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Co-regulator NCOA5 and cancer

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Abstract: *NCOA5* encodes a co-regulator for estrogen receptors (ERα and ERβ), orphan nuclear receptors (REV-ERBα and REV-ERBβ) and liver X receptor. It can influence many cellular processes by either promoting or inhibiting gene expression through its two important functional motifs: LxxLL (co-activator) and ΦxxΦΦ (co-repressor). Many reports have revealed the important roles of NCOA5 in diseases, such as diabetes, reproductive defects and autoimmune disease. In this review, we focus on its function in cancers and summary the current research progresses regarding its different roles in various cancers.

Abbreviations

AF-2:	activation function 2
AR:	androgen receptor
BD:	Bechet's disease
BID:	bifunctional interaction determinant
CIA:	coactivator independent of AF-2
CRC:	colorectal cancer
DBD:	DNA-binding domain
ERs:	estrogen receptors
ESCC:	esophageal squamous cell carcinoma
FASN:	fatty acid synthase
GCs:	glucocorticoids
HCC:	hepatocellular carcinoma
IL-6:	interleukin 6
LBD:	ligand-binding domain
LXR:	liver X receptor
mTOR:	mechanistic target of rapamycin
NCOA5:	nuclear receptor co-activator 5
NCOAs:	nuclear receptor co-activators
NF-κB:	nuclear factor-κB
NRs:	nuclear receptors
ODNs:	oligodeoxynucleotides
PTC:	papillary thyroid carcinoma
RD-rich region:	arginine and aspartic rich region
RORA:	RAR-related orphan receptor alpha
RRM:	RNA recognition motifs
T2D:	type 2 diabetes
TGF-β:	transforming growth factor beta
TNF-α:	tumor necrosis factor α

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Introduction

Nuclear receptors (NRs) are a kind of transcriptional regulators that widely exist in animals. They regulate many physiological processes, such as reproduction, development, homeostasis and metabolism (Gronemeyer *et al.*, 2004). One of the structure characteristics of the NRs is their central DNA-binding domain (DBD), which directs the receptor to specific DNA sequences known as hormone response elements. The ligand-binding domain (LBD) localized in the C-terminal half of the receptor is considered as a molecular switch that alters the receptor to a transcriptional promoter upon binding ligand. The LBD is an indispensable property of hormone recognition and guarantees specificity as well as selectivity of the physiologic response. The activities of NRs are often linked to interactions with general classes of molecules that appear to serve co-regulators (co-activator or co-repressor) function. Co-regulators are recruited by NRs to participate in the modulation of NR-mediated transcription activity. At the C-terminal of LBD domain of NRs, there is a helical motif called activation function 2 (AF-2) which is responsible for co-regulator-receptor interaction. The AF-2 integrity is necessary for ligand-dependent co-activator binding (Feng *et al.*, 1998) and its deficiency often facilitate the binding of co-repressor (Schulman *et al.*, 1996). The specific interaction between co-regulators and NRs is mediated by helix motifs. In general, the co-activator contains a helical motif consisting of the sequence LxxLL (L is leucine and x can be any amino acid) (Heery *et al.*, 1997; Le Douarin *et al.*, 1996) and can

