

Gene Section

Review

NCOA1 (Nuclear receptor coactivator 1)

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Abstract

Review on NCOA1, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords

Nuclear receptor coactivator 1 (NCOA1), transcription regulation, nuclear hormone receptors

Identity

Other names

SRC1, KAT13A, RIP160, F-SRC-1, bHLHe42, bHLHe74

HGNC (Hugo)

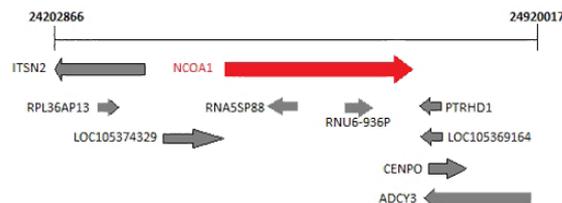
NCOA1

Location

2p23.3 (Carapeti et al., 1998); Start: 24,492,050 bp; End: 24,770,702 bp; 278,652 bp; Orientation: Plus strand (GRCh38.p7)

Local order

From telomere to centromere: ITS2, RPL36AP13, LOC105374329, NCOA1, RNA5SP88, RNU6-936P, PTRHD1, LOC105369194, CENPO, ADCY3



Local order of NCOA1. Local order is shown together with leading and subsequent genes on chromosome 2. The direction of arrows indicates transcriptional directions on the chromosome and arrow sizes approximate gene sizes.

DNA/RNA

NCOA1 is the firstly cloned nuclear hormone receptor co-activator (Onate et al., 1995; Xu et al., 2009). The canonical transcript (ENST00000348332.7; NM_003743) includes 21 exons, 19 of which are encoded (GRCh38.p10; <http://www.ensembl.org>).



Numbers and illustrative sizes of exons of human NCOA1. Red boxes are the coding region and black boxes are the non-coding ones.

Transcription

Four alternatively spliced isoforms of NCOA1 have firstly been illustrated (Kamei et al., 1996). Compared to NCOA1a, NCOA1b lacks the N-terminal domain, and NCOA1c, d and e have unique C-terminal sequences. NCOA1a and b have been shown to display diverse abilities to increase the estrogen receptor α (ESR1 (E α)) activity in cell lines (Kalkhoven et al., 1998; Xu et al., 2009). According to Ensembl database, there are eleven different transcripts of NCOA1 gene. Six of these transcripts encode two different proteins while five of them cannot encode protein. Lengths of the transcripts vary between 7405-501 bp (GRCh38.p10; <http://www.ensembl.org>).

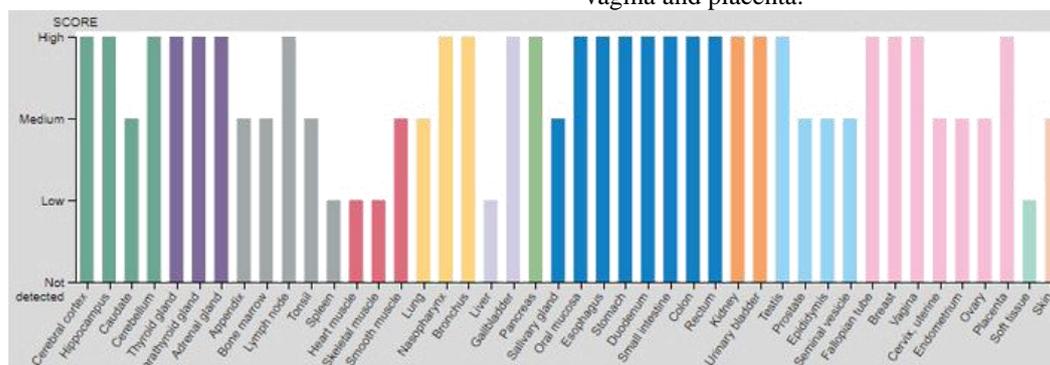
Protein

NCOA1 gene encodes two similar proteins. The length of the canonical protein is 1441 amino acids with a molecular mass of 156,757 Da (UniPort ID: Q15788) and the length of the second protein is 1248 amino acids with a molecular mass of 135,621 Da (UniProt ID: B5MCN7). Like the other SRCs (NCOA2 and NCOA3 (SRC-2 and 3)), NCOA1 consists of three structural domains. The protein-protein interaction is performed via an N-terminal basic helix-loop-helix-Per/ARNT/Sim (bHLH-PAS)

domain. This domain is highly conserved amongst p160 SRC family and promotes interaction with the transcription factors, such as myogenin, MEF-2C and TEF. The central domain which consists of LXXLL motifs forming amphipathic alpha-helices supports interaction with nuclear hormone receptors. The C-terminal domain includes two transcription activation domains, AD1 and AD2. AD1 binds and recruits CREBBP and EP300 (CBP and p300 histone acetyltransferase (HAT)) for chromatin remodeling, which is critical for SRC-mediated transcriptional activation. AD2 interacts with histone methyltransferases, coactivator-associated arginine methyltransferase 1 (CARM1) and protein arginine methyltransferases (PRMT1). The C-terminus of NCOA1, like SRC-3, also includes a HAT activity domain (Torchia et al., 1997; Xu et al., 2009).

Expression

Chen et al. showed that NCOA1 was expressed in placental labyrinth (Chen et al., 2010). According to The Human Protein Atlas database, NCOA1 is highly expressed in cerebral cortex, hippocampus, cerebellum, thyroid gland, parathyroid gland, adrenal gland, lymph node, nasopharynx, bronchus, gallbladder, pancreas, oral mucosa, esophagus, stomach, duodenum, small intestine, colon, rectum, kidney, urinary bladder, testis, fallopian tube, breast, vagina and placenta.



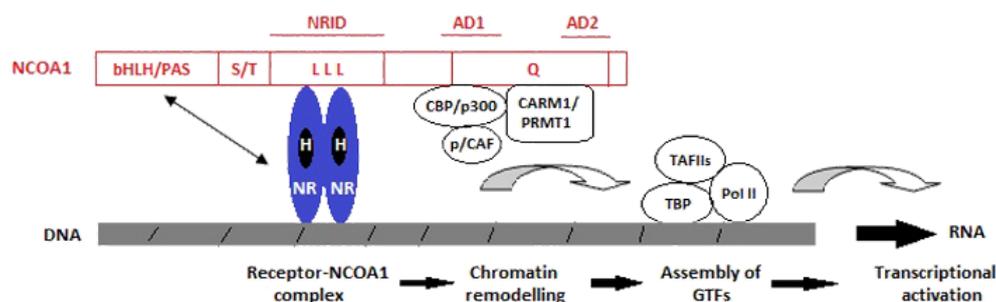
Expression profile of NCOA1 in human tissues. Data taken from The Human Protein Atlas (<http://www.proteinatlas.org>) in February, 2018.

Localisation

NCOA1 is synthesized in cytoplasm and imported into nucleus, and localized as speckles in both cytoplasm and nucleus. Localization to nucleus is performed thanks to nuclear localization signal located in between amino acids 18 and 36. After it

display its function, it is exported to cytoplasm back, which is thought to inhibition of hormone action via NCOA1 degradation in cytoplasm. Exportation to cytoplasm back occurs owing to nuclear export signal located between amino acids 990 and 1038 (Amazit et al., 2003).

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Structure and functions of NCOA1 protein. When hormone (H) is bound to nuclear hormone receptors (NR), they recruit NCOA1 and interact with it via LXXLL motif in NCOA1. NCOA1 interacts with CBP, p300, KAT2B (p/CAF), CARM1 and PRMT1 and recruits these coactivators to the chromatin for chromatin remodeling. Remodeling of chromatin enables binding of transcription factors and RNA polymerase II on the promoter region. NR interacts with NCOA1 via not only NRID domain but bHLH/PAS domain, which is also important for function of NCOA1. Data adapted from Xu et al., 2009.

