p160 nuclear receptor coactivator family members and their role in rare fusion-driven neoplasms (Review)

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Abstract. Gene fusions with translocations involving nuclear receptor coactivators (NCoAs) are relatively common among fusion-driven malignancies. NCoAs are essential mediators of environmental cues and can modulate the transcription of downstream target genes upon binding to activated nuclear receptors. Therefore, fusion proteins containing NCoAs can become strong oncogenic drivers, affecting the cell transcriptional profile. These tumors show a strong dependency on the fusion oncogene; therefore, the direct pharmacological targeting of the fusion protein becomes an attractive strategy for therapy. Currently, different combinations of chemotherapy regimens are used to treat a variety of NCoA-fusion-driven tumors, but given the frequent tumor reoccurrence, more efficient treatment strategies are needed. Specific approaches directed towards inhibition or silencing of the fusion gene need to be developed while minimizing the interference with the original genes. This review highlights the relevant literature describing the normal function and structure of NCoAs and their oncogenic activity in NCoA-gene fusion-driven cancers, and explores potential strategies that could be effective in targeting these fusions.

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Abbreviations: Abl, Abelson murine leukemia virus; AHRR, aryl-hydrocarbon receptor repressor; AML, acute myeloid leukemia; AR, androgen receptor; ARMS, alveolar rhabdomyosarcoma; ASO, antisense oligonucleotide; Bcl-2, B-cell lymphoma 2; bHLH, basic helix-loop-helix domain; C2C12, mouse skeletal muscle cell line; CARM, coactivator associated arginine methyltransferase; CBP, CREB binding protein; CYP1, cytochrome P450 family 1; ERMS, embryonal rhabdomyosarcoma; ESR1, estrogen receptor 1; GREB1, growth regulating estrogen receptor binding 1; GTF2I, general transcription factor III; HEY1-NCoA2, gene fusion in mesenchymal chondrosarcoma; IL, interleukin; KAT, acetylase; MAPK, mitogen-activated protein kinase; MCS, mesenchymal chondrosarcoma; NCoA, nuclear receptor coactivator; NR, nuclear receptor; PAS, Per-Arnt-Sim domain; PDGFR, platelet-derived growth factor receptor; PDX, patient derived xenograft; PRMT, protein arginine methyltransferase; PROTAC, proteolysis-targeting chimera; RID, receptor interaction domain; TBP, TATA-box binding protein; TF, transcription factors; TGF, transforming growth factor; UTROSCT, uterine tumor resembling ovarian sex cord tumor

Key words: fusion-driven cancers, oncogenic fusions, nuclear receptor coactivators, p160

Contents

1. Background

Pediatric cancers typically present similar pathohistological features to adult cancers, but at the same time, they can have a strikingly different molecular signature. Therefore, successful treatment of adult and pediatric cancers can greatly differ (1,2). One of the most representative molecular characteristics of pediatric cancers is a low mutational burden, where either a single gene can be highly mutated or a gene fusion can be formed as a byproduct of genomic rearrangements (3,4). Gene fusions are the most frequent oncogenic driver (and often unique driver) of many subtypes of pediatric cancer and are thus typically used as a biomarker for unequivocal diagnosis (1,5). In pediatric lymphomas, leukemias, and soft tissue sarcomas, gene fusions are present in 90, 50, and 30% of all cases, respectively (6). Inactivation or knockout of the gene fusion can directly inhibit tumor growth, implying that drugs selectively targeting the chimeric oncoprotein should be developed (7).

Gene fusions can contribute to oncogenicity by generating new chimeric proteins that can result either in the loss of function of the original gene or the gain of function of the new

chimeric protein. The chimeric protein expression can diverge into rearrangements of critical molecular pathways and thus disturb normal cell function. Furthermore, the expression of the fusions can also affect the expression profile of oncogenes and/or tumor suppressor genes (3,4). The combinations and distributions of preserved domains in gene fusions seem to be non-random (8). In general, a DNA-binding domain is at the 3'-end of a fusion oncogene, and a potent proto-oncogene (tyrosine kinase, transcription factor, or a histone modifier) is at the 5'-end (9).

Nuclear receptor coactivators (NCoA) function as a critical link between activated nuclear receptors (NR) and the transcription machinery. They are responsible for transducing the NR signals in the presence of the ligand, resulting in the induction of the transcription of NR target genes (10,11). A subset of NCoAs belong to the p160 coactivator family and are essential coregulators in several physiological processes, such as inflammatory and metabolic pathways, where they transform the environmental signals into epigenome alterations and transcriptional responses (12). When a p160 family member becomes a partner gene in a new gene fusion, the new chimeric protein becomes a strong oncogenic driver through the regulation of transcription. Oncogenic fusions with p160 family members at their C-terminal are very frequent in a variety of pediatric malignancies (13-15). These domains contain large intrinsically disordered regions that lack hydrophobic pockets where small molecules could bind, making chimeric proteins impossible to directly target with small molecule inhibitors (16).

Here we provide an overview of the known literature on NCoA1/2/3 structure, regulation, and function. Next, we explore and comment on the role of p160 family members as a fusion partner gene and a contributing factor in tumorigenesis. We are focused on cancers that have at least one reported gene alteration involving a p160 family member fused to another gene, and try to understand the common approaches that could target these types of cancers. We then further summarize recent research on these tumors, and explore current and future treatment possibilities. Lastly, we provide insights into technologies that could be utilized to directly target these undruggable oncogenic fusions.

2. The structure and function of the p160 coactivator family

The p160 coactivator family consists of three members: NCoA1 (SRC1), NCoA2 (SRC2/TIF2/GRIP1), and NCoA3 (SRC3/p-CIP/RAC3/ACTR/AIB1/TRAM-1) (17,18). In humans, these genes present 54-58% of sequence identity, and they are believed to have originated from gene duplication events (19) (Fig. 1). The most conserved regions among all three members are the basic helix-loop-helix (bHLH) and Per/Arnt/Sim (PAS) domains, commonly annotated as bHLH/PAS at the N-terminal end (20).

bHLH domains are known to mediate dimerization with other transcription factors as well as DNA binding, signal sensing, and signal transduction (20,21). Nonetheless, DNA binding activity still hasn't been described for p160 family members. The bHLH-PAS domain of p160 family members is well characterized as a protein-protein interaction region, capable of binding to secondary coregulators (including CoCoA, GAC 63, and Flii), and transcription factors such as p53, MEF2C, TEAD2, and STAT (20-22) (Fig. 2A). The PAS-B domain has been shown to interact with LXXLL motifs, where L represents leucine and X stands for any amino acid. These LXXLL motifs are located on the C-terminal domains of all three NCoA homologs, where they contribute to their homo- and hetero-dimerization, as well as dimerization with other proteins containing LXXLL (23,24).