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TABLE 1

Comparison of seven nuclear receptor co-activators

NCOAs	Genomic Location	Protein Molecular Weight	Domains (N-terminal → C-terminal)	Expression	Combined with NRs	AF-2 dependent
NCOA1	2p23.3	160 kDa (1441 aa)	bHLH/PAS → S/T → three LxxLL → AD1 and AD2 (contain a Q-rich) The C-terminal of NCOA1 and NCOA3 contain HAT domains	High expression in various tissues	PR, ER, TR	Yes
NCOA2	8q13.3	160 kDa (1464 aa)		High expression in testis	GR, ER	Yes
NCOA3	20q13.12	160 kDa (1424 aa)		High expression in testis	ER, PR, TR, RXR, RAR	Yes
NCOA4	10q11.22	70 kDa (614 aa)	LxxLL → FxxLF	High expression in lung, ovary	AR, ER, PR, GR, VDR, TR, AhR, PPARαγ	Yes
NCOA5	20q13.12	65 kDa (579 aa)	R/D → ΦxxΦΦ/LxxLL	High expression in various tissues	ER, REV-ERBs, LXR	No
NCOA6	20q11.22	250 kDa (2063 aa)	AD1 → LxxLL1 → AD2 → LxxLL2 → STL	High expression in various tissues	RXR, RAR, TR, GR, ER, VDR, PPAR, LXR	Yes
NCOA7	6q22.31-q22.32	140 kDa (942 aa)	LysM → Gram → ERbd → TLDc	High expression in cervix uterine	ER, AhR	Yes

Note: NCOAs, nuclear receptor co-activators; bHLH/PAS, basic helix-loop-helix-Per/ARNT/Sim homologous domain; S/T, serine/threonine-rich regions; LxxLL, LxxLL motif (L, leucine; x, any amino acid); AD, transcriptional activation domains; Q, glutamine-rich regions; HAT, histone acetyltransferase domains; FxxLF, FxxLF motif (F, phenylalanine, L, leucine); R/D, arginine- and aspartic acid-rich region; ΦxxΦΦ, ΦxxΦΦ motif (Φ, hydrophobic residue); STL, Ser, Thr and Leu-rich regions; LysM, lysin motif; GRAM, GRAM domain; ERbd, estrogen receptor binding domain; TLDc, Tre2/Bub2/Cdc16 (TBC), Lysin Motif (LysM), Domain Catalytic; AF-2, activation function 2; NR: nuclear receptor; AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor; TR, retinoid x receptor; GR, glucocorticoid receptor; VDR, vitamin D receptor; RXR, retinoid x receptor; RAR, retinoic acid receptor; LXR, liver x receptor; PPAR, peroxisome proliferator-activated receptor; AhR, aryl hydrocarbon receptor.

directly contact with the hydrophobic cleft that formed on the surface of LBD of NRs. Similarly, co-repressors interact with NRs by touching the hydrophobic cleft on the surface of LBD of NRs with a core helical motif that contains a consensus sequence ΦxxΦΦ (Φ is hydrophobic residue) (Perissi *et al.*, 1999).

There are seven nuclear receptor co-activators (NCOAs) that are serially named as NCOA1 to NCOA7 (Table 1) (Mahajan and Samuels, 2008; Sauvé *et al.*, 2001; Shao *et al.*, 2002; Süllner *et al.*, 2012; Xu *et al.*, 2009; Yeh and Chang, 1996). These factors function as co-regulators for different NRs. For example, NCOA1 (also known as SRC1) is a transcriptional co-activator for steroid and nuclear hormone receptors (Oñate *et al.*, 1995) and NCOA4 is an androgen receptor co-activator (Kollara and Brown, 2012; Peng *et al.*, 2008; Yeh and Chang, 1996). In addition to the NCOA family, about 250 other putative co-activators have been identified. The widely studied co-activators include CBP, p300, TRAP220/DRIP205/PBP, PGC-1 and NRIF3 *et al.*, etc. (Mahajan and Samuels, 2008). Nuclear receptor co-activator 5 (NCOA5), also known as CIA (co-activator independent of AF-2), was first discovered in 2000 (Sauvé *et al.*, 2001). Compared to other NCOAs members, NCOA5 is unique. First, it is a co-regulator with both activation and repression capability in regulating transcription. Second, among of the seven NCOAs, NCOA5 is the only one that can play the co-activator function but not dependent on AF-2. As for other numbers of NCOA family, the existing studies have only proved that they can act as co-activators for various NRs, but the studies have not found that they can function as co-repressors. NCOA5 participates in many physiological and pathological processes. Current research has revealed that NCOA5 is relevant to many diseases including cancers. Like its dual functional capability in gene regulation, NCOA5 can play a role not only as a tumor promoter, but also as a tumor suppressor, depending on the type of tissue.

Structure and Function of NCOA5

Location of NCOA5

Human NCOA5 gene is located on chromosome 20q13.1 (Bento *et al.*, 2008; Lewis *et al.*, 2010), which is within the 400 kb region of *CD40* gene. It is a susceptible gene for type 2 diabetes (T2D) and is associated with an increased risk of rheumatoid arthritis and many autoimmune diseases (Bento *et al.*, 2008; Lewis *et al.*, 2010; Zervou *et al.*, 2011). Human NCOA5 encodes a protein which contains 579 amino acids and is widely and highly expressed in various tissues. In mouse embryos, Ncoa5 is highly expressed in heart and kidney, but rarely in liver (Sauvé *et al.*, 2001). NCOA5 protein localizes in the nucleus of mammalian cells (Rivera-Reyes *et al.*, 2018; Sauvé *et al.*, 2001; Yuan *et al.*, 2020).

Structural characteristics of NCOA5

NCOA5 has three obvious structural characteristics (Fig. 1A). There are overlapping LxxLL (co-activator) and ΦxxΦΦ (co-repressor) motifs in the middle region near the C-terminal, which constitutes the bifunctional interaction determinant (BID) recognized by estrogen receptors (ERα and ERβ) and orphan nuclear receptors REV-ERBα and REV-ERBβ (REV-ERBs) (Sauvé *et al.*, 2001). At the N-terminal, there is an arginine and aspartic rich region (RD-rich region), which shows transcriptional inhibitory activity near it (Sauvé *et al.*, 2001). RNA recognition motif (RRM) also exist at the

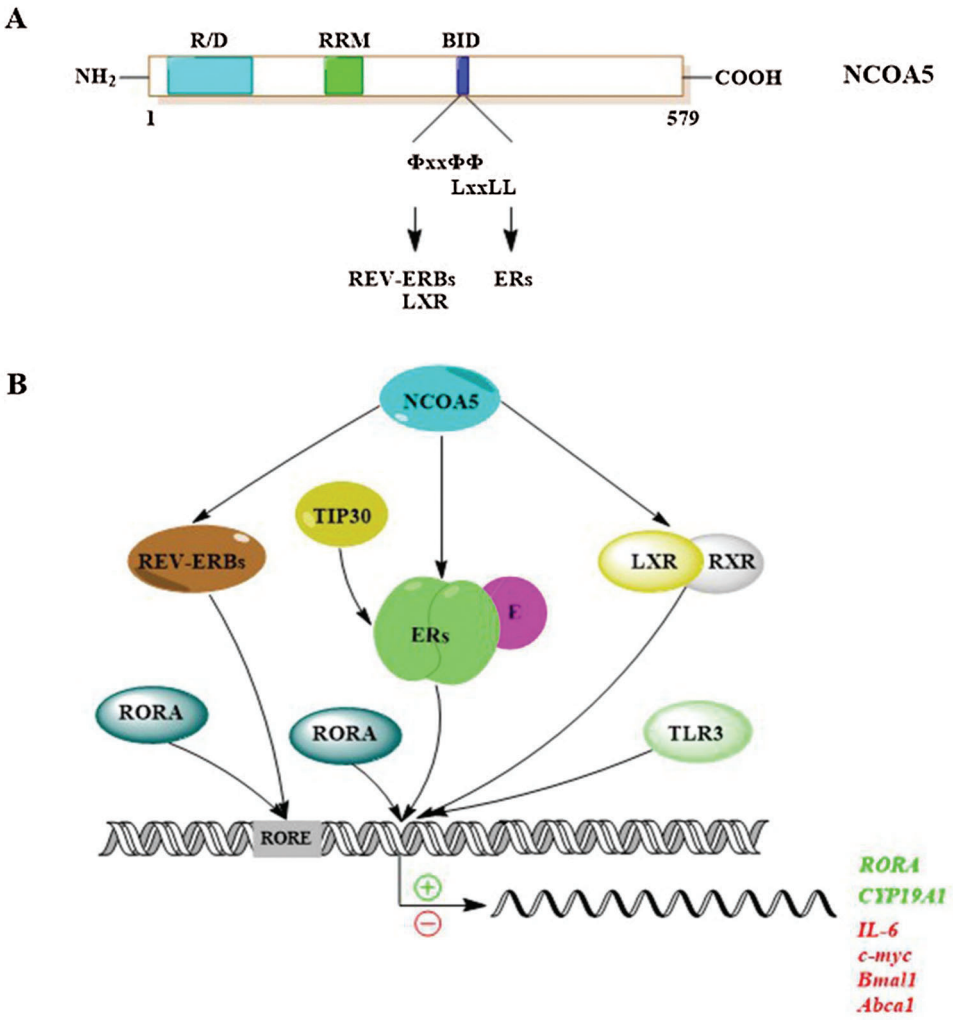

FIGURE 1. Schematic representation of human NCOA5 and the role of NCOA5 in gene expression regulation. (A) NCOA5 contains an RD-rich domain, an RRM domain and two overlapping motifs (LxxLL and ΦxxΦΦ). The LxxLL (co-activator) and ΦxxΦΦ (co-repressor) motifs constitute the BID recognized by estrogen receptors (ERα and ERβ) and orphan nuclear receptors REV-ERBs (REV-ERBα and REV-ERBβ). (B) Under the action of estrogen, NCOA5, as a co-regulator of ERs, can recognize and bind with ERs through its BID mediated by AF-2 at the C-terminal of ERs' LBD, and is recruited to the promoter of ERs-targeted genes to regulate the expression of genes. The NCOA5 can be recruited to the promoter of *c-myc* gene by estrogen-binding ERα and cooperate with TIP30 to inhibit the transcription of *c-myc*. NCOA5 and ERα can bind to *RORA* promoter and participate in the up-regulation of *RORA* by estrogen. NCOA5 also interacts with RORA at the RORA binding site in the promoter of *CYP19A1*, and it cooperates with *RORA* to promote the expression of *CYP19A1*. By cooperating with REV-ERBs, NCOA5 represses the expression of clock gene *Bmal1*. In addition, NCOA5, as a co-repressor of LXR, can be recruited to the *Abca1* promoter to inhibit the expression of *Abca1*, thereby reducing cholesterol efflux. NCOA5, Nuclear receptor co-activator 5; R/D, arginine and aspartic rich region; RRM, RNA recognition motifs; BID, bifunctional interaction determinant; ΦxxΦΦ, ΦxxΦΦ motif (Φ, hydrophobic residue); LXXLL, LXXLL motif (L, leucine; x, any amino acid); E, estrogen; ERs, estrogen receptors; REV-ERBs, nuclear receptor superfamily 1, group D members; RORE, ROR response elements; RORA, retinoic acid related orphan nuclear receptor; TIP30, Tat-interacting protein 30; LXR, liver X receptor; RXR, retinoid X receptor; TLR3, Toll-like receptor 3.

N-terminal, which has a binding affinity to both RNA and single stranded DNA, and can bind CpG ODNs to participate in immune response (Iliev *et al.*, 2013).

