000).

The regulation of Snail activity mainly involves the central part of the protein which contains most sites for post-translational modification: serine phosphorylation sites (Ser92, 96, 100, 104, 107) in the SRD as well as two lysine oxidation sites (Lys98 and 137), and the NES for Crm1-dependent nuclear export. Two additional serine phosphorylation sites are found N-terminal at Ser11 and C-terminal at Ser246. Phosphorylation of Ser 96, 100, 104 and 107 by GSK3beta is associated with nuclear export, ubiquitination by beta-TrCP1 or FBXL14 and proteasomal degradation (Dominguez et al., 2003; Zhou et al., 2004; Vinas-Castells et al., 2010). Snail is positively regulated by phosphorylation of Ser11, 92 and 246 and its protein stability is increased by interaction with SCP, PKA, CK2, PAK1 and LOXL2 (Peinado et al., 2005; Yang et al., 2005; Wu et al., 2009; MacPherson et al., 2010).

Limited information is available on the factors directly controlling the SNAI1 promoter. Snail up-regulation in cells has been reported as a result of diverse stimuli including cytokines (Interleukin-6), growth factors (TGFbeta, FGF, PDGF, EGF) and activation of their corresponding receptor tyrosine kinases as well as activation of developmental signaling pathways such as Wnt and Hedgehog. Notably, TGFbeta has been described as important EMT trigger leading to HMGA2 and Smad binding at the SNAI1 promoter (Thuault et al., 2008). Another example is Snail expression stimulated by HGF via the MAPK pathway and Egr-1

which also includes a negative feedback mechanism due to Snail binding at the Egr-1 promoter (Grotegut et al., 2006). Also, a conserved 3' enhancer element has been described which interacts with the SNAI1 promoter (Palmer et al., 2007). Furthermore, Snail has been found to control its own expression by binding to an E-box in its own promoter (Peiro et al., 2006). A more detailed overview over the complex signaling pathways regulating Snail expression is given in several recent review publications (Peinado et al., 2007; De Herreros et al., 2010).

Consequences of Snail up-regulation not only include the repression of E-cadherin transcription, but the negative as well as positive control of a series of genes involved in a range of biological functions such as cell-cell adhesion, cell-extracellular matrix interaction, cell polarity, cytoskeleton, cell cycle, survival, and angiogenesis leading to a phenotypic shift towards more mesenchymal cellular characteristics (De Craene et al., 2005; Higashikawa et al., 2008). In the context of tumor-associated EMT these mesenchymal-like characteristics have been correlated with a greater resistance to different therapeutic modalities (Kajita et al., 2004; Kurrey et al., 2009), escape from attack by the immune system (Kudo-Saito et al., 2009), and adoption of a cancer stem cell phenotype (Mani et al., 2008; Morel et al., 2008).

The importance and the exact biological implications of Snail expression in human tumors remain a focus of current research (Schwock et al., 2010). Some of the challenges in this area may be due to the transient and dynamic nature of tumor-associated EMT. Also, it has been proposed that Snail is required as initial trigger in EMT, whereas maintenance of the phenotype is taken over by other factors potentially leaving behind a mesenchymal cell devoid of Snail expression (Peinado et al., 2007). Another intriguing recent observation is the presence of Snail in tumor-associated stroma and its impact on tumor prognosis (Franci et al., 2009).

Homology

Human Snail protein is 97.3, 87.2, 87.5, 57.3 and 58.4 identical to SNAI1 in chimpanzee (Pan troglodytes), SNAI1 in dog (Canis lupus familiaris), Snai1 in mouse (Mus musculus), snai1a and snai1b in zebrafish (Danio rerio), respectively.