The serine and threonine-rich region (S/T-rich) that follows the bHLH-PAS domain is a hotspot for posttranslational modifications, important for p160 protein regulation (17). Immediately after the S/T-rich region lies the receptor interaction domain (RID) that contains three LXXLL motifs, called nuclear receptor boxes (NR boxes) (18). The three NR boxes are necessary for binding to a hydrophobic pocket in the Nuclear Receptor ligand-binding domain (LBD). This interaction represents the first physical contact between NR and the coactivator before the signal is transmitted to secondary coregulators (22).

The C-terminal region of p160 family members consists of two activation domains, called AD1 and AD2, which act as potent mediators of epigenetic enzymatic activities required to modulate gene transcription (17,25). The AD1 domain [also called CBP-interaction domain (CID) or p300-interaction domain (PID)], recruits secondary coregulators which are responsible for chromatin remodeling. The AD1 domain also contains LXXLL motifs important for interaction with CBP/p300, AP1, members of the bHLH-PAS protein family such as AHR, ARNT/HIF-1β, and transcription factor NF-κB amongst others (26,27). One of the roles of the AD1 is to recruit components of the RNA Pol II transcription preinitiation complex and RNA helicase A, which initiate the transcription (22,28). The AD1 can also recruit histone methyltransferases such as coactivator-associated arginine methyltransferase 1 (CARM1) and protein arginine N-methyltransferase 1 (PRMT1), leading to chromatin remodeling and decondensation (29).

Immediately after the AD2 domain, there is a weak intrinsic histone acetyltransferase (HAT) activity contributing to the acetylation of the downstream transcriptional machinery components (30). Due to the HAT activity, the NCoA homologs have HAT names, such as KAT13A for NCoA1, KAT13B for NCoA2, and KAT13C for NCoA3 (31). Certain splicing isoforms (for example, NcoA1a) contain an additional LXXLL motif in their extreme C-terminal end, contributing to NR binding (32,33). Finally, a Q-rich region with abundant glutamine repetitions lies between AD1 and AD2 and is important for the mediation of ligand-independent NR signal transduction activity (34,35).

The structural prediction by Alpha Fold for NCoA1 shows a structured bHLH/PAS domain, while the rest of the protein presents a high component of unstructured regions (36) (Fig. 2B). Structural predictions of the other p160 family members show a similar pattern. The crystal and NMR structures of the NCoA1 PAS-B domain in a complex with a STAT6-derived peptide were solved (37,38) (Fig. 2C). Another NMR structure of the AD1 domain of NCoA1 showed details of the interaction with a peptide derived from the CREB binding protein (CBP) (Fig. 2D). Additional structures of small

Figure 1. Structural and functional domains of p160 protein family members. At the N-terminal end, there is a conserved bHLH and a PAS region. Immediately after is the S/T, followed by the nuclear RID in the center. On the C-terminal, there is a large area of intrinsically disordered domains: Two ADs (AD1 and AD2) separated by a glutamine-rich region (Q). The LXXLL motifs are depicted as black boxes and are indicated by numbers in each NCoA. There is a weak HAT activity mapped to the end of the AD2 region. The numbers at the end of the C-terminal end represent the length of each protein. bHLH, basic helix-loop-helix; PAS, Per-Arnt-Sim; S/T, serine and threonine repetition region; RID, receptor-interacting domain; AD, activation domain; HAT, histone acetyltransferase.

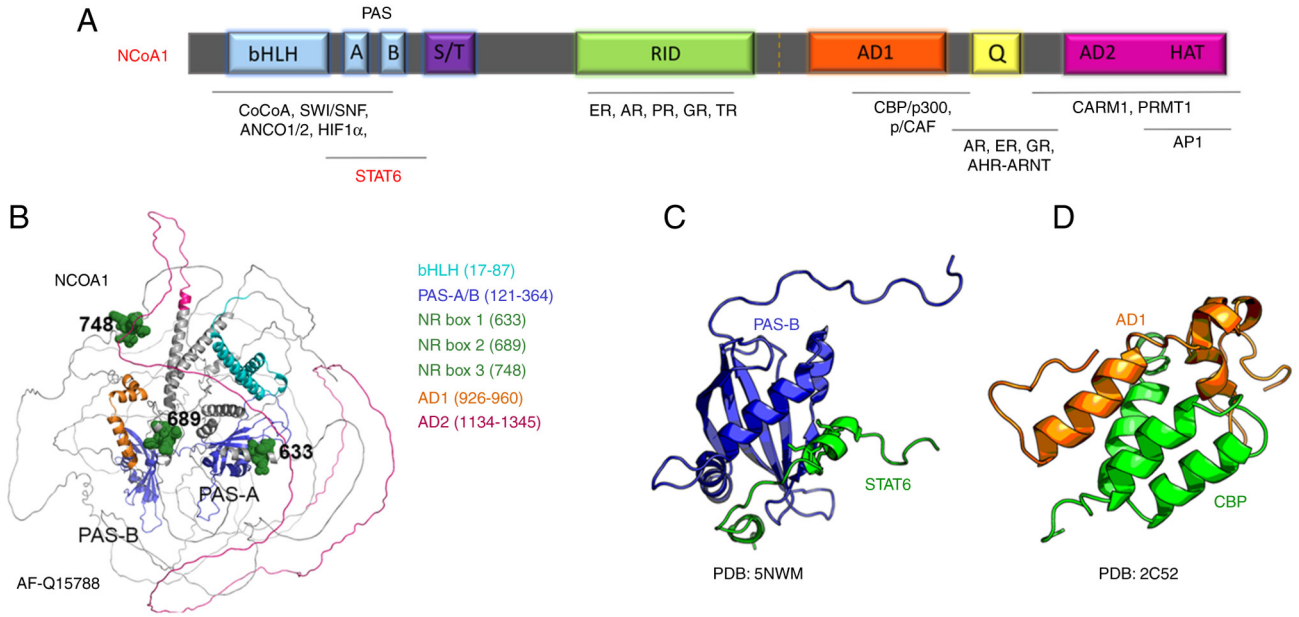

Figure 2. The p160 family members binding protein partners and known and predicted structures of p160. (A) Known proteins that bind to the p160 family members with NCoA1 as an example. STAT6 is color-coded and matches NCoA1 as it binds to its PAS A/B domain. Other binding proteins are depicted in black and they bind to different p160 family members. (B) The structural prediction by Alpha Fold for NCoA1 with structured bHLH/PAS domain. The rest of the protein is highly unstructured. The Alpha Fold ID number is AF-Q15788. (C) The NMR structure of the NCoA1 PAS-B domain in a complex with a STAT6 derived peptide. The PDB ID number is 5NWM. (D) NMR structure of the AD1 domain of NCoA1 (920-970) in complex with a peptide derived from the CREB binding protein (CBP) (2059-2117). The PDB ID number is 2C52. bHLH, basic helix-loop-helix; PAS, Per-Arnt-Sim; S/T, serine and threonine repetition region; RID, receptor-interacting domain; AD, activation domain; HAT, histone acetyltransferase.

peptides of NCoA1/2/3 with protein interactors are available and demonstrate the ability of these proteins to function as binding platforms for multiple proteins to promote epigenetic modifications and transcription.

The stability and activity of p160 proteins can be modulated by post-translational modifications (PMTs), such as phosphorylation, sumoylation, ubiquitination, acetylation, and methylation (39,40). Several phosphorylation sites have been identified in Ser/Thr-Pro motifs, which are targets of proline-directed kinases, including CDKs, MAPK, cAMP-PKA, and NF-κB kinase-mediated signaling pathways (39,41,42). The majority of these Ser/Thr phosphorylation sites are located either in the S/T-rich region, while some sites reside in the Q-rich domain at the C-t. Changes in phosphorylation state have been shown to influence the NCoA preference for different NRs (42-44). In addition, phosphorylation can modulate the interaction with CBP/p300, and in some cases also induce the degradation of some p160 members (41,45).

Tyrosine phosphorylation has also been implicated in the regulation of NCoAs. For example, phosphorylation at Tyr-1357 by c-Abl kinase was reported to increase the binding of NCoA3 to p300 and ERα, while decreasing its association with the repressor CARM1. This phosphorylation site is conserved in NCoA2 while missing in NCoA1 (46).

Ubiquitination plays an important role in the stability of p160 family members. The addition of a long polyubiquitin

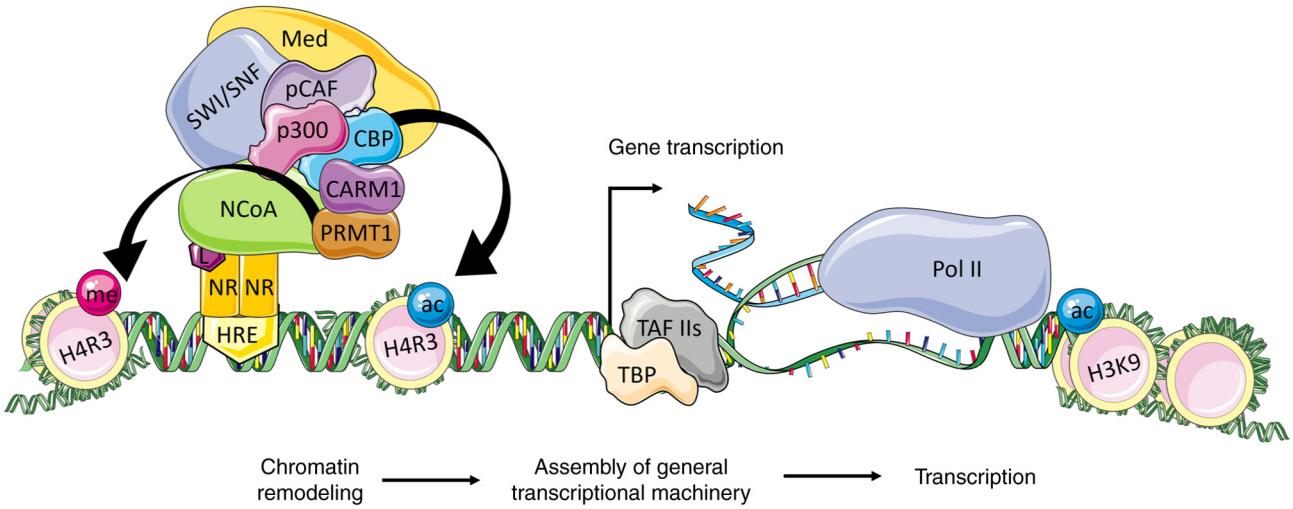

Figure 3. The NCoA coactivation of transcription in the ligand-dependent pathway. The p160 family members interact via the RID domain with the ligand-activated nuclear receptor that is bound to its HRE. The activated NCoA binds CBP/p300 to its AD1 domain and CARM1/PRMT1 to its AD2 domain. The CBP and p300 acetylate histones and facilitate the recruitment of SWI/SNF complex for further chromatin remodeling. This leads to changes in the DNA topology, exposing the regulatory DNA sequences to the basal transcription machinery. The Med is activated by p300 and NCoA and facilitates the recruitment of TBP and TAFs to form the link with RNA polymerase II and initiate the transcription of target genes. NR, nuclear receptor; HRE, hormone-responsive elements; L, ligand; NCoA, nuclear receptor coactivator; CBP, p300 and pCAF, histone acetyltransferases; CARM1 and PRMT1, histone methyltransferases; SWI/SNF, ATP-dependent chromatin remodeling complex; Med, mediator complex; TBP, TATA-box-binding protein; TAFs, TBP associated factors; ac, acetylation; me, methylation; H3K9, histone H3 Lys9; H4R3, H4 Arg3.

chain to the C-terminal region of p160 proteins mediates their proteasomal degradation via the 26S ubiquitin-proteasome pathway. The AD2 domain in NCoA2 was shown to be essential for 26S proteasome degradation (47). Sumoylation of p160 family members directs the subcellular localization and can affect protein-protein interactions (48-50), while acetylation can have an impact on the regulation of hormonal signaling (51). The methylation of p160 family members occurs by CARM1 recruitment, leading to disruption of CBP/p300/p160 interactions and transcriptional repression (52).