Functions of NCOA5

As an AF-2-independent regulator, the NCOA5's function on gene expression regulation is mediated by its co-activator motif LxxLL and co-repressor motif ΦxxΦΦ. NCOA5 has both gene activation and gene repression functions and participates in many important cellular activities through its regulation of gene expression (Fig. 1B). NCOA5 is a co-regulator for ERα, ERβ and REV-ERBs (Sauvé *et al.*, 2001). NCOA5 mainly recognizes and binds to the C-terminal region of ERα through BID, which can be conformationally altered by selective estrogen receptor regulators (Sauvé *et al.*, 2001; Shiau *et al.*, 1998). The LxxLL motif of NCOA5 plays an important role in the NCOA5-ERα interaction mediated by AF-2 induced by estradiol (E2), while the ΦxxΦΦ motif interacts with ERα mutant lacking AF-2 in an E2-dependent or independent way (Sauvé *et al.*, 2001). Under the action of estrogen, NCOA5 can be recruited to interleukin 6 (*IL-6*) gene promoter after binding with ERα, and then binds to the NF-κB site of *IL-6* promoter to negatively regulate the transcription of *IL-6* (Gao *et al.*, 2013). Similarly, NCOA5 can also regulate the transcription of other ERα-targeted genes, such as *c-myc* (Jiang *et al.*, 2004) and *RORA* (Sarachana and Hu, 2013).

NCOA5 also binds to orphan nuclear receptor through ΦxxΦΦ core motif in a way independent of AF-2 (Sauvé *et al.*, 2001). In addition, Gillespie *et al.* (2015) reported that NCOA5 physically interacted with liver X receptor (LXR) and acted as LXR co-repressor to inhibit *Abca1* expression. The attenuated *Abca1* level resulted in repression of macrophages cholesterol efflux.

NCOA5 also participates in many cellular activities. It can directly interact with the transcription factor ZAP3 to form ZAP3 complex, which also contains protein phosphatase 1 that directly interacts with ZAP3 (Ulke-Lemée *et al.*, 2007). Therefore, it was suspected that NCOA5 might participate in RNA modification by affecting the nucleoside kinase activity of ZAP3 complex (Ulke-Lemée *et al.*, 2007). NCOA5 can bind to the T-box of transcription factor TBX18, thus weakening the transcriptional inhibitory activity of TBX18 and promoting the development of human dilative nephropathies (Rivera-Reyes *et al.*, 2018). NCOA5 may be involved in the regulation of proliferation of oligodendroglia cells by bornavirus-like nucleoprotein 1 (He *et al.*, 2016). NCOA5 also has the capability to negatively regulate androgen receptor (AR), fatty acid synthase (FASN) and transforming growth factor beta (TGF-β). Studies have confirmed that NCOA5 deficiency can up-regulate the expression of FASN and AR in livers at mRNA and protein levels, and promote the expression of TGF-β1, a target protein downstream of AR (Gao *et al.*, 2013). Under the stimulation of amino acids (Met and Leu), NCOA5 can bind to the promoter of the mechanistic target of rapamycin (mTOR) and promote the transcription activation of mTOR in bovine mammary epithelial cells, thus promoting the synthesis of β-casein (Yuan *et al.*, 2020). Jubb *et al.* (2017) reported that Ncoa5 was a glucocorticoids (GCs)-induced gene in macrophages and might be involved in downstream target genes induction. They considered NCOA5 as a transcription factor, but did not provide the experiment data to support this hypothesis. Studies on planarian and mice showed that NCOA5 was a conservative component of pluripotent stem cells and it was necessary for the regeneration and maintenance of planarian pluripotent stem cells (Böser *et al.*, 2013). Genomic analysis also showed that NCOA5 was associated with dermal hyperpigmentation in chicken (Hou *et al.*, 2020).

It has been found that NCOA5 is closely related to many human diseases. For example, apart from dilative nephropathies mentioned above, NCOA5 is also involved in the pathogenesis of Bechet's disease (BD) (Rustemoglu *et al.*, 2017), T2D (Gao *et al.*, 2013) and male mouse infertility (Gao *et al.*, 2019). NCOA5 polymorphism is associated with susceptibility to BD (Deng *et al.*, 2018; Rustemoglu *et al.*, 2017) and psoriasis (Zervou *et al.*, 2011). In addition, NCOA5 is also involved in the occurrence and development of many human cancers, such as hepatocellular carcinoma, breast cancer, thyroid cancer, etc. Its role in promoting or inhibiting cancer depends on the type of tissue. The functions and molecular mechanisms of NCOA5 in several cancers are summarized below.