Implicated in

Various cancers

Note

Involvement of Snail as a major factor in craniosynostosis was excluded (Paznekas et al., 1999; Twigg and Wilkie, 1999). Expression of SNAI1 at the transcript level has been detected in benign conditions such as tissue fibrosis (Sato et al., 2003; Yanez-Mo et al., 2003; Jayachandran et al., 2009), a range of malignant neoplasms (Cheng et al., 2001; Rosivatz et al., 2002; Takeno et al., 2004), and in normal tissue adjacent to tumor (Pena et al., 2009). Early studies based on detection of the SNAI1 transcript found associations with lymph node metastasis (Cheng et al., 2001; Blanco et al., 2002) and malignant effusion (Elloul et al., 2005) in breast cancer. A mouse model reported by Moody et al. (2005) implicated Snail expression with mammary cancer recurrence. Other studies described associations between elevated SNAI1 transcript levels and hypoxia in ovarian cancer (Imai et al., 2003), downregulation of Vitamin D Receptor in colon cancer (Palmer et al., 2004; Pena et al., 2005), invasion and distant metastasis in oesophageal squamous cell carcinoma (Takeno et al., 2004), invasiveness (Sugimachi et al., 2003) and poor prognosis (Miyoshi et al., 2005) in hepatocellular carcinoma, and spindle cell phenotype in synovial sarcoma (Saito et al., 2004). However, it has been pointed out that transcript levels may not correlate well with Snail protein which is tightly regulated and subject to a short half-life previously reported as approximately 25 minutes (Zhou et al., 2004). Also, transcript levels may be confounded by Snail expression in the stromal tumor component if no micro-dissection is performed (Peinado et al., 2007). Immunohistochemical detection of Snail has been documented for a range of cancers including the upper gastrointestinal tract (Rosivatz et al., 2006; Natsugoe et al., 2007; Usami et al., 2008; Kim et al., 2009), head and neck (Yang et al., 2007; Peinado et al., 2008; Yang et al., 2008; Zidar et al., 2008; Schwock et al., 2010), colorectum (Roy et al., 2005; Franci et al., 2009), neuroendocrine tumors of the ileum (Fendrich et al., 2007), uterine cervix (Franci et al., 2006), endometrium (Blechschmidt et al., 2007), ovary (Blechschmidt et al., 2008; Jin et al., 2009; Tuhkanen et al., 2009), prostate (Heeboll et al., 2009), breast (Zhou et al., 2004), bladder (Bruyere et al., 2009), adrenal gland (Waldmann et al., 2008), thyroid gland (Hardy et al., 2007), parathyroid gland (Fendrich et al., 2009) as well as pheochromocytoma (Waldmann et al., 2009) and sarcomas (Franci et al., 2006). Differences in immunoreactivity seem to depend on the individual tumor entity examined as well as technical issues (Schwock et al., 2010).

Neoplasms of the gastro-intestinal tract

Note

Rosivatz et al. (2006) examined Snail expression in adenocarcinomas of the upper gastrointestinal tract. 7.9% (27/340) of their cases were reported with positive staining for Snail. There was no correlation between Snail and E-cadherin expression or Snail and clinicopathological parameters. Natsugoe et al. (2007) examined 194 cases with oesophageal squamous cell carcinoma. 61.7% (84/194) were reported with positive staining. Snail expression was associated with deep invasion, increased lymph node metastasis, and advanced stage. No correlation was found between Snail and E-cadherin expression. Usami et al. (2008) reported a cohort of 72 cases of oesophageal squamous

cell carcinoma for which 38% (27/72) were considered positive. Elevated Snail expression was found at the invasion front, and was associated with lymphatic and venous vessel invasion, lymph node metastasis and tumor stage. Furthermore, a recent study by Kim et al. (2009) reported Snail positivity in 42.9% (245/571) of gastric carcinomas where it was associated with invasion and lymph node metastasis. Snail staining was an independent indicator of prognosis by multivariate analysis in this study. Fendrich et al., 2007 examined Snail expression in neuroendocrine tumors of the ileum. 59% (22/37) of the primary tumors and 6 of 7 liver metastases were reported with immunoreactivity for Snail. 53% (16/30) of the neuroendocrine tumors displayed positivity for Snail as well as Sonic Hedgehog. Roy et al. (2005) found a proportion of 78% (46/59) cases with positive staining in their study on colorectal cancers as well as a trend towards increased presence of Snail in tumors with distant metastasis. A more recent study on colorectal cancer by Franci et al. (2009) reported a similarly high proportion of 79% (128/162) of cases with Snail immunoreactivity. Interestingly, in this study a correlation between stromal Snail expression and decreased survival was found.

Neoplasms of the head and neck

Note

Yang et al. (2007) reported a proportion of 37.4% (n=147) of primary head and neck squamous cell carcinomas with positive immunoreactivity for Snail. Snail expression was associated with lymph node metastasis, and co-expression with Nijmegen breakage syndrome 1 (NBS1) indicated short metastasis-free period and overall survival. Another study by Yang et al. (2008) reported a positive correlation between Snail and reduced metastasis-free and overall survival. Peinado et al. (2008) examined a large cohort of laryngeal squamous cell carcinomas for which 16% (40/251) were reported Snail positive including 3% (8/251) high-positive. They found a correlation between Snail and LOXL2 expression, but no association between Snail and disease-free or overall survival. Zidar et al. (2008) reported their findings on two cohorts of head and neck squamous cell carcinomas specifically distinguishing between spindle cell carcinomas and those of moderately differentiated phenotype. 19/30 of the spindle cell, but only 4/30 cases in the moderately differentiated group were found to display positive immunoreactivity. There was no correlation between Snail and E-cadherin expression. Schwock et al. (2010) examined a cohort of 46 cases of oral squamous cell carcinoma including corresponding metastases. Nuclear Snail-positivity equal or in excess of a 5% threshold was observed in 10 tumors and 5 metastases which corresponded to 12 cases. Individual Snail-positive tumor cells below this threshold, however, were present more frequently and found in primary tumors of 30 patients. Snail expression in tumor cells in excess of 10% was rare, but associated with poor outcome by univariate analysis.