Function

NCOA1 increases the transcriptional activities of nuclear hormone receptors in a hormone-dependent manner. In addition to nuclear hormone receptors, NCOA1 and other SRCs are the coactivators of other transcription factors including NF- κ B, Smads, E2F1, STATs, HIF1A, TP53, RB1, ETV4 (polyoma enhancer activator 3 (PEA3)) and ETS2. They support gene transcription by interacting with kinases, ubiquitin/sumoligases, phosphatases, histone acetyltransferases and histone methyltransferases (Qin et al., 2009; McBryan et al., 2012; Xu et al., 2009). Due to its role in transcription, NCOA1 and other SRCs have a role in different physiological functions, including cell cycle and energy metabolism. NCOA1 itself is critical for organ physiology. It has been showed that NCOA1 deficiency strongly influenced mice reproductive organ development (Xu et al., 1998). NCOA1^{-/-} mice also displayed partial resistance to sex steroids and thyroid hormone (Weiss et al., 1999; Kamiya et al., 2003). NCOA1 is also important for the gluconeogenesis. In liver, it is a coactivator of CEBPA (CEBP α) which regulates the pyruvate carboxylase gene, the limiting enzyme for gluconeogenesis, together with PPAR γ (PPAR γ). Activated PPAR γ recruits NCOA1 and other coregulators, such as PGC-1 and CBP/p300 in brown fat, and deficiency in NCOA1 results in drawbacks in activity of PGC-1. This drawback further decreases energy expenditure and causes obesity with high fat diet (Xu et al., 2009).

Phosphorylation is critical in the functioning of SRC family proteins. Phosphorylation of SRCs alters their affinities for certain nuclear hormone receptors (Lopez et al., 2001; Rowan et al., 2000; Wu et al., 2004; Giamas et al., 2009). Moreover, phosphorylation by different kinases via different Ser/Thr amino acids results in determination of down-stream processes. NCOA1 could be phosphorylated by EGF, IL6, CAMP, CCNA2 (cyclin A2)/ CDK2, CDK1 and MAPK. Cyclin

A2/Cdk2- and EGF-mediated phosphorylation increases progesterone receptor (PGR)-dependent transcription while IL-6-induced phosphorylation supports androgen receptor (AR)-dependent transcription via ligand independency. Additionally, cAMP-mediated phosphorylation of NCOA1 recruits p300 and CBP and activates PR-dependent transcription via ligand independency and MAPK-induced NCOA1 phosphorylation enhances the affinity of NCOA1 towards AR in prostate cancer cells (Rowan et al., 2000; Wu et al., 2004; Giamas et al., 2009; Ueda et al., 2002; Rowan et al., 2000b; Gregory et al., 2004; Xu et al., 2009; Moore and Weigel, 2011). In addition to phosphorylation, SUMOylation of NCOA1 at Lys731 and Lys774 by SUMO1 was showed to increase the interaction between PR and NCOA1, and upregulate PR-mediated transcription (Chauchereau et al., 2003). In hormone-dependent progesterone receptor activity, NCOA1 was shown to be down-regulated in hormone-dependent manner like PR to activate the transcription of target genes. NCOA1 down-regulation was illustrated to be predominantly in cytoplasmic compartment via proteasomal degradation and the down-regulation of NCOA1 together with PR is critical for the regulation of transcription (Amazit et al., 2011).

The interaction of NCOA1 with PR to regulate gene expression was partly underlined in a study where KAT7 (HBO1) (a member of the MYST acetylase family) was illustrated to modulate interaction of NCOA1 and PR in a hormone-dependent manner in human testis cell line, CV1 and human embryonic kidney cell line, HEK293 (Georgiakaki et al., 2006). NCOA1 has been shown to affect developmental processes. NCOA1 and NCOA3 double knockout mice died at early embryonic stage while single knockout mice lived normally, pointing a cooperative role of NCOA1 and NCOA2 in embryo survival. Moreover, morphologies of labyrinths of NCOA1 (together with NCOA3) knockout mice embryos were abnormal via altered expression of genes responsible for placental morphogenesis, and glucose metabolism (Chen et al., 2010).