NCOA5 and Cancer

NCOA5 and hepatocellular carcinoma

Because the early symptoms of Hepatocellular carcinoma (HCC) are not obvious, it is very difficult to find HCC patients in their early stages. Most HCC patients are diagnosed in advanced stages and the prognosis for these patients is poor, which lead to the higher mortality of HCC (Gerbes *et al.*, 2018; Llovet *et al.*, 2016). Many genes are involved in HCC initiation and progression (Yao *et al.*, 2021, Tian *et al.*, 2021). NCOA5 is one of the genes related to liver cancer development. By establishing *Ncoa5*$^{+/-}$ mice, Gao *et al.* (2013) found that *Ncoa5*$^{+/-}$ male mice spontaneously form hepatocellular carcinoma at 18 months old.

The role of NCOA5 in the progression of HCC is closely related to inflammatory cytokines and estrogen signals. Inflammation can promote the occurrence of HCC, while estrogen can prevent the development of HCC to some extent. It was found that compared with adjacent non-tumor tissues, the expression of NCOA5 in HCC tissues decreased significantly, however, the expression of the shortened NCOA5 lacking transcription activation domain increased significantly (Gao *et al.*, 2013). Compared with *Ncoa5*$^{+/+}$ male mouse livers, the mRNA and protein levels of IL-6 and TNF-α in Kupffer cells of *Ncoa5*$^{+/-}$ male mouse livers were dramatically increased, and the expression of *Socs3* mRNA and phospho-STAT3 (Tyr705) protein also increased significantly; the expressions of AR and FASN in livers were also significantly up-regulated at mRNA and protein levels (Gao *et al.*, 2013; Gao *et al.*, 2019). These factors contributed to the occurrence of HCC (Che *et al.*, 2020; He and Karin, 2011; He *et al.*, 2010; Johnson *et al.*, 2012; Ma *et al.*, 2008). IL-6 signaling pathway plays important role in HCC development. Through negatively regulating IL-6 expression, NCOA5 acted as a tumor suppressor in HCC. In mechanism, NCOA5, as a co-regulator of ERα, was recruited to the NF-κB site of IL-6 promoter after binding with ERα under the stimulation of estrogen, and negatively regulating the transcription of IL-6 induced by NF-κB in Kupffer cells (Gao *et al.*, 2013; Libermann and Baltimore, 1990). The deficiency of IL-6, which is the main activator of STAT3 signaling pathway in liver, can reduce the activation of STAT3 and inhibit HCC development (He and Karin, 2011; Naugler *et al.*, 2007). In the meantime, NCOA5 deficiency can enhance the recruitment of RNA Pol II in *IL-6* promoter and promote the transcription of IL-6 (Gao *et al.*, 2013). Lack of the suppression of NOCA5 on IL-6 expression will induce inflammatory reaction in liver. In the meantime, the up-regulated IL-6 will activates STAT3-SOCS3 and negatively regulates liver insulin signal that leads to glucose intolerance, steatosis and other traits in male mice. All of these changes form a tumor microenvironment suitable for HCC and promote the tumorigenesis (Gao *et al.*, 2013; He *et al.*, 2010). The expression of p21 is closely related to the development of HCC (Ehedego *et al.*, 2015; Marhenke *et al.*, 2014). Recent studies (Williams *et al.*, 2020) have found that NCOA5 deficiency can also up-regulate the expression of $p21^{WAF1/CIP1}$ mediated by p53 and NF-κB in hepatocytes, accompanied by the increase of pro-inflammatory chemokines CCL2, IL-6, and immunosuppressive cells, as well as the increased exhaust of CD8+ T cells, which can promote the formation of a pro-tumorigenic environment and the development of HCC.