Neoplasms of the genitourinary tract

Note

87 primary endometrioid-type adenocarcinomas of the endometrium and 26 unrelated metastases were examined in a study by Blechschmidt et al. (2007). Among the primary tumors and the metastases a proportion of 28.7% and 53.8% were reported with positive Snail staining, respectively. Snail immunoreactivity in metastases was found to correlate with higher grade and reduced E-cadherin expression. A subsequent study by Blechschmidt et al. (2008) on 48 primary ovarian neoplasms and 50 metastases found Snail immunoreactivity in 37.5% and 52%, respectively. A borderline significant difference in overall survival with Snail expression in metastases was noted. There was no correlation between Snail and E-cadherin expression in this study. A similar study by Jin et al. (2009) examined 41 serous adenocarcinomas of the ovary with 14 matched metastases, 12 serous borderline tumors, 5 cystadenomas and 4 normal ovarian controls. There was a range of Snail immunoreactivity with increased nuclear positivity noted in the carcinoma group. Tuhkanen et al. (2009) compared 74 ovarian carcinomas with 24 borderline tumors, 21 benign ovarian neoplasms and 14 normal controls. Increased nuclear staining was noted with increasing malignancy both in the epithelial as well as the stromal compartment. 23% (17/74) of the ovarian carcinomas were reported to show focal Snail positivity. No association with clinicopathological factors was seen in this study. Heeboll et al., 2009 examined Snail in 327 prostate cancer specimens, 15 specimens with high-grade prostatic intraepithelial neoplasia (PIN), 30 specimens from patients with benign prostatic hyperplasia and 30 benign prostate tissue controls. Approximately 50% of the prostate cancers were found to have high Snail immunoreactivity compared to only 7% of the high-grade PIN specimens. Snail expression in this study was associated with Gleason score, but not with progression or prognosis. Bruyere et al., 2009 studied Snail expression in transitional cell carcinoma of the bladder using a microarray of 87 cases. Strong Snail positivity was found in 43.7% and weak positivity in the remainder of the cases. Snail immunoreactivity in this study was prognostic for tumor recurrence by uni- and multivariate analysis.

Breast cancer

Note

Zhou et al. (2004) reported a study on Snail expression in breast cancer which found positive staining in 56% (72/129) of their cases; 17 with low and 55 with high Snail immunoreactivity. Snail correlated with GSK-3beta inhibition and E-cadherin downregulation, and clinically with metastasis in this study.

Endocrine neoplasms

Note

Waldmann et al. (2008) reported their findings with Snail expression in adrenocortical carcinomas obtained in a study including 26 primary tumors as well as two lymph node and one liver metastases. 65% (17/26) primary tumors showed staining for Snail with strong positivity found at the invasion front of 7 tumors and in 2 of 3 metastases. Snail positivity was associated with advanced stage, decreased survival and higher risk for distant metastases. The same group reported a study on Snail in pheochromocytomas including 44 primary tumors, 3 lymph node and 2 peritoneal metastases (Waldmann et al., 2009). Snail positivity was reported for 28% (13/47) cases, and positive staining was associated with malignant behaviour. Hardy et al. (2007) published their results focused on thyroid neoplasms. 18/31 follicular and 28/32 papillary thyroid cancers as well as all of 4 lymph node metastases of papillary thyroid cancer were found to stain positive for Snail whereas normal thyroid tissue was negative. Snail staining was reported to be restricted to the invasive front and associated with a concomitant reduction in E-cadherin reactivity. The authors of this study also included their findings from a Combi-TA mouse model showing development of papillary thyroid carcinomas. Fendrich et al. (2009) recently published results of a study focused on parathyroid neoplasms including 9 cases of parathyroid carcinoma, 25 adenomas and 25 cases of hyperplasia. Snail staining was positive in all cases of hyperplasia and 22/25 adenomas. In carcinomas a change in staining pattern towards the invasion front was noted.

Mesenchymal neoplasms

Note

Franci et al. (2006) studied Snail in a series of different neoplasm which included sarcomas and infantile fibromatosis as well as epithelial neoplasms (squamous cell carcinoma of the uterine cervix and adenocarcinoma of the colon). High Snail expression was present in fibrosarcomas and other sarcomas. Snail expression in neoplasms of epithelial origin was restricted to the tumor-stroma interface.

To be noted

Note

Mouse model.

A CombitTA conditional mouse model of Snail expression has been described without morphological alterations, but associated with the development of both epithelial and mesenchymal tumors (leukemias) (Perez-Mancera et al., 2005). Notably, suppression of the Snail transgene did not rescue the malignant phenotype, indicating that the alterations induced by Snail were irreversible.

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