In short, the binding of the NR to a specific ligand induces conformational changes in its ligand binding domain (LBD), enabling the dissociation of corepressors, and binding of NCoAs through its LXXLL motifs. This interaction is essential to mediate the NR responses (53). Once the NR-bounded NCoA is activated, it recruits CBP, p300, p/CAF, and other transcriptional factors, leading to acetylation modulation of core histones, and chromatin decondensation (54). Since histone acetylation is not sufficient to activate the transcription of target genes, NCoA also serves as an important scaffold for the assembly of the transcription machinery and recruitment of transcription factors (TFIIB, TBP, TAFs, TFIIH) at the promoter and/or enhancer regions of NR targeted genes (55) (Fig. 3).

3. The role of p160 protein domains in fusion-driven cancers

All members of the p160 coactivator family have been identified as partner genes in many aggressive gene-fusion-driven cancers. Usually the truncated p160 members are positioned at the C-terminal of the chimeric protein, where they retain their C-terminal domains (AD1, Q-rich region, and AD2). The N-terminal region of the chimeric protein is mostly a DNA-binding gene partner. This makes the N-terminal domains of the newly generated gene fusion a facilitator of the DNA binding to target locations, while the C-terminal domains can recruit CBP/p300 and other transcription factors, resulting in the reprogramming of the cellular transcriptional profile (Table I).

The p160 RID domain is usually missing in the fusions, making the chimeric proteins less likely to interact with the ligand-dependent NR signaling pathways. In contrast, ligand-independent pathways that rely on the Q-rich region and/or LXXLL motifs could still be active (10,11). For instance, in the case of several NRs, it has been reported that the C-terminal LXXLL motifs in p160 members can contribute to nearly wild-type binding efficiency to the LBD domain in the NR such as estrogen receptors (ER), glucocorticoid receptors, retinoic acid receptors, and retinoic X receptors (54). Furthermore, the splicing isoform of NCoA1 (NCoA1a) is capable of binding glucocorticoid and androgen receptors (AR) solely through its additional extreme C-terminal LXXLL motif (32). These examples suggest that the C-terminal domain of p160 members could mediate some of the NR-dependent functions even in the absence of their RID domain, which could be preserved in the p160-fusion-driven malignancies.

4. Oncogenic gene fusions with NCoA as a gene partner

Among the three p160 family members, NCoA2 is the gene most frequently involved in the formation of oncogenic fusions, predominantly in pediatric cancers (Table I). These fusions have been detected in mesenchymal chondrosarcoma (56), variants of rhabdomyosarcoma (57), soft tissue angiofibroma (58), kidney spindle cell sarcoma (59), uterine adenosarcoma (60), ovarian sex cord tumor (61), biphenotypic sinonasal sarcoma (62), and myelogenous leukemia/fibroblastic

Table I. Fusion oncogenes with p160 family members as a partner gene and their corresponding tumor type.

First author, year	Gene fusion	Translocation	Type	(Refs.)
Wachtel, 2004	PAX3-NCoA1	t(2;2)(p23;q35)	Alveolar habdomyosarcoma	(64)
Yoshida, 2004	PAX3-NCoA2	t(2;8)(q36;q13)/ t(2;8)(q35;q13)	Alveolar/embryonal rhabdomyosarcoma	(13)
Wachtel, 2004	NCoA1-PAX3	t(2;2)(q35;p23)	Rhabdomyosarcoma	(64)
Alaggio, 2006	SRF-NCoA2	t(6;8)(p12;q11)	Spindle cell rhabdomyosarcoma	(92)
Tan, 2020	TEAD1-NCoA2	t(8;11)(q13;p15)	Spindle cell rhabdomyosarcoma	(116)
Alaggio, 2004	VGLL2-NCoA2	t(6;8)(q22;q13)	Spindle cell rhabdomyosarcoma	(92)
Avenarius, 2020	WHSC1L1-NCoA2		Spindle cell rhabdomyosarcoma	(117)
Argani, 2018	MEIS1-NCoA2	t(2;8)(p14;q13.3)	Spindle cell rhabdomyosarcoma	(59)
Bennett, 2020	ESR1-NCoA2	t(8;20)(p13.3;q13.3)	Spindle cell rhabdomyosarcoma	(118)
Piscuoglio, 2016	ESR1-NCoA3	t(6;20)(q25.1;q13.3)	Müllerian adenosarcomas	(60)
Bekers, 2017	GTF2I-NCoA2	t(7;8)(q11;q13)	Soft tissue angiofibroma	(58)
Panagopoulos, 2016	NCoA2-ETV4	t(8;17)(q13;q21)	Soft tissue angiofibroma	(119)
Bekers, 2017	AHRR-NCoA2	t(5;8)(p15;q13)	Soft tissue angiofibroma	(58)
Teramura, 2020	AHRR-NCOA3	t (5;8) (p15;q13)	Spindle cell sarcoma	(120)
Zhou, 2020	ETV6-NCoA2	t(8;12)(q13;p13)	Acute myeloid leukemia	(121)
Zhuravleva, 2008	MOZ-NCoA2	t(8;16) (p11;p13)	Acute myeloid leukemia	(122)
Esteyries, 2008	MOZ-NCoA3	t(8;20)(p11;q13)	Acute myeloid leukemia	(123)
Wang, 2012	HEY1-NCoA2	t(8;8)(q13;q21)	Mesenchymal chondrosarcoma	(56)
Chang, 2020	GREB1-NCoA2	t(2;8)(p25;q13)	Uterine sarcoma	(124)
Lacambra, 2019	PRRX1-NCoA1	t(1;2)(q24.2;p23.3)	Fibroblastic neoplasms	(63)
Lacambra, 2019	PRRX1-NCoA2	t(1;8)(q24.2;q13.3)	Fibroblastic neoplasms	(63)
Yu, 2016	LACTB2-NCoA2	t(8;8)(q13;q13)	Colon-Rectum adenocarcinoma	(125)
Cao, 2019	NCoA1-ALK		Lung adenocarcinoma	(126)
Yoshihara, 2015	NCoA2-LEPROTL1	t(8;8)(p12;q13)	Lung adenocarcinoma	(127)
Yoshihara, 2015	NCoA2-XKR9	t(8;8)(q13;q13)	Lung adenocarcinoma	(127)
Yoshihara, 2015	NCoA2-NCALD	t(8;8)(q13;q22)	Breast adenocarcinoma	(127)
Yoshihara, 2015	NCoA2-ARFGEF1	t(8;8)(q13;q13)	Breast adenocarcinoma	(127)
Robinson, 2011	NCoA2-ZNF704	t(8;8)(q13;q21)	Breast adenocarcinoma	(128)
Yoshihara, 2015	RAB10-NCoA1	t(2;2)(p23;p23)	Breast: Adenocarcinoma	(127)
Yoshihara, 2015	SH2D6-NCoA2	t(2;8)(p11;q13)	Bladder transitional cell carcinoma	(127)
Yoshihara, 2015	NCoA2-ST18	t(8;8)(q11;q13)	Melanoma	(127)

neoplasms (63). The other two family members have likewise been implicated in mesenchymal lesions, but interestingly they are mostly present in adult tumors. Translocation in NCoA1 and NCoA3 has been observed in rhabdomyosarcoma (NCoA1) (64), uterine adenosarcoma (NCoA3) (65), ovarian sex cord tumor (NCoA3) (61), biphenotypic sinonasal sarcoma (NCoA1) (62), and myelogenous leukemia/fibroblastic neoplasms (NCoA1) (63), among others.

Mesenchymal chondrosarcoma. Mesenchymal chondrosarcoma (MCS) is a rare neoplasm that is characterized by the presence of primitive mesenchymal cells mixed with sections of cartilage differentiation. MCS typically arises from bone, and current treatment includes surgical resection coupled with cytotoxic chemotherapy (66). MCS is one of the most aggressive subtypes of chondrosarcoma, evidenced by low survival rates and limited treatment options (67). MCS presents similar histological features to many other soft tissue sarcomas, making its correct diagnosis significantly challenging (2). The discovery of a recurrent oncogenic fusion between HEY1 and NCoA2, occurring in over 80% of MCS samples, made it possible to distinguish MCS and has been used as a diagnostic biomarker (56,68). In HEY1-NCoA2 fusion, the bHLH domain of HEY1, which strongly binds DNA is preserved at the N-terminal end, while at the C-terminal AD1, Q-rich, and AD2 domains of NCoA2 are preserved (69).

Pioneering IHC staining-based studies of MCS tumor samples showed reactivity for PDGFR-α, PDGRF-β, c-KIT,

Bcl-2, cPKC-α, TGF- β1, SOX9, c-Jun, p-JNK, p-p38MAPK, IL-6, MMP2, TIMP2, and collagen types II and X (68,70), suggesting that these pathways could be targeted in new potential therapeutic approaches. A recent study used iPSC-MSCs to characterize the fusion binding sites in the genome via ChIP-seq, and the transcriptional modifications induced. The authors found that the DNA binding profile of the HEY1-NCoA2 fusion is very similar to the binding profile of HEY1, confirming the hypothesis that HEY1 directs DNA binding. However, HEY1 is typically a transcriptional repressor, while the NCoA2 activation domains preserved in the fusion result in transcriptional activation of these HEY1-targeted genes. The HEY1-NCoA2 fusion binds to promoter regions of the genes HES1, PDGFB, PDGFR-α, BCL-2, and SOX4. These results are consistent with previous findings of MCS biology and could help to develop new effective targeted therapies for this disease (71).

A recent study showed that the expression of HEY1-NCoA2 gene fusion in human primary chondrocytes promoted their proliferation, enhanced the expression of PDGFR-α, PDGRF-β, SOX9, LAMTOR1, MTOR, RHEB, PKC-α at the transcriptional level and the expression of FGFR1, ABL1, AXL, COL2A1, PDGFR-α, and PDGRF-β at the protein level (72). When cells expressing the fusion were treated with the multi-kinase inhibitor imatinib mesylate (targeting ABL, PDGRF-β, and c-KIT), a targeted reduction in the cell population expressing the fusion was observed. Interestingly, patient derived xenograft mouse models (PDX) of MCS also responded to imatinib mesylate treatment, suggesting that HEY1-NCoA2 fusion-expressing cells rely on signaling pathways that are inhibited by this multikinase inhibitor (72). An additional study performed in a HEY1-NCoA2 expressing MCS cell line demonstrated that BCL-2 inhibitors can sensitize MCS cells to chemotherapy, which could have clinical importance, as MCS tumors have shown a high reoccurrence rate after chemotherapy treatment (73).

A mouse model derived from mice embryonic osteochondrogenic cells transduced with the HEY1-NCoA2 fusion presented high rates of tumor development when implanted subcutaneously in nude mice. The tumors recapitulated morphological and molecular features of human mesenchymal chondrosarcoma, including nuclear expression of SOX9, a master regulator of chondrogenic differentiation. The cells expressing the fusion presented upregulation of Notch signaling, HEY1, and HES1. Single cell analysis of mouse mesenchymal chondrosarcoma suggested that the fusion expression results in incomplete chondrogenic differentiation, while ChIP seq analysis evidenced an association of the HEY1-NCoA2 fusion with active enhancers and open chromatin marks. A protein interaction with the Runx2 transcription factor was identified, and co-regulation of transcripts by these two proteins seems to be important for the altered transcriptional profile observed in MCS. Finally, the authors explored the efficacy of HDAC inhibitors to target *in vivo* and *in vitro* MCS models and found that treatment of tumor cells with panobinostat effectively reduced their growth and increased the apoptosis (74).

Angiofibroma of soft tissue. Soft tissue angiofibroma is typically a benign fibrovascular tumor that arises in the deep soft tissue of the lower extremities and is characterized by the proliferation of spindle cells with abundant collagenous stroma and prominent branching thin-walled vessels. These tumors stain positive for epithelial membrane antigen (EMA), desmin, CD34, CD68, CD163, smooth muscle actin (SMA), and ER. Surgical resection is usually sufficient for the successful management (75). In this tumor a gene fusion was identified between the Aryl Hydrocarbon Receptor Repressor (AHRR) and NCoA2, forming AHRR-NCoA2 (76). The AD1, Q-rich, and AD2 domains of NCoA2 are preserved and fused to the N-terminal region of AHRR, which includes a bHLH/PAS domain, important for dimerization and DNA targeting (77).