Baldwin et al. showed that high-risk human papillomavirus type 16 (HPV16) E7 oncoprotein affected the localization and function of NCOA1; relocalized NCOA1 into cytoplasm and decreased NCOA1-mediated gene expression and NCOA1-dependent histone acetyltransferase (HAT) activity in vivo and in vitro in cervical cancer cell line, HeLa (Baldwin et al., 2006).

NCOA1 has also been linked to glucose metabolism. Under glucose deprivation, NCOA1 was proved to stabilize 26S proteasome and affect the expression of complex I of the mitochondrial electron transport chain (Motamed et al., 2014).

Homology

NCOA2 (SRC-2, TIF2 or GRIP1) and NCOA3 (SRC-3, p/CIP, RAC3, AIB1, ACTR or TRAM-1) are homologous to NCOA1 and these three proteins are included in a family, called p160 SRC (Torchia et al., 1997; Xu et al., 2009).

Mutations

A single nucleotide polymorphism (SNP) in NCOA1 (rs1804645; P1272S) was demonstrated to decrease ER activation while it increase protein life-time via blocking phosphorylation by glycogen synthase 3 (GSK3B) in bone. Moreover, this SNP was linked to a decrease in hip and lumbar bone mineral density in women receiving tamoxifen (Hartmaier et al., 2011).

Another SNP in NCOA1 (rs7948087) was associated to multiple myeloma phenotype in Chinese Han population (Peng et al., 2017).

Four different SNPs in NCOA1 (rs11894248, rs17791703, rs7572475 and rs9309308) were linked to Kawasaki disease in Taiwanese people (Chen et al., 2014).

Two chromosomal rearrangements affecting NCOA1 in patients with sarcoma subtypes were identified. In one study, a novel t(2;2)(q35;p23) translocation generating PAX3/NCOA1 fusion protein has been shown (Wachtel et al., 2004). Similar fusion protein was proved to be a result of inv(2)(q35p23) mutation (Huang et al., 2016).

According to ClinVar database, huge chromosomal deletions and duplications in regions including NCOA1 gene have been submitted. These mutations showed to be pathogenic, benign or with uncertain significance.

Implicated in

Top note

NCOA1 has widely been studied particularly in breast and prostate cancer through its interaction status with estrogen receptor alpha, progesterone receptor and androgen receptor.

Breast Cancer

NCOA1 has been shown to be generally over-expressed in breast cancer. Moreover, its over-expression has been correlated with ERBB2 expression, metastasis, cancer recurrence and poor disease-free survival (Wang et al., 2006; Fleming et al., 2004; Myers et al., 2004; Hudelist et al., 2003; McBryan et al., 2012; Qin et al., 2014; 2015). Furthermore, NCOA1 has also been demonstrated to be a predictor of breast cancer recurrence after therapy (Redmond et al., 2009). In a cohort study, NCOA1 was found to be over-expressed in 155 of 312 breast cancer patients underwent radical resection, and NCOA1 expression was demonstrated to be correlated with Ki-67 and HER-2 expression. Moreover, NCOA1 and NANOG coexpression was showed to be significantly poorer postoperative disease-specific survival than those with no expression in the HER-2-positive group (Jin et al., 2016). In a study, NCOA1 expression has also been correlated with a favorable response to tamoxifen in patients with recurrent breast cancer (Berns et al., 1998). However, it has been showed that protein kinase A (PKA)-mediated phosphorylation of estrogen receptor alpha at S305 caused alteration in orientation between ER α and NCOA1 leading to active transcription complex even in the presence of tamoxifen, resulting tamoxifen resistance in T47D and MCF7 breast cancer cell lines (Zwart et al., 2007). Not only tamoxifen response, NCOA1 was shown to be involved in resistance to aromatase inhibitors in patient with breast cancer and breast cancer cell model. NCOA1 was proved to be over-expressed in aromatase-resistant cells and patient tumors. NCOA1 was demonstrated to interact with transcription factor Ets2 and regulate transcription of MYC and MMP9 by which it affected tumor aggressiveness (McBryan et al., 2012). In breast adenocarcinoma cell line, MCF7, NCOA1 has been illustrated to have a role in ER α -mediated cell growth (Tai et al., 2000; Cavarretta et al., 2002). What is more, NCOA1 was shown to co-operate with MUC1, an ER α interactive protein (Wei et al., 2006). NCOA1 has been also involved in cell proliferation and invasion via autocrine/paracrine activity of the SDF-1 α -CXCL12 signaling pathway in MCF7 cell lines (Kishimoto et al., 2005). In another study, NCOA1 has been proved to support epithelial-mesenchymal transition (EMT), invasion, migration and metastasis of breast tumor cells via activating PEA3-mediated Twist (TWIST1) expression (Qin et al., 2009; Xu et al., 2009). In human ductal breast epithelial cell line, T47D, cyclin A2/Cdk2 was proved to phosphorylate NCOA1 and thus increase NCOA1/PR interaction and PR activity. Cyclin A2/Cdk2 as well as Cdk1 was further showed to phosphorylate seventeen sites in NCOA1 protein (Moore and Weigel, 2011). In vivo animal model studies have also proved the function of NCOA1 in breast tumorigenesis. Importantly, in

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vivo NCOA1 knockdown was showed to cause reduction in expression of ERBB2, activation of Akt, inhibition of colony stimulating factor 1 (CSF1) and prevention of macrophage recruitment to the tumor environment (Wang et al., 2009). Metastasis-focused study in mice figured out that NCOA1, together with FOS, up-regulated macrophage attractant CSF1 and increased macrophage recruitment, and metastasis (Qin et al., 2014). In a study conducted by Qin et al. NCOA1 was determined to up-regulate VEGFA by associating with FOS and HIF1 α , potentiating angiogenesis in breast cancer mice models (Qin et al., 2015). Wang et al. proposed cardiac glycoside bufalin as an inhibitor of both SRC-3 and NCOA1, and showed that bufalin treatment decreased tumor growth in a mouse xenograft model of breast cancer (Wang et al., 2014).

Prostate Cancer

The expression profile of NCOA1 was not high in human tumors in general (Maki et al., 2006). Still, some studies proposed the expression of NCOA1 was correlated with tumor grade (Agoulnik et al., 2005; Gregory et al., 2001; Fujimoto et al., 2001). In one study, NCOA1 was shown to be more located to nucleus in androgen-independent prostate tumors (Maki et al., 2006). NCOA1 was demonstrated to increase AR-dependent cell proliferation in prostate cancer cell lines. Thus, NCOA1 knockdown was parallel to inhibition of proliferation in androgen-dependent prostate cancer cell lines, LNCaP and C4-2 while it did not affect the proliferation of AR-negative prostate cancer cell lines, PC-3 and DU145 (Agoulnik et al., 2005). This effect was further characterized by Luef et al. and proved that the effect was a result of upregulation of protein kinase D1 (PRKD1) which was negatively regulated by AR. They also showed that the expression of NCOA1 was high in patients with prostate cancer (Luef et al., 2016). Overall, NCOA1 supports prostate carcinogenesis in an androgen-dependent and -independent manner (Xu et al., 2009). However, in vivo murine studies have showed that NCOA1 did not affect the prostate cancer tumorigenesis while other SRC family member, SRC-3 was critically affected (Tien et al., 2006).

Endometrial Cancer

NCOA1 phosphorylation was demonstrated to significantly enhance agonistic activity of tamoxifen in endometrial cancer, pointing a possible function of NCOA1 in tamoxifen-induced proliferation and enhancement in risk of endometrial cancer via tamoxifen therapy (Shang and Brown, 2002; Shah and Rowan, 2005).

Hepatoma

NCOA1 together with PPARGC1A (PGC1 α) was proved to be down-regulated in hepatoma cell line, HepG2 where it critically coactivates hepatocyte nuclear factor 4 α (HNF4A) which is fundamental for

liver development and hepatic gene expression. Overexpression of both NCOA1 and PGC1 α increase the expression of HNF4 α -regulated genes and triggered differentiation of HepG2 cells (Martinez-Himenez et al., 2006). Ma et al. showed that MIR105-1 targeted NCOA1 in hepatocellular carcinoma. They checked the expression levels of miR-105-1 and demonstrated that it was down-regulated in samples from patients with hepatocellular carcinoma compared to those of normal individuals. Moreover, down-regulation of miR-105-1 and up-regulation of NCOA1, as a result, were correlated with shorter overall survival (OS) and progression free survival (PFS) in hepatocellular carcinoma (Ma et al., 2017).

Colon cancer

In colorectal cancer-derived cell lines, DLD-1, HT29 and HCT116, leptin and insulin signaling, via ERK1/2, were showed to increase MIR4443 targeting and down-regulating both TRAF4 and NCOA1. Down-regulation of TRAF4 and NCOA1 was illustrated to suppress invasion and proliferation of these cell lines (Meerson and Yehuda, 2016).

Cervical cancer

In cervical cancer cell line, HeLa overexpressing HPV16 E7, this epitope has been shown to relocalize NCOA1 into cytoplasm and decrease NCOA1-dependent transcription via disrupting association with HAT (Baldwin et al., 2006).

Myeloma

In a cohort study with multiple myeloma patients in China, single nucleotide polymorphism in NCOA1 gene (rs7948087) was shown to strongly associate with multiple myeloma phenotype, pointing NCOA1 as a susceptibility gene for multiple myeloma patients in Chinese Han population (Peng et al., 2017).

Head and neck squamous cell carcinoma

In a clinical study, Pavon et al. showed that expression of NCOA1 and creatine kinase mitochondrial 1 (CKMT1) had prognostic significance in advanced-stage head and neck carcinoma (Pavon et al., 2015).

Sarcoma

Rhabdomyosarcoma is a soft sarcoma and is able to subclassified in to two groups: embryonal rhabdomyosarcoma ID: 5193> and alveolar rhabdomyosarcoma. In a microarray-based study, a novel translocation t(2;2)(q35;p23) causing a fusion PAX3/NCOA1 protein (Wachtel et al., 2004). In another study, in biphenotypic sinonasal sarcoma cases where t(2;4)(q36;q31) PAX3/MAML3 fusion has already been known, novel PAX3/NCOA1 fusion has been demonstrated via inv(2)(q35p23). These cases were underlined to display desmin

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reactivity and a small component of rhabdomyoblastic cells (Huang et al., 2016).

Endometriosis

Endometriosis (EMS; ectopic endometrium) is an estrogen-dependent and inflammatory complex disease where immunological factors and angiogenesis play a pivotal role in its pathogenesis (Gazvani and Templeton, 2006; Rizner 2009). Shi et al. showed that the expression of NCOA1 was greater in ectopic endometrium than that of normal endometrium, and NCOA1 was involved in the expression of stromal cell-derived factor 1 (SCDF1/CXCL12) whose expression was induced by estradiol (Shi et al., 2014).

Obesity

NCOA1 together with p/CIP was demonstrated to control insulin signaling in vitro and in vivo. Knockout of these genes resulted in increase in glucose uptake and insulin sensitivity in both regular chow- and high fat diet-fed mice. Moreover, knockouts also brought about resistance to age-related obesity and glucose intolerance through increase in the levels of insulin receptor substrate 1 (IRS1; Wang et al., 2012).

Inflammation

Isoflavone biochanin A treatment of thymoma cell line, EL4 increased the levels of IL7 which was linked to autoimmunity, chronic inflammation and protection against infections. This function of Biochanin A was proved to be a result of enhanced interaction between retinoic acid receptor-related orphan receptor RORC and NCOA1 via phosphorylation of signal transducer and activator of transcription 3 (STAT3; Takahashi et al., 2017).

Kawasaki disease

Kawasaki disease is a self-limited, acute and systemic vasculitis. Chen et al. showed that four SNPs (rs11894248, rs17791703, rs7572475 and rs9309308) in NCOA1 were associated with Kawasaki disease in 327 Taiwanese people (Chen et al., 2014).

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