NCOA5 can also affect HCC development through regulating cell cycle. It has been found that NCOA5 can inhibit the expression of cyclin B1 and increase cell

senescence triggered by DNA damage in HCC cells, which leads to cell cycle (G2/M phase) arrest, thus inhibiting cell proliferation and tumor growth (Liu *et al.*, 2017). The single nucleotide mutation of NCOA5 (T445A) can partially reduce the tumor growth inhibitory function of NCOA5, which promotes the development of HCC and increases the susceptibility of HCC to T2D comorbidity (Liu *et al.*, 2017).

Although a lot of evidence have proved that NCOA5 plays a tumor suppressor role in HCC, it also has been found to have oncoprotein function. He *et al.* (2018) reported that NCOA5 promoted epithelial-mesenchymal transition in HCC LM3 cells. Knockout of *NCOA5* in LM3 cells through CRISPR/Cas9 technology led to the increased expression of E-cadherin and the decreased expression of N-cadherin. Subsequently, the migration capability of LM3 cells was dramatically inhibited. In the meantime, the cancer stem cell features of LM3 cells are diminished. These results revealed that even in the same tumor, NCOA5 might play different roles due to the difference of the tumor microenvironment.

NCOA5 and breast cancer

Breast cancer is the most common type of cancer and one leading cause of cancer related death among women worldwide. The progression of breast cancer is strongly linked to chronic inflammation and the association between inflammatory pathways and breast cancer has been well-defined (Huang *et al.*, 2016). As a regulator of IL-6, NCOA5 is thought to be related to inflammation. The expression of NCOA5 in breast cancer tissues was significantly higher than that in normal tissues, and the high expression of NCOA5 was associated with a decreased overall survival in breast cancer patients (Xia *et al.*, 2021; Ye *et al.*, 2017). Ye *et al.* (2017) found that the high NCOA5 expression, old age (>60) and HER-2 expression were three independent high risk factors in luminal breast cancer. Moreover, the high NCOA5 expression alone is also an independent risk factor in HER-2 positive breast cancer patients (Xia *et al.*, 2021). Under the action of E2, NCOA5, as a co-activator of ERα, can be recruited to *RORA* promoter to promote the transcriptional activation of *RORA* (Sarachana and Hu, 2013). NCOA5 can also act as a co-regulator of RORA to regulate the aromatase gene *CYP19A1* which can locally produce estrogen (Sarachana and Hu, 2013). All these regulations established by NCOA5 will lead to the increased estrogen level in cells and finally promote the proliferation of breast cancer cells (Odawara *et al.*, 2009). On the other hand, *RORA* high expression can also promote the proliferation of breast cancer cells by stimulating the transcriptional activation of ERα and cyclin D1 induced by E2 (Dong *et al.*, 2010). Therefore, NCOA5 may be involved in regulating the proliferation of ER positive breast cancer cells by regulating the transcription activity of ERα and RORA. In addition, it was found that NCOA5 inhibited ERα-mediated *c-myc* transcription by interacting with the coding region of *c-myc* gene instead of the promoter in MCF-7 cells (Jiang *et al.*, 2004). It implied that NCOA5 might function as a tumor suppressor. Because of these contradictory reports, we are not clear about the exact role of NCOA5 in breast cancer development and more studies are needed in this aspect.

NCOA5 and colorectal cancer

It has been found that NCOA5 is up-regulated in human colorectal cancer (CRC) tissues and has the capability to promote CRC progression (Sun *et al.*, 2017). In mechanism, NCOA5 mainly participates in the regulation of CRC cell cycle by promoting the transition from G1 phase to S phase. NCOA5 significantly up-regulates cyclin D1 and MMP9 and down-regulates P27, thus promoting the proliferation, migration, and invasion of CRC cells. Knocking down NCOA5 can block G1 phase of CRC cell cycle and inhibit the above process. Therefore, NCOA5 may be a potential target for CRC treatment.

TABLE 2

Gene expression of NCOA5 in human tumors

Measurement	Change (N)	Pathology association	References
Hepatocellular carcinoma			
mRNA expression	Decrease in tumor (30)	ND	Gao *et al.* (2013)
Breast cáncer			
mRNA expression	Increase in tumor (20)	worse overall survival	Huang *et al.* (2016)
Esophageal squamous cell carcinoma			
Protein expression	low in 46.2% of samples (119)	worse differentiation, LNM+, advanced T status and stage	Chen *et al.* (2014)
Protein expression	Decrease in tumor (10)	ND	Chen *et al.* (2014)
Cervical cáncer			
mRNA expression	Decrease in tumor (37)	ND	Liang *et al.* (2019)
Protein expression	low in 79% of samples (71)	worse overall survival	Liang *et al.* (2019)
Papillary thyroid carcinoma			
mRNA expression	Decrease in tumor (17)	high risk of LNM	Zheng *et al.* (2018)
Osteosarcoma			
Protein expression	Decrease in tumor (145)	poor prognosis	Wu *et al.* (2018)
mRNA expression	Decrease in tumor (145)	poor prognosis	Wu *et al.* (2018)

Note: N, number of samples; ND, not determined; LNM, lymph node metastasis.

NCOA5 and other cancers

Esophageal squamous cell carcinoma (ESCC) is the most common type of esophageal cancer with poor prognosis and overall survival (Pennathur *et al*., 2009). Chen *et al.* (2014) found that the expression of NCOA5 in ESCC was decreased and the low NCOA5 expression led to unfavorable consequences for ESCC patients, such as tumor development, recurrence and lymph node metastasis (LNM). The function of NCOA5 in ESCC is involved in its regulation on IL-6. The low expression of NCOA5 can promote the expression of IL-6, and then activate STAT3 signaling pathway to facilitate ESCC progression (Chen *et al*., 2014; Sugimura *et al*., 2012). Similar to its function in ESCC, the expression of NCOA5 in human cervical squamous cell carcinoma is also significantly reduced. The downregulation of NCOA5 can promote the proliferation, migration and invasion of cancer cells by activating Notch3 signaling pathway, while the overexpression of NCOA5 has the opposite effects (Liang *et al*., 2019). The tumor suppressor role of NCOA5 was also found in papillary thyroid carcinoma (PTC) and osteosarcoma. The expression of NCOA5 in both cancers was reduced (Wu *et al*., 2018; Zheng *et al*., 2018). Low expression of NCOA5 often caused LNM for PTC patients (Zheng *et al*., 2018) and was not beneficial for patients survival (Wu *et al*., 2018). Therefore, studies have proved that NCOA5 plays an important role in the occurrence and development of human cancer and is a risk factor for poor prognosis and worse overall survival (Table 2).

Conclusion

NCOA5, as a co-regulator with both co-activation and co-repression capability on gene expression, plays bi-functional roles in cancer development. So far, NCOA5 has been revealed to be a tumor suppressor in most of cancers studied. Although the mechanism of NCOA5 function in suppressing HCC has been dissected, we know little about its function and mechanism in other cancers. Due to its complicated function in gene regulation, it should not be surprising that NCOA5 may have different roles in various cancers. Estrogen receptor activity is highly relevant to steroid hormone related cancers, such as breast cancer and prostate cancer. Orphan nuclear receptors (REV-ERBα and REV-ERBβ) are essential components of the circadian clock. The disruption of circadian clock frequently leads to cancer development (Shafi and Knudsen, 2019). NCOA5, as a co-regulator of estrogen receptor (ERα and ERβ), orphan nuclear receptor (REV-ERBα and REV-ERBβ) and liver X receptor that are involved in many important life activities, is worthy of our more studies on its roles in cancer as well as in other important physiological processes. These studies will deepen our understanding on the function of NCOA5 and underlying mechanisms and help us to develop a potential drug target for curing diseases that is related to NCOA5 in future.

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