The fusion of a repressor with the transactivation domains of a p160 family member is expected to result in the activation of genes that would normally be repressed by the AHRR. Consistent with this hypothesis, a study using soft tissue angiofibroma samples expressing the fusion gene found overexpression of AHR target genes or genes associated with AHR signaling, including CYP1A1, CYP1B1, and genes encoding toll-like receptors (77). Particularly the overexpression of CYP1A1 in many angiofibroma samples has recently led to a proposal to utilize CYP1A1 as a diagnostic marker for these tumors (78).

In other rare cases of soft tissue angiofibroma, other gene fusions were also detected including GTF2I-NCoA2 (58), GAB1-ABL1 (58), and more recently, AHRR-NCoA3 (79).

Acute myeloid leukemia. Acute myeloid leukemia comprises a group of heterogeneous cancers that typically harbor acquired somatic mutations or genomic rearrangements. Translocations involving chromosome 8 comprise approximately 2% of AML cases and include several gene fusions with transcriptional coactivators, such as MOZ-p300 and MOZ-NCoA2 (14,80,81). Monocytic leukemia zinc finger (MOZ) belongs to the MYST family of histone acetyltransferases, where in MOZ-NCoA2 fusion the two N-terminal domains of MOZ, C4HC3 zinc finger domain, and the HAT domain are preserved, while NCoA2 keeps its C-terminal activation domains (80). The expression of MOZ-NCoA2 was shown to be sufficient to immortalize myeloid progenitors *in vitro* and to induce AML *in vivo*, driven by the critical interaction between MOZ-NCoA2 and p300/CBP (80,82). In addition, the MOZ-NCoA2 fusion was shown to repress cell senescence in mice (83). This oncogenic fusion results in the loss of NCoA2's ability to respond to NR activation, while constitutively enhancing transcription of MOZ target genes (80).

Several studies focused on dissecting the mechanisms by which this gene fusion promotes tumorigenesis. The bromodomain containing protein Brpf1 was identified to direct the MOZ-NCoA2 fusion to the target loci, while M-CSFR and STAT5 signaling have been shown to contribute to clonal expansion and stem cell maintenance in these tumors (84-86). A recent study provided evidence of a connection between transcription factor MLL and the MOZ-NCoA2 fusion, resulting in the constitutive activation of CpG-rich promoters, including higher histone acetylation (HK329ac) at the Hox and Myc loci. The histone methyltransferase DOT1L was also identified as an important component of this system, as it helps to maintain the transcriptionally active state of chromatin. Inhibition of DOT1L and MLL induced differentiation of MOZ-NCoA2 transformed cells, whereas inhibition of p300/CBP activity induced cytotoxicity (87).

Another study using an AML mouse model expressing the MOZ-NCoA2 fusion suggested that the components of the Polycomb repressive complex 1 (PRC1) and E3 ubiquitin-protein ligase (Ring1A, and Ring1B) maintain the stemness of cells in AML (88). It has also been suggested that the recruitment of lysine demethylase KDM4C by MOZ-NCoA2, results in the removal of repressive methylation marks, promoting the opening of chromatin. In parallel, recruitment of PRMT1 leads to a high level of H4R3me2, also promoting the opening of chromatin at the MOZ-NCoA2 binding loci, causing leukemia progression (89).

Rhabdomyosarcoma. Rhabdomyosarcoma (RMS) is a high-grade malignant neoplasm of skeletal myoblast-like cells and is the most common form of soft tissue sarcoma in children (90). RMS is divided into four subgroups: embryonal rhabdomyosarcoma (ERMS), alveolar rhabdomyosarcoma (ARMS), spindle cell/sclerosing rhabdomyosarcoma, and pleomorphic rhabdomyosarcoma (91). About 70% of ARMS are driven by gene fusions involving PAX3/7 and FOXO1. However, PAX1-NCoA1/2 fusions have also been detected in some cases of ARMS and ERMS. The *in vitro* studies on murine cell lines grown in soft agar colony assays showed a transforming activity of fusions that contain NCoA1/2 fusion partner, where the presence of the NCoA's transactivation domain was crucial for the transformation of cells (57,64). In another study where the mouse myoblast cell line C2C12 was transduced with PAX3-NCoA2, the fusion protein acted as a transcriptional activator of PAX3-regulated genes. Differentiation into myotubules was restrained, while cells exhibited higher proliferation rates, motility, and induction of cell cycle progression. Mice with injected transduced C2C12 cells were able to form tumors that shared pathological features with ERMS samples. In comparison with a similar model harboring the PAX3-FOXO1A fusion gene, the PAX3-NCoA2 fusion presented a less aggressive phenotype (13).

Besides PAX-NCoA fusions, other transcription factors involved in skeletal muscle differentiation were also reported in cases of spindle cell rhabdomyosarcoma, such as SRF-NCoA2, TEAD1-NCoA2, and VGLL2-NCoA2 (91-93). In all fusions mentioned above, the NCoA1/2 portion retains the C-terminal AD1, Q-rich, and AD2 domains (57). The presence of these gene fusions in spindle cell RMS cases seems to be correlated with a more favorable prognosis when compared with cases that harbor MYOD1 mutations, another common marker of spindle cell RMS (94).

Uterine tumors resembling ovarian sex-cord tumors. Uterine tumors resembling ovarian sex-cord tumors (UTROSCT) are rare mesenchymal neoplasms of unclear histogenesis. Morphologically, UTROSCT presents features of sex cord elements, and tumor cells can be arranged in cords, trabeculae, tubules, clusters, or sheets that can present a reticular appearance (95). Similar to MCS and RMS, it has been suggested that malignant UTROSCT cells derive from pluripotent mesenchymal cell precursors (96-99). UTROSCT can harbor gene fusions with NCoA as a C-terminal or N-terminal gene partner (15). In comparison to previously described tumors which predominantly occur in a pediatric population, these tumors mainly affect middle-aged women (15,96).

Molecular analysis of 26 UTROSCT samples using FISH and a targeted RNA sequencing method detected NCoA1/3 rearrangements with either ESR1 (estrogen receptor 1) or GREB1 (growth regulating estrogen receptor biding 1) in 81.8% of tumor samples, with the most common gene fusion being ESR1-NCoA3 (15). GREB1 and ESR1 are key factors in the sex hormone pathway and are highly expressed in uterine tissue. Cells of UTROSCT tumors harboring fusion with GREB1-NCoA2 have larger morphology, are more mitotically active and exhibit more aggressive behavior (100). Because of the high occurrence of NCoA1/3 gene fusions in those tumors, it has been suggested that they could be used for the diagnosis of endometrial stromal neoplasia with sex cord-like differentiation (15). More recently, an additional fusion between GTF2A1 (general transcription-initiation factor IIA, subunit 1) and NCoA2 was detected in UTROSCT, which further expands the molecular rearrangements observed in these tumors (101). The ESR1-NCoA2/3 gene fusion can also be present in rare Müllerian adenosarcomas in both benign epithelial and malignant mesenchymal components (60,65,99).

A recent study of a 23-patient cohort showed inconsistent expression of sex cord markers, epithelial markers, smooth muscle markers, and hormone receptors in the different tumor samples analyzed by immunohistochemistry. Expression of CD56, WT1, SF-1, and CD99 was detected in a high percentage of analyzed samples, and diffused expression of ER and PR was detected in all cases. Although there was a high molecular variability amongst samples, 5 different types of gene fusions were detected, all containing NCoA fusion partners with GREB1-NCoA2 fusions being the most common (102,103). A recent study found that malignant UTROSCT is more likely to have higher mitotic activity, high expression of stromal PD-L1, and a gene alteration involving NCoA2 (104).

5. Perspectives on new and existing therapies

It has been shown that cancer cells can be addicted to the fusion oncogenes. Especially in pediatric tumors, fusion depletion can lead to cancer cell death, indicating that loss of a fusion reverses the malignant progression (105). This feature makes NCoA-oncogenic fusions attractive therapeutic targets. However, most NCoA-fused oncogenes retain intrinsically disordered domains of C-terminal NCoA partners, or even both fusion partners, which makes them difficult to target with small molecules (16). In addition, there is a tight regulation of p160 family members' physiological activities, as they play an important role in sustaining normal cell homeostasis. Therefore, targeting p160 members in gene fusions should be specific to the fusion protein only.

The management of pediatric tumors, driven by NCoA-fusion genes usually comprises surgical resection and chemotherapy. Unfortunately, these treatments have often shown to be ineffective, due to recurrence and the development of resistance. Nonetheless, in recent years new creative therapeutic approaches have emerged, that have the potential to bring new therapeutic opportunities, as we describe in the next sections.

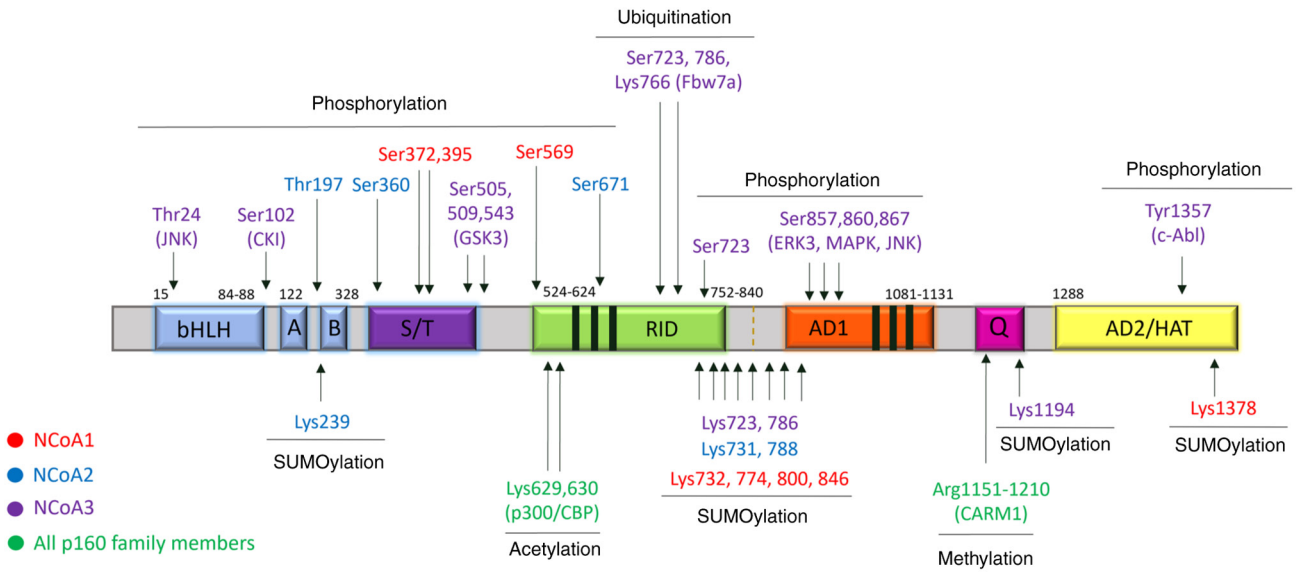

Figure 4. Post-translational modifications of NCoAs. The amino acids correspond to the phosphorylation, ubiquitination, sumoylation, acetylation, and methylation sites and are indicated above and under the diagram respectively, color-coded corresponding to the p160 family member. The known enzymes responsible for post-translational modification are marked in the brackets under the amino acid residue sites. bHLH, basic helix-loop-helix; PAS, Per-Arnt-Sim; S/T, serine and threonine repetition region; RID, receptor-interacting domain; AD, activation domain; HAT, histone acetyltransferase.

Inhibiting the fusion activity. The activity of NCoA proteins can be rapidly modulated by post-translational modifications, namely serine/threonine and tyrosine phosphorylation, sumoylation, ubiquitylation, and methylation (Fig. 4). These modifications can be leveraged to manipulate the activity of the fusion genes by inhibiting or promoting the activities of the enzymes that perform the modifications. One example is the conserved phosphorylation at Tyr1357 in the AD2 domain of NCoA3 and the equivalent position in NCoA2. This specific tyrosine residue is phosphorylated by c-Abl kinase and results in an altered interaction with CARM1, p300, and activated receptors upon IGF1, EGF, and estrogen treatment (46). Tyr-1357 phosphorylation results in decreased binding of AD2 to CARM1 and an increased affinity to p300 and steroid receptor interaction, enhancing NCoA transcription activity (46). Inhibition of this phosphorylation event using c-Abl inhibitors presents a potential therapeutic opportunity that could be combined with other approaches to target cancers dependent on the fusion transcriptional activities (46,106). Further characterization of posttranslational modifications and their effect could help develop new therapeutic opportunities to target modifications that control the fusion oncogenic properties.

Another approach to tackle the effects of the fusion protein in tumorigenesis is to identify and target the functions of transcriptionally activated genes that can significantly contribute to tumor development. For example, multiple lines of evidence have indicated the importance of wild-type kinases in contributing to the maintenance of fusion-driven tumors (68,70-72). Efforts towards understanding the molecular changes upon expression of these fusions could reveal relevant druggable targets that are crucial for the maintenance or development of tumorigenic and/or metastatic properties. This would allow the repurposing of drugs developed for other cancers or conditions in rare pediatric tumors for which the *de novo* drug development may not be feasible. Finally, drugs that alter the state of chromatin, like HDAC inhibitors could help counteract the constitutive upregulation of genes by the fusion transactivation domains (74).

Silencing the fusion. New direct therapeutic approaches, which decrease the undruggable target's expression rather than its activity or effectors are currently being investigated.

Antisense technologies are one of the most promising approaches, based on the specific targeting of the RNA that is causing a disease. In the case of fusion-driven pediatric cancers, the targeted RNA can be the fusion's pre-mRNA or mRNA that drives the tumor. Antisense technologies include single-stranded antisense oligonucleotides (ASOs) or double-stranded antisense drugs (siRNAs). Antisense refers to the mode of action of all these drugs, that relies on the Watson and Crick base pairing of an oligo nucleotide-like molecule with the target RNA (107). The binding of the drug to the targeted RNA can typically result on the degradation of the RNA, the inhibition of translation or the modulation of the pre mRNA splicing. Some ASO therapies have already been approved and used in clinics (such as ASO therapy for spinal muscular atrophy, Duchenne muscular dystrophy, and hereditary transthyretin-mediated amyloidosis, among others), and more are currently in development stages for treating cancer (108).

CRISPR/Cas9 technologies can be used to produce random genomic rearrangements that generate inactive forms of targeted genes, including oncogenic fusions (109,110). A recent study showed the feasibility of using gene editing to target gene fusions in cancer of three independent PDX models of Ewing Sarcoma. Two intronic sequences of the EWSR-FLI1 fusion were simultaneously targeted, one on each partner gene. This led to either the elimination of crucial fusion protein domains or changes in the gene-fusion reading frame, without affecting the unfused gene's exonic sequences or protein expression (111). This strategy has the advantage of

using the NHEJ pathway, which is active in all cells, making it easy to use. The targeting of intronic regions flanking the breaking point of the fusion makes the approach suitable for patients with different breaking points. Finally, the fact that exonic regions are not targeted makes the approach safer, since exonic regions of the normal unfused alleles should remain unmodified. The advantage of this method over other strategies based on targeting the fusion region is that it should not affect the natural unfused forms of the partner genes (112).

Targeted protein degradation also holds promise as a new type of therapy for undruggable targets. In proteolysis-targeting chimeras (PROTACs), the ubiquitin/proteasome system is directed specifically toward a given protein to induce its selective degradation (113,114). The PROTAC system utilizes heterobifunctional molecules consisting of a binding ligand for the protein of interest (such as chimeric oncoprotein) followed by a small linker and a binding ligand for E3 ligase. Simultaneous binding of the target protein and the E3 ligase to the PROTAC results in ubiquitination and proteasomal degradation of the target protein and release of the PROTAC, which can participate in another targeting cycle (113). This feature allows the PROTAC to be utilized in multiple targeting cycles, reducing the concentration needed to achieve therapeutic effects (114).

Several PROTACs are currently under different stages of clinical trials, targeting the AR and ER among other proteins (114). A PROTAC approach targeting NCoA1 has recently been described, using a small peptide (Y2L) that mimics the LXXLL helical fragment of STAT6, which has a high affinity and specificity for the NCoA1 PAS-B domain. In the PROTAC, Y2L is linked to a tetrapeptide (RLAA), an N-degron fragment that binds the UBR box (a class of E3 ligases). The study showed that the PROTAC was effective in inducing the specific degradation of NCoA1, resulting in the impairment of NCoA1 transcriptional activity and suppression of cell invasion and migration *in vitro* and *in vivo* (115).

6. Conclusion

Many pediatric cancers express oncogenic fusions as the only driver of tumorigenesis. The p160 protein family members have a prominent representation among these gene fusions. In some cases, it has been demonstrated that only the expression of the oncogenic fusion was sufficient to induce tumors. Conversely, the inhibition or deletion of the oncogenic fusion in cancer cells led to cancer cell death or cell differentiation, imposing the importance of direct elimination of the fusion from these tumors.

Classical therapeutic approaches with small inhibitors rely on the manipulation of the activity of the oncogenic fusion or the inhibition of its transcriptional targets. The possible disadvantages of these approaches are the requirement of a deep understanding of the regulatory mechanisms and molecular pathways affected by the expression of the oncogenic fusion and the selection for resistance to small inhibitors. In the near future, more promising strategies could rely on targeting the expression of gene fusion itself, using technologies based on CRISPR/Cas9, antisense oligonucleotides, and proteolysis-targeting chimeras. These technologies have a big potential not only to directly target chimeric proteins that were traditionally considered 'undruggable targets', but also to overcome drug resistance. Since other pathologies are already benefiting from the progress of these new approaches, it would be highly beneficial to profit from these experiences in pediatric fusion-driven tumors as well.

Clinically, targeting the gene fusion expression holds great promise for future therapies where its effects can be addressed directly. In addition, detailed knowledge of the molecular pathways affected (for example, recent progress on MCS) suggests potential combinatorial therapies for efficient targeting of the tumors. One clear example is the treatment of MCS cells with BCL-2 inhibitors that sensitize MCS cells to chemotherapy, or the proposed use of imatinib or panobinostat specifically in MCS. These findings can rapidly evolve into clinical studies and provide treatment alternatives while approaches that directly target the expression of the fusion gene are being developed.

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Authors' contributions

PST wrote, edited and reviewed the manuscript and prepared the figures and tables. DS wrote, edited and reviewed the manuscript. Data authentication is not applicable. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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