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# Gene Section
## Review

# SPRY1 (Sprouty Homolog 1, Antagonist Of FGF Signaling (Drosophila))

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## Abstract

Review on SPRY1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

## Identity

**Other names:** hSPRY1

**HGNC (Hugo):** SPRY1

**Location:** 4q28.1

## DNA/RNA

### Description

SPROUTY1 (SPRY1) is located on the plus strand of chromosome 4 (124319541-124324915) and contains three exons (Figure 1A).
The third exon is the coding exon.

### Transcription

Four transcript variants exist for SPRY1, all of which encode the same protein (according to UCSC genome browser (hg19)).
Transcript variant 1 contains three exons, the last of which is the coding exon.
Transcript variant 2 lacks exon 2 but retains the same coding exon as transcript variant 1.
Transcript variants 3 and 4 also lack exon 2, have alternative promoters, and retain the same third coding exon (Figure 1B).

## Protein

### Description

SPRY1 is a member of the SPRY gene family, which is composed of four genes (SPRY1, SPRY2, SPRY3, and SPRY4). SPRY1 protein is composed of 319 amino acids, which include a conserved serine-rich motif and a conserved cysteine-rich domain (Figure 1C). The C-terminal cysteine-rich domain of SPRY1 contains 23 cysteine residues, 19 of which are shared among the four family members (reviewed in Guy et al., 2009). This cysteine-rich domain facilitates homo- and heterodimer formation between SPRY proteins (Ozaki et al., 2005).
SPRY1 functions as a regulator of fundamental signaling pathways and its activity is regulated by post-translational modifications. Spry1 is phosphorylated in response to the growth factors, fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) (Mason et al., 2004). Xenopus xSpry1 is phosphorylated on the tyrosine 53 (Tyr53) residue in response to FGF treatment (Hanafusa et al., 2002). The xSpry1 Y53F mutant, which prevents this phosphorylation event, functions as a dominant-negative suggesting that phosphorylation is required for xSpry1 inhibitory activity toward growth signaling pathways (Hanafusa et al., 2002).

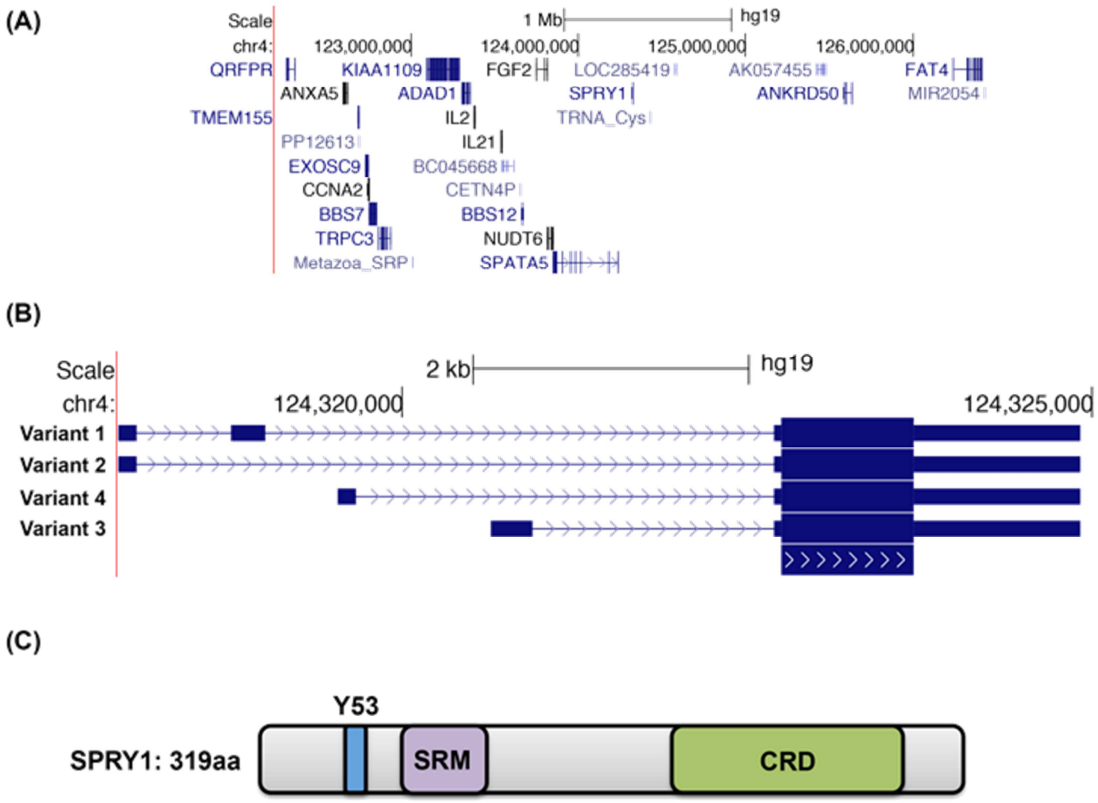


**Figure 1. SPROUTY1 (SPRY1) genomic context, transcript variants, and protein structure. (A)** UCSC genome browser (hg19) snapshot of SPRY1 genomic context on chromosome 4q28.1. Image modified from: UCSC genome Bioinformatics. **(B)** UCSC genome browser (hg19) snapshot of the four SPRY1 transcripts. All transcripts retain the same coding exon. Image modified from: UCSC genome Bioinformatics. **(C)** Schematic of SPRY1 protein. Highlighted is the conserved N-terminal tyrosine 53 (Y53) that is phosphorylated in response to growth factor treatment, the serine-rich motif (SRM) that is phosphorylated upon growth factor treatment, and the conserved C-terminal cysteine-rich domain (CRD).

Serine residues of Spry1 are also phosphorylated in response to FGF (Impagnatiello et al., 2001). Finally, Spry1 can be palmitoylated, and serves as a possible mechanism of membrane localization (Impagnatiello et al., 2001).

## Expression

Spry1 is expressed in localized domains throughout organogenesis in the developing mouse embryo and in adult tissues (Minowada et al., 1999). Spry1 is expressed during the development of the brain, salivary gland, lung, digestive tract, lens, and kidney (Minowada et al., 1999, Zhang et al., 2001, Boros et al., 2006). Notably, Spry1 is expressed in the developing mouse kidney at the condensing mesenchyme and the ureteric tree (Gross et al., 2003). During mouse embryonic development Spry1 expression patterns strongly correlate with regions of FGF expression, which may directly promote Spry1 gene activation (Minowada et al., 1999). For example, Spry1 expression is induced in response to FGF8 in explant cultures of the mouse mandibular arch (Minowada et al., 1999).

Spry1 expression is dynamically regulated in response to environmental stimuli, although the kinetics of activation vary depending on the specific cell line or stimulus used. Serum starved NIH-3T3 cells treated with FGF, PDGF, epidermal growth factor (EGF) or phorbol 12-myristate-13-acetate (PMA), upregulate Spry1 mRNA expression 30-60 minutes after stimulation (Ozaki et al., 2001). However, at time-points beyond 2 hours, Spry1 mRNA expression is downregulated in serum-starved NIH-3T3 cells treated with FGF (Gross et al., 2001).

Taken together these results may reflect a transient burst of Spry1 mRNA induction in response to growth factor signaling. In mouse microvascular endothelial cells (1G11), Spry1 mRNA expression is modulated as cells are serum deprived and stimulated with FGF.

Spry1 expression increases upon serum starvation, decreases after 2 hours of FGF treatment, and then increases after 6-18 hours of FGF treatment (Impagnatiello et al., 2001).

Spry1 mRNA expression is increased in Th1 cells upon activation of T-cell receptor (TCR) signaling pathways (Choi et al., 2006).

SPRY1 protein expression increases in U937 cells upon interferon α or β treatment (Sharma et al., 2012). Finally, SPRY1 mRNA expression increases when human umbilical vein endothelial cells

(HUVECs) are subject to hypoxic conditions (Lee et al., 2010).
Spry1 activity is also regulated by transcription factors such as Wilms Tumor 1 (WT1), which binds directly to the Spry1 promoter to activate its expression (Gross et al., 2003). Furthermore, Spry1 expression is directly repressed by microRNA-21 (miR-21) (Thum et al., 2008). Importantly, miR-21 mediated repression of Spry1 leads to increased Ras-extracellular signal regulated kinase (Erk) signaling pathway activation causing cardiac fibrosis and dysfunction (Thum et al., 2008).

## Localisation

SPRY1 is primarily expressed in the cytoplasm and its localization to the plasma membrane is modulated upon serum deprivation and growth factor treatment. Impagnatiellio et al. demonstrated that in freely growing HUVECs, SPRY1 is localized to perinuclear and vesicular structures as well as the plasma membrane. Upon serum deprivation, SPRY1 remains cytoplasmic but is no longer detected at the plasma membrane. In response to FGF treatment, SPRY1 is again localized to the plasma membrane (Impagnatiello et al., 2001). Similarly, ectopic Spry1 in COS-1 cells translocates to membrane ruffles upon EGF treatment (Lim et al., 2002).

## Function

Elegant studies in Drosophila identified dSpry as a novel inhibitor of FGF and EGF signaling pathway activation during tracheal branching, oogenesis, and eye development, with specificity towards regulating the Ras-Erk cascade (Hacohen et al., 1998; Casci et al., 1999; Kramer et al., 1999; Reich et al., 1999). Similarly, subsequent studies using mammalian cell lines and mouse models revealed that SPRY1 negatively regulates receptor tyrosine kinase (RTK) signaling pathway activation in various cellular contexts. As a result, SPRY1 controls organ development and fundamental biologic processes including cell proliferation, differentiation, survival, and angiogenesis (reviewed in Mason et al., 2006; Edwin et al., 2009).
In vivo loss-of-function experiments in mice demonstrated that Spry1 is a key regulator of proper organ and tissue development. Spry1 knockout ($Spry1^{-/-}$) mice have striking defects in branching morphogenesis of the kidney, develop kidney epithelial cysts, and a disease resembling the human condition known as congenital anomalies of the kidney and urinary track (Basson et al., 2005; Basson et al., 2006). Conditional deletion of Spry1 in satellite cells demonstrated that Spry1 is required for the muscle stem cell quiescence during muscle cell regeneration as well as the maintenance of muscle stem cell quiescence during ageing (Shea et al., 2010; Chakkalakal et al., 2012). Studies conditionally deleting both Spry1 and Spry2 revealed that Spry1 and Spry2 are also critical regulators of proper lens and cornea, as well as brain development. The conditional deletion of the combination of Spry1 and Spry2 results in lens and cornea defects, and cataract formation (Kuracha et al., 2011; Shin et al., 2012). Spry1 and Spry2 conditional double knockout mutants lack proper patterning of the murine brain, and altered gene expression downstream of Fgf signaling pathway activation (Faedo et al., 2010).
SPRY family members including SPRY1 function as inhibitors of Ras-Erk signaling, although the point at which SPRY inhibits pathway activation remains controversial (reviewed in Mason et al., 2006). In the developing mouse kidney, Spry1 antagonizes the glial cell line-derived neurotrophic factor (GDNF)/Ret signaling pathway to control Erk activation (Basson et al., 2005). Similarly, conditional deletion of the combination of Spry1 and Spry2 in the murine lens leads to elevated Erk activation, as well as activation of downstream FGF target genes (Kuracha et al., 2011; Shin et al., 2012). In cell lines, Spry1 regulates signaling pathway activation in response to various defined stimuli. Spry1 inhibits Ras-Erk pathway activation in response to growth factors including FGF, PDGF, and VEGF, correlating with the ability of Spry1 to control cell proliferation and differentiation (Gross et al., 2001; Impagnatiello et al., 2001). By contrast, overexpression of SPRY1 in HeLa cells leads to increased Ras-Erk pathway activation in response to EGF (Egan et al., 2002). Recent evidence demonstrates that SPRY1 is involved in inhibiting ERK and p38 MAPK activation in response to interferons, limiting expression of interferon-stimulated genes and decreasing interferon-mediated biologic responses (Sharma et al., 2012).
Growing evidence also links the SPRY family as critical regulators of phosphoinositide 3-kinase (PI3K)-protein kinase B (PKB, also known as AKT) and phospholipase C gamma (PLCγ)- protein kinase C (PKC) pathway activation. In an inner medullary collecting duct cell line, Spry1 knockdown results in enhanced and prolonged phosphorylated, activated Akt in response to GDNF treatment (Basson et al., 2006). Spry1 binds to PLCγ and inhibits PLCγ pathway activation, resulting in decreased inositol triphosphate (IP3), calcium, and diacylglycerol (DAG) production (Akbulut et al., 2010).
SPRY1 regulates TCR signaling pathway activation in a cell-type specific manner. In Th1 cells (Choi et al., 2006) and CD4+ cells (Collins et al., 2012), Spry1 inhibits signaling pathway activation, while in naïve T-cells Spry1 potentiates signaling pathway activation (Choi et al., 2006).

Spry1 binds to numerous signaling intermediates including linker of activated T-cells (LAT), PLCγ1, and c-Cbl to suppress Ras-Erk, nuclear factor of activated T-cells (NFAT) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway activation (Lee et al., 2009).

# Implicated in

## Breast cancer

**Note**

SPRY1 is significantly downregulated in the majority of breast cancer cases.

This down-regulation was observed by comparing the expression of SPRY1 in breast cancer tumors and matched normal tissues using cDNA arrays (39/50 (78%) of paired samples) and quantitative real-time PCR (qRT-PCR) (18/19 (94%) of paired samples) (Lo et al., 2006). This data suggests that SPRY1 has tumor suppressive activity in breast cancer.

## Clear cell renal cell carcinoma (ccRCC)

**Note**

Gene expression profiling of 29 ccRCC patient tumors revealed that SPRY1 expression serves as a prognostic biomarker associated with good outcome (Takahashi et al., 2001).

## Embryonal rhabdomyosarcoma subtype (ERMS)

**Note**

cDNA microarray and Affymetrix microarray experiments revealed that SPRY1 mRNA expression is elevated in ERMS tumors compared to alveolar rhabdomyosarcoma subtype (RMS) tumors.

Oncogenic Ras mutations leading to elevated Ras-Erk pathway activation in ERMS cell lines, result in increased SPRY1 protein expression. Inhibition of SPRY1 in ERMS cell lines decreases cell growth, survival and xenograft formation (Schaaf et al., 2010).

This data suggests that in ERMS tumors driven by oncogenic Ras with elevated SPRY1 expression, targeting SPRY1 may prove to be efficacious.

## Glioma

**Note**

Analysis of a glioma dataset containing expression data from 276 tumor samples revealed that SPROUTY (SPRY1, SPRY2, and SPRY4) genes are coordinately upregulated in EGFR amplified gliomas (Ivliev et al., 2010).

The role and significance of SPRY1 in glioma has not been functionally addressed.

## Hepatocellular carcinoma

**Note**

An initial study comparing hepatocellular carcinoma tumors with non-tumor livers, found that SPRY2 was significantly downregulated, while SPRY1 was not significantly downregulated in tumor tissue (Fong et al., 2006).

qRT-PCR analysis of tissues from hepatocellular carcinoma patients revealed that SPRY1 expression levels are upregulated in 68% of patients, while SPRY2 and SPRY4 are commonly downregulated (79% and 75%, respectively).

The upregulated SPRY1 levels were found in patients that did not display cirrhosis in their non-tumor tissue (Sirivatanauksorn et al., 2012).

Recent evidence suggests that downregulation of SPRY1 in liver cancers occurs through miR-21 mediated repression (Jin et al., 2013).

## Medullary thyroid carcinoma (MTC)

**Note**

SPRY1 has been proposed to have tumor suppressive activity in MTC. $Spry1^{-/-}$ mice display evidence of thyroid cell hyperplasia. Overexpression of Spry1 in an MTC cell line with low Spry1 expression reduces cell proliferation and tumor formation in xenografts through activation of the CDKN2A locus.

The majority of human MTC samples tested display promoter methylation and downregulation of SPRY1 expression, in line with the proposed tumor suppressive role of SPRY1 in MTC (Macia et al., 2012).

## Non-small cell lung cancer (NSCLC)

**Note**

SPRY1 mRNA expression is upregulated in NSCLC tumors compared to matched normal lung tissues, while SPRY2 mRNA expression is commonly downregulated (Sutterluty et al., 2007).

## Ovarian cancer

**Note**

SPRY1 mRNA and protein expression varies in ovarian cancer cell lines. 4/7 cell lines (SKOV-3, CAOV-3, OV-90, and IGROV-1) display significantly lower SPRY1 protein expression, 1/7 cell lines (OVCAR-3) display significantly higher SPRY1 protein expression, and 2/7 cell lines (1A9 and A2780) display equivalent SPRY1 expression, as compared to normal primary human ovarian cells (Moghaddam et al., 2012).

## Prostate cancer

**Note**

SPRY1 expression is downregulated in prostate cancer.

This downregulation was observed by comparing prostate cancer tissue to normal tissues using immunohistochemistry (40% of 407 of paired samples) and qRT-PCR (16/20 of samples assessed) (Kwabi-Addo et al., 2004). Moderate down-regulation of SPRY1 mRNA expression was also detected in an independent study (Fritzsche et al., 2006). In addition, SPRY1 protein levels are significantly decreased in prostate cancer cell lines (LNCaP, Du145, and PC-3) compared to prostatic epithelial cell lines. Overexpression of SPRY1 in LNCaP and PC-3 cells significantly inhibits cell growth (Kwabi-Addo et al., 2004). Increased methylation of the SPRY1 promoter and miR-21 mediated repression are in part responsible for abnormal SPRY1 silencing that occurs in prostate cancer (Kwabi-Addo et al., 2009; Darimipourain et al., 2011). More recently, it was confirmed in vivo that Spry1 and Spry2 function together to inhibit prostate cancer progression (Schutzman and Martin, 2012). The conditional deletion of both Spry1 and Spry2 in mouse prostate epithelium results in ductal hyperplasia and low-grade prostatic intraepithelial neoplasia. Notably, the deletion of Spry1 and Spry2 synergizes with reduction of Pten to increase the grade and invasiveness of prostate tumorigenesis through increased PI3K-Akt and Ras-Erk signaling pathway activation (Schutzman and Martin, 2012).

# To be noted

**Note**

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