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COMPREHENSIVE REVIEW

Chromodomain Helicase DNA-Binding Proteins in Stem Cells and Human Developmental Diseases

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Dynamic regulation of gene expression is vital for proper cellular development and maintenance of differentiated states. Over the past 20 years, chromatin remodeling and epigenetic modifications of histones have emerged as key controllers of rapid reversible changes in gene expression. Mutations in genes encoding enzymes that modify chromatin have also been identified in a variety of human neurodevelopmental disorders, ranging from isolated intellectual disability and autism spectrum disorder to multiple congenital anomaly conditions that affect major organ systems and cause severe morbidity and mortality. In this study, we review recent evidence that chromodomain helicase DNA-binding (CHD) proteins regulