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SARCOMAS (SR PATEL, SECTION EDITOR)

Mesenchymal Chondrosarcoma: a Review with Emphasis on its Fusion-Driven Biology

Marc El Beaino[1] · Jason Roszik[2] · John A. Livingston[3] · Wei-Lien Wang[4] · Alexander J. Lazar[4] · Behrang Amini[5] · Vivek Subbiah[6] · Valerae Lewis[1] · Anthony P. Conley[3]

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Abstract

Mesenchymal chondrosarcoma is a rare but deadly form of chondrosarcoma that typically affects adolescents and young adults. While curative intent is possible for patients with localized disease, few options exist for patients in the unresectable/metastatic setting. Thus, it is imperative to understand the fusion-driven biology of this rare malignant neoplasm so as to lead to the future development of better therapeutics for this disease. This manuscript will briefly review the clinical and pathologic features of mesenchymal chondrosarcoma followed by an appraisal of existing data linked to the fusions, *HEY1-NCOA2* and *IRF2BP2-CDX1*, and the associated downstream pathways.

Keywords Mesenchymal chondrosarcoma · Chondrosarcoma · Fusion · Translocation · Notch · HEY1 · NCOA2 · IRF2BP2 · CDX1 · Chromatin remodeling · TGF beta · Apoptosis · Genomics · Pathways

Introduction

Mesenchymal chondrosarcoma is a rare malignant neoplasm known for exhibiting features of primitive appearing mesenchymal cells mixed with islands of cartilage differentiation. This entity was first described by Lichtenstein and Bernstein in 1959 and represents less than 5% of all chondrosarcoma cases diagnosed each year in the USA [1]. The peak incidence occurs in the third decade of life, though the range involves children as young as 7 years and elderly individuals as old as 80 years [2, 3•]. This disease generally arises from bone, but extra-osseous variants have been known to involve areas such as visceral organs and meninges (Fig. 1). Frequent sites of involvement include the vertebrae, ribs, pelvic bones, and craniofacial bones (mandible and maxilla), with a predilection toward late local and distant recurrences [4, 5]. For many centers, the treatment of this tumor is still a subject of debate [6]. Localized disease should be managed surgically with wide margin resection with or without radiation, and consideration should be given to the use of systemic chemotherapy [2, 4, 7]. While multimodal strategies reported in the past did not appear to substantially improve prognosis, a recent European Musculoskeletal Oncology Society study reported a reduced risk of recurrence and superior survival metrics (progression-free and overall survivals) with the use of cytotoxic chemotherapy in the neoadjuvant and/or adjuvant setting for localized disease [7, 8]. For patients with metastatic disease, systemic chemotherapy is the primary form of therapy with surgical resection considered for cases in which surgery may result in remission. The approach of our center to localized mesenchymal chondrosarcoma involves neoadjuvant, anthracycline-based chemotherapy, radiation therapy (unless contraindicated), and surgical resection with wide margins. Unfortunately, there is scarcity of available data on mesenchymal chondrosarcoma, which is limited to small-sample retrospective

This article is part of the Topical Collection *on Sarcomas*

✉ Anthony P. Conley
aconley@mdanderson.org

[1] Department of Orthopaedic Oncology, MD Anderson Cancer Center, Houston, TX 77030, USA

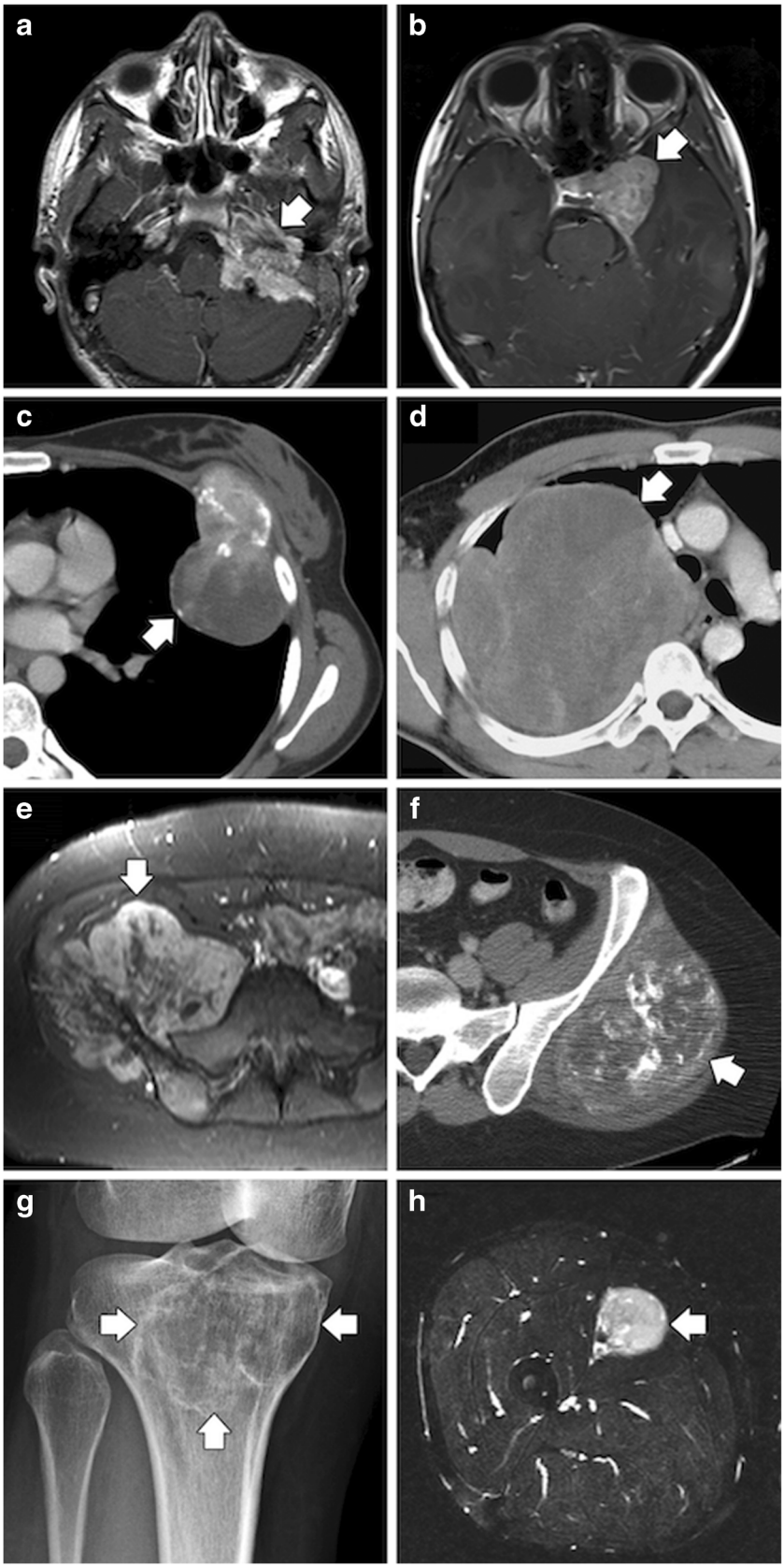
[2] Department of Melanoma Medical Oncology, MD Anderson Cancer Center, Houston, TX 77030, USA

[3] Department of Sarcoma Medical Oncology, MD Anderson Cancer Center, Houston, TX 77030, USA

[4] Department of Pathology, MD Anderson Cancer Center, Houston, TX 77030, USA

[5] Department of Diagnostic Radiology, MD Anderson Cancer Center, Houston, TX 77030, USA

[6] Department of Investigational Therapeutics, MD Anderson Cancer Center, Houston, TX 77030, USA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◀ **Fig. 1** Spectrum of imaging appearance of mesenchymal chondrosarcoma. **a** Fourteen-year-old boy with a lesion arising from the left temporal bone. **b** Nine-year-old girl with a soft tissue mass centered in the left middle cranial fossa compressing the temporal lobe. **c** Twenty-one-year-old woman with a mass arising from a left anterior rib. Note internal calcifications. **d** Thirty-five-year-old man with a soft tissue mass in the left hemithorax. **e** Eighteen-year-old woman with a mass arising from the right ilium. **f** Thirty-six-year-old man with a soft tissue mass in the left gluteal musculature. Note internal calcifications. **g** Forty-six-year-old woman with a lytic lesion of the proximal tibial metaphysis. **h** Twenty-four-year-old man with a soft tissue nodule in the anterior compartment of the thigh

studies without prospective mesenchymal chondrosarcoma-specific trial data [2, 4, 9–11]. A recent evaluation of 205 mesenchymal chondrosarcoma patients through the Surveillance, Epidemiology, and End Results (SEER) database demonstrated 5- and 10-year overall survival rates of 51 and 43%, respectively [3•]. Clearly, better therapeutic options are needed for the treatment of patients with mesenchymal chondrosarcoma.

A recurrent translocation, *HEY1-NCOA2*, has been recently identified in the great majority (at least 80%) of mesenchymal chondrosarcomas [12, 13]. This finding is of interest since molecular characterization of this disease may shed light on its pathogenesis and the potential therapeutic avenues that could be explored. The following review aims to (1) summarize the different structural components of the *HEY1-NCOA2* fusion, (2) identify potential pathways that might be modulated by it, and (3) suggest future therapeutic strategies for the management of mesenchymal chondrosarcoma.

Pathology of Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is characterized by having a prominent primitive component comprised of round to spindled cells punctated with islands of mature cartilage (Fig. 2a). The combination of these two components is virtually diagnostic, but a small core needle biopsy sampling only one component or the other can be diagnostically challenging. The primitive cell component has a non-specific immunohistochemical profile but shows SOX9 nuclear reactivity indicative of a chondroid lineage (Fig. 2b). Demonstration of the characteristic *HEY1-NCOA2* fusion by a variety of methodologies can be useful in diagnostically challenging cases.

Structure and Function of HEY1

HEY1 (hairy/enhancer-of-split related with YRPW motif 1) is a gene located on the long arm of human chromosome 8 (Fig. 3). It encodes an evolutionary conserved protein of the hairy and enhancer of split-related family of basic helix-loop-helix (bHLH) transcriptional repressors [14]. Three different regions were isolated in *HEY1*. They include the bHLH domain which mediates the DNA-binding properties of the protein, the Orange domain, which interacts with the bHLH domain to drive and extend the protein interaction and HEY dimerization, and the C-terminus YRPW domain (Fig. 4) [14, 15].

Through its C-terminus bHLH and N-terminus YRPW motifs, HEY1 is thought to act mainly as a transcriptional repressor (Fig. 5). Inhibition of gene promoters is driven by direct DNA binding and dimerization of HEY1 to gene sequences rich in CACGTG/CACGCG and/or CGCGCG, two E-box-like sequences bound with high affinity to the HEY1 DNA-binding domain [14]. This association initiates the recruitment of corepressors to the DNA area of interest, which inhibits target gene expression. Epigenetic modulation is another mechanism through which HEY1 exerts its inhibitory effects. The amino- and the carboxy-terminal-repressive HEY1 domains depend on histone deacetylase-dependent and independent mechanisms, respectively, to suppress target genes [16]. HEY1 transcriptional activity does not seem to be limited to repression only, since many gene targets are overexpressed upon its stimulation [14]. Of note, E-box motifs have not been found in the activated gene promoters, which raises the possibility of a protein-protein interaction mechanism to mediate gene activation [14].

HEY1 is a downstream mediator and effector of the activated Notch developmental and stemness pathway. Gene expressions that are modulated by HEY1 up- or downregulation involve multiple embryological processes, including musculoskeletal, neurological, and cardiovascular development [14, 17–21]. Through its interaction with GATA transcription factors, HEY1 inhibits erythropoiesis- and cardiogenesis-related genes [22–24]. FBXO45 (F-box only protein 45) is required for proper neural development [25]. It associates with SKP1 (S-phase kinase-associated protein 1) to form an atypical protein-ubiquitin ligase complex [25, 26]. Through its bHLH and Orange sequences, HEY1 indirectly inhibits FBXO45 activity through redirection of the ubiquitination complex toward other proteins (Fig. 5) [27]. In the embryonic murine inner ear, it also maintains the hairy mechano-sensory cell population and stemness [21].

HEY1 dysregulation alters the expression of genes that intervene in musculoskeletal development [14, 16]. The Notch network is important for the prevention of the premature differentiation of myogenic precursors by sustaining stem/progenitor cell self-renewal, whereas myogenin and MyoD are crucial muscle regulatory factors for muscle differentiation [28, 29]. HEY1 exerts its inhibitory effects on myogenesis at least in part through targeting of myogenin promoters by increasing their methylation and compromising MyoD recruitment to its target promoters (Fig. 5) [16]. HEY1 interaction with GATA does not seem to be relevant in myogenesis as compared to erythropoiesis and cardiogenesis, despite the fact that many myogenic gene promoters contain GATA binding sites in their sequences [16].

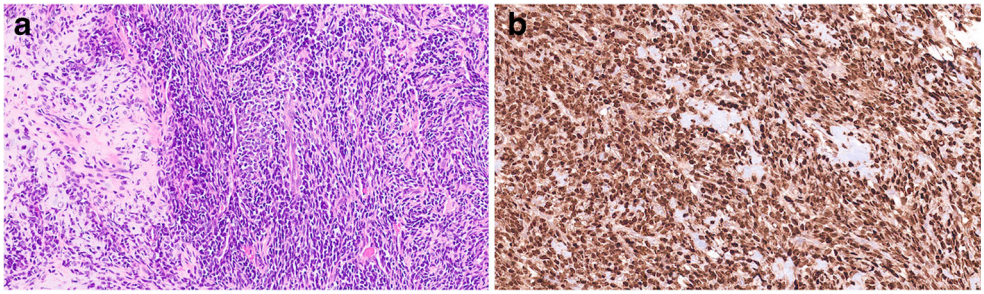

Fig. 2 **a** Mesenchymal chondrosarcoma shows a mixture of primitive cells juxtaposed to islands of mature chondroid tissue (H&E). **b** Immunohistochemistry for SOX9 reveals strong nuclear reactivity in the primitive cell component, indicative of chondroid lineage

There are conflicting data in the literature regarding HEY1 involvement in bone and cartilage formation. In C2C12 mesenchymal stem cells, microarray analysis showed *HEY1* to be among the most overexpressed gene upon BMP (bone morphogenetic protein)-induced osteogenic differentiation [30]. In pre-osteoblasts MC3T3 cells, HEY1 abrogated Runx2 transcriptional activity, which is an essential transcription factor for bone development [31]. In mice, HEY1 repression did not affect osteogenic maturation and mineralization, while its induction inhibited mesenchymal stem cell osteogenic differentiation and mineralization properties [32]. Mice overexpressing HEY1 exhibited also a 76% increase in the number of hypertrophic chondrocytes [32]. In response to BMP9, which induces mesenchymal stem cells differentiation into osteoblasts precursors, *HEY1* was among the most stimulated genes [33]. However, in this study, HEY1 knockdown reduced BMP9-mediated osteogenic differentiation both in vivo and in vitro, while increasing chondrogenic cell numbers and chondroid matrix formation. High HEY1 levels were also linked to high invasive and metastatic potential in mice injected with osteosarcoma cell lines [34••].

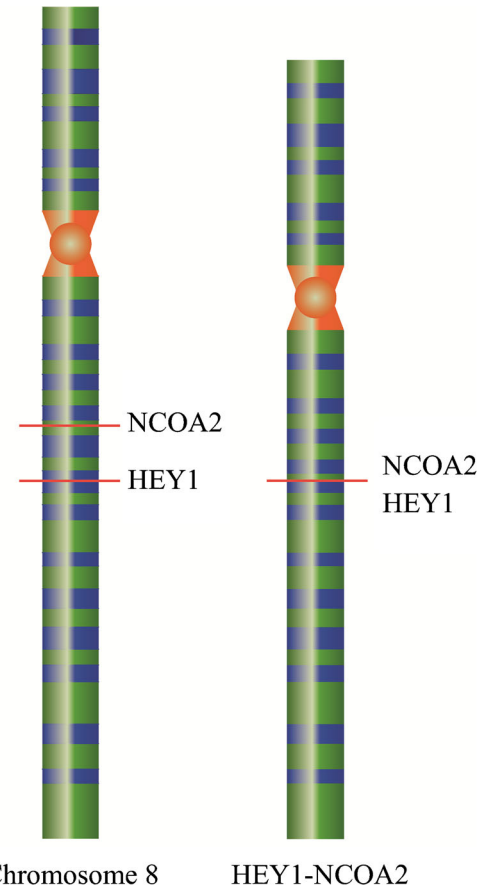

Fig. 3 On the left, normal chromosome 8 on which wild-type *NCOA2* and *HEY1* genes are shown. The pathognomonic *HEY1-NCOA2* fusion is pictured on the right

Structure and Function of NCOA2

NCOA2 (nuclear receptor coactivator 2) belongs to the p160 nuclear receptor coactivator family and is located on the long arm of human chromosome 8 (Fig. 3). It encodes a transcriptional coactivator protein for nuclear hormone receptors. Three distinct regions are identified in this gene. They encompass an *N*-terminus bHLH domain that mediates DNA binding and protein dimerization, a central area with three LXLL motifs that drive NCOA2 interaction with nuclear hormone receptors, and a C-terminus region that contains two transcriptional activation sequences with a relevant role in chromatin remodeling (Figs. 4 and 5) [35]. Without directly binding DNA, NCOA2 associates with nuclear receptors, recruits histone methyltransferases to specific sequences, and mediates chromatin remodeling and transcription of specific target genes. AD1 (activation domain 1) interacts with transcriptional coactivators (CBP and P300), whereas AD2 (activation domain 2) interferes with histone methyltransferases, coactivator-associated arginine methyltransferase 1 (CARM1), and protein arginine methyltransferase 1 (PRMT1) [35–37].

NCOA2 rearrangements have been identified in several hematologic (Table 1) and solid tumors (Table 2). This gene's fusion with *SRF*, *TEAD1*, and *VGLL2* has been found in infantile spindle cell rhabdomyosarcomas [43, 44]. In a rare variant of alveolar rhabdomyosarcoma, a t(2;8) translocation generated a *PAX3-NCOA2* chimeric oncogene [45]. Fusions

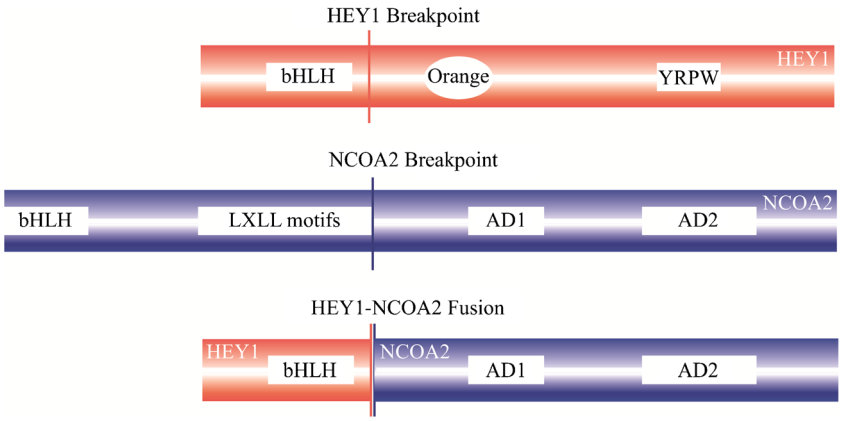

Fig. 4 Schematic representation of the wild-type *HEY1* and *NCOA2* gene sequences, as well as the *HEY1-NCOA2* translocation, which retains the *HEY1* bHLH and the *NCOA2* two activation domains

with *AHRR* and *GTF2I* have also been found in soft-tissue angiofibromas [48–50]. *NCOA2* is also involved in *MYST3-NCOA2* and *ETV6-NCOA2* translocations in leukemias expressing both T-lymphoid and myeloid markers [38, 41]. Carapeti et al. detected and confirmed the presence of the *KAT6A-NCOA2* fusion in acute myeloid leukemias [39, 40]. The transforming properties of *KAT6A-NCOA2* and *PAX3-NCOA2* were biologically elucidated [45, 55]. The former

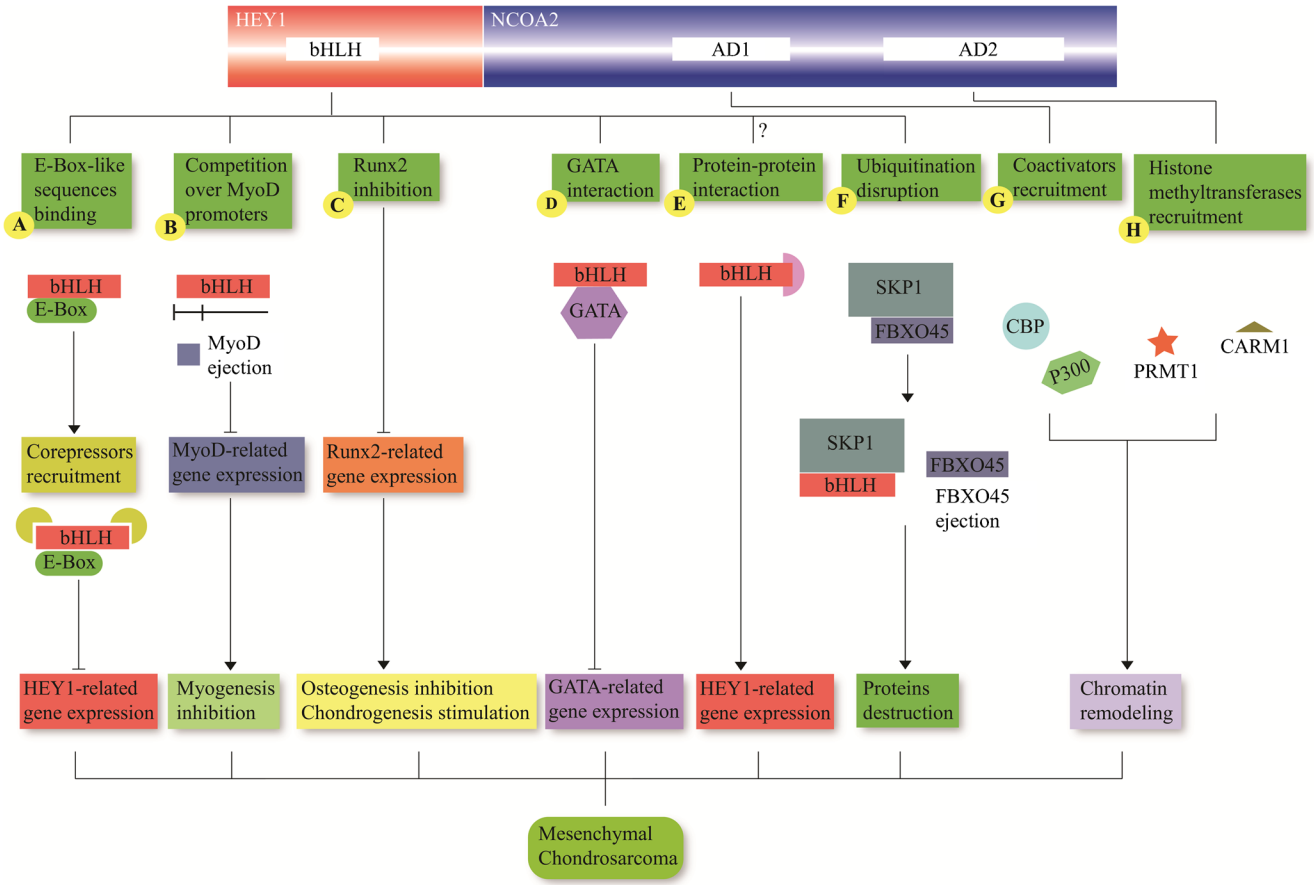

Fig. 5 Blunt arrows (⊥) indicate inhibition while sharp arrows (→) indicate stimulation. **a** *HEY1* bHLH domain binds E-box-like sequences, which leads to recruitment of corepressor factors to mediate HEY1-related gene expression. **b** *HEY1* bHLH inhibits myogenesis through a promoter competition mechanism with MyoD. **c** This domain inhibits Runx2 to induce and inhibits chondrogenesis and osteogenesis, respectively. **d** It interacts with GATA to promote the expression of the genes modulated by it. **e** *HEY1* bHLH might interact with other proteins to modify genes expression. **f** It competes with FBXO45 and promotes a ubiquitination mechanism disruption, which is responsible of some proteins destruction. The **g** AD1 and **h** AD2 domains of *NCOA2* recruit coactivator elements and histone methyltransferases that lead to epigenetic modifications via chromatin remodeling

Table 1 Hematologic malignancies with *NCOA2*-based translocations

Chimeric transcript	Genetic translocation	Disease
KAT6A-NCOA2 (*MYST3-NCOA2*)	t(8;16)(p11;p13) or inv8(p11;q13)	Acute myeloid leukemia [38–40]
ETV6-NCOA2	t(8;12)(q13;p13)	Acute biphenotypic leukemia [41]
ETV3-NCOA2		Indeterminate cell histiocytosis [42]

relies on its interaction with CBP through AD1 for acute myeloid leukemia transformation, whereas the latter requires the presence of both activation domains for alveolar rhabdomyosarcoma genesis.

LACTB2-NCOA2 was identified as a rare but recurrent fusion by whole-genome and transcriptome sequencing in colorectal cancer [56••]. In this study, high NCOA2 levels profoundly abolished colorectal cancer cell line proliferation, colony formation, migration, and invasiveness while increasing their apoptotic rate. In nude mice, NCOA2 overexpression repressed colorectal xenograft growth.

In prostate cancer, NCOA2 was respectively upregulated in 8 and 37% of primary and metastatic tumors [57]. In mice, high NCOA2 levels were sufficient to induce early stages of human prostatic cancer [58]. The same study showed that tumor cells with high NCOA2 expression were more invasive compared to their control counterparts. In prostate cancer cells, NCOA2 overexpression was transcriptionally inhibited by the androgen receptor. *NCOA2* inhibition in androgen-dependent cells made them more sensitive to androgen deprivation therapy and stopped tumor growth at low grade stages [58].

Structure of *HEY1-NCOA2* Fusion

HEY1 and *NCOA2* were fused in at least 80% of mesenchymal chondrosarcomas as detected by RT-PCR, FISH, and genome-wide screen of exon-level expression data and appears to be disease defining [13, 51, 59]. The chimeric fusion is generated from an intra-chromosomal deletion between exon 4 of *HEY1* and exon 13 of *NCOA2* (Figs. 3 and 4) [59]. Similarly to all fusions involving *NCOA2*, *HEY1-NCOA2* bears the DNA-binding domain of *HEY1* and the two C-terminal activation domains of *NCOA2* (Fig. 4) [12, 51]. The histone methyltransferase-interacting domain of *NCOA2* is also conserved.

Genomics of Mesenchymal Chondrosarcoma

Despite being specific to mesenchymal chondrosarcoma, *HEY1-NCOA2* fusion does not seem to be the only recurrent translocation identified in this disease. Therefore, fusion heterogeneity should not be excluded even though one translocation might be more frequent compared to others. Nyquist et al. reported a case of mesenchymal chondrosarcoma with an in-frame t(1;5)(q42;q32) fusion resulting in an *IRF2BP2-CDX1* translocation between exon 1 of the *IRF2BP2* gene on chromosome 1 and intron 1 of the *CDX1* gene on chromosome 5 [60]. *CDX1* encodes a transcription factor, with an irregular expression in intestinal cancer [61–63]. IRF2BP2 contains a zinc finger motif that can bind DNA. It has the ability to interact with *TP53* tumor suppressor and *IRF2* oncogene to affect tumorigenesis [64, 65]. Nevertheless, *TP53*

Table 2 Solid tumors with fusions involving *NCOA2*

Chimeric transcript	Genetic translocation	Disease
SRF-NCOA2	t(6;8)(p12;q11)	Infantile spindle cell rhabdomyosarcoma [43]
TEAD1-NCOA2	t(8;11)(q13;p13)	Infantile spindle cell rhabdomyosarcoma [43]
VGLL2-NCOA2	t(6;8)(q22;q13)	Infantile spindle cell rhabdomyosarcoma [44]
PAX3-NCOA2	t(2;8)(q35;q13)	Congenital embryonal rhabdomyosarcoma [45, 46]
	t(2;12;8)(q11;q22;q13)	Embryonal rhabdomyosarcoma [47]
AHRR-NCOA2	t(5;8)(p15;q13)	Soft tissue angiofibroma [48]
	t(5;8;17)(p15;q13;q21)	Soft tissue angiofibroma [49]
GTF2I-NCOA2	t(7;8)(q11;q13)	Soft tissue angiofibroma [50]
HEY1-NCOA2	t(8;8)(q13;q21)	Mesenchymal chondrosarcoma [12, 13, 51]
NCOA2-ARFGEF1	t(8;8)(q13;q13)	Breast adenocarcinoma [52]
NCOA2-LEPROTL1	t(8;8)(p12;q13)	Lung adenocarcinoma [52]
NCOA2-NCALD	t(8;8)(q13;q22)	Breast adenocarcinoma [52]
NCOA2-ST18	t(8;8)(q11;q13)	Melanoma [52]
NCOA2-XKR9	t(8;8)(q13;q13)	Lung adenocarcinoma [52]
NCOA2-ZNF704	t(8;8)(q13;q21)	Breast adenocarcinoma [53, 54]
SH2D6-NCOA2	t(2;8)(p11;q13)	Bladder transitional cell carcinoma [52]

anomalies have been reported in previous studies including one report that showed 39% of these alterations (loss of protein expression) involving the small cell area while only 7% of the cartilaginous portions of mesenchymal chondrosarcoma samples harbored similar aberrations [66]. Within this same report, the retinoblastoma pathway was the most altered network with 3 of 11 (70%) samples having a homozygous loss of the *CDKN2A/p16* locus [66]. Contrary to conventional chondrosarcomas and dedifferentiated chondrosarcomas, no mutations in the *IDH1* or *IDH2* genes were noted in this same study. Aside from the presence of fusions, no consistent additional genetic abnormalities have been discovered for this disease.

Potentially Activated Pathways in Mesenchymal Chondrosarcoma

Notch Signaling Pathway

As a member of the Notch signaling network, HEY1 is involved in multiple processes. The effects of the Notch pathway are cell dependent but often promote oncogenesis through apoptosis repression, proliferation, and epithelial-to-mesenchymal stimulation [67–69]. Nuclear HEY1 expression, in particular, has been associated with local lymph node and neurovascular bundle invasion, as well as adverse prognosis in pancreatic adenocarcinoma [70]. HEY1 has been shown to dramatically reduce gene expression levels of *COL2A1*, which is responsible for encoding the alpha 1 chain of type II collagen, an essential component of the cartilaginous extracellular matrix [71]. This occurs by binding to the N-box domains in intron 1 of *COL2A1*, thus modulating the interaction between SOX9 and COL2A1. In line with these findings, Notch pathway inhibition in general, HEY1 more specifically, might be of interest in mesenchymal chondrosarcoma.

Chromatin Remodeling

HEY1-NCOA2 exerts, at least to some extent, its pathogenetic impact by affecting chromatin configuration. Pathogenesis may involve recruitment of coactivators or corepressors through NCOA2 or HEY1 domains to HEY1 target genes, respectively (Fig. 5). Therefore, in mesenchymal chondrosarcoma, chromatin modulation through DNA methylation and HDAC inhibitors might also be useful as epigenetic modifier treatments.

Apoptosis

A recent report showed that malignant mesenchymal chondroblasts have higher expression of CD99, PKC-α, PDGFR-α, and Bcl-2 antigens, with proliferation pathways centering around PKC-α and PDGFR-α networks [72]. A separate study confirmed the high protein expression of Bcl-2 and Bcl-xL in mesenchymal chondrosarcoma [73]. Activated PKC-α phosphorylates Bcl-2 and subsequently slows apoptosis. CD99 is a mediator of MAPK pathway activation via the PKC pathway and has been shown to be positive in mesenchymal chondrosarcoma [74–76]. Compared to malignant chondrocytes, malignant mesenchymal chondroblasts exhibit higher expression of Akt and mTOR [77]. PDGFR-α is an upstream inducer of Akt signaling in mesenchymal chondrosarcoma. Therefore, it is worth mentioning the potential role of mTOR and/or PDGFR inhibitors in the management of mesenchymal chondrosarcoma.

TGF-β1 Signaling

Transforming growth factor beta (TGF-β) superfamily represents a large group of conserved genes that encode ligands and receptors which interact with Smad transcription factors to regulate gene transcription [78]. Along with BMP, TGF-β signaling assists in the regulation and maintenance of SOX9, which is considered the master regulator of cartilage development. Van Oosterwijk et al. have demonstrated that mesenchymal chondrosarcoma expresses high levels of p-SMAD2 by immunohistochemistry, particularly in the small cell components of the tumor [73]. This protein directly interacts with TGF-β. Furthermore, p-SMAD1 and PAI-1 were highly expressed in approximately half of the small cell component and in the third of the cartilaginous components. These findings suggest a possible therapeutic role for small molecule inhibitors of the TGF-β signaling pathway.

Limitations

Efforts have been made to generate mesenchymal chondrosarcoma cell lines that will provide researchers tools to study this disease. It was not until recently that a novel mesenchymal chondrosarcoma cell line (MCS170) was reported by the Leiden group in the Netherlands, in which the *HEY1-NCOA2* translocation was identified by FISH, RT-PCR, and sequencing analyses [79••]. A crucial driver role of a genetic translocation is implied by its recurrence, its association with few or no other genetic abnormalities, and its current restriction to one tumor phenotype [80]. Despite the fact that the HEY1 DNA-binding and the NCOA2 transcriptional activation domains are always preserved in the generated *HEY1-NCOA2* translocation, the contribution of each region to the effects of the fusion may be context and cell dependent (Fig. 5). The area that is responsible for the normal function of the wild-type protein might also be absent in the genetic fusion [80]. This is the case of *NCOA2* that is characterized by its DNA-binding domain, which is lacking in the *HEY1-NCOA2* translocation. There also might be a difference

in the genes regulated by the wild-type transcription factor compared to its respective chimeric counterpart. Moreover, the activity of the amino-terminal end seems more complicated than being a simple potentiator of the transcription of the carboxy-terminal partner targets [81].

Conclusions

Discovery of the *HEY1-NCOA2* translocation as a specific and recurrent fusion in mesenchymal chondrosarcoma is an important breakthrough for characterizing and understanding the pathogenesis of this disease. The subsequent identification of the pathways modulated by this fusion would help guide and develop drugs to assess their efficacy in treating mesenchymal chondrosarcoma. Based on the available data on individual HEY1 and NCOA2, *HEY1-NCOA2* fusion evokes many different mechanisms to promote sarcomagenesis, such as direct DNA binding, protein-protein interaction, and epigenetic modification. It is likely that the combination of these pathway dysregulations is what allows this single translocation and resulting chimeric fusion protein to drive the biology of this rare and aggressive sarcoma.

Compliance with Ethical Standards

Conflict of Interest Marc El Beaino declares that he has no conflict of interest.

Jason Roszik declares that he has no conflict of interest.

John A. Livingston declares that he has no conflict of interest.

Wei-Lien Wang declares that he has no conflict of interest.

Alexander J. Lazar declares that he has no conflict of interest.

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Valerae Lewis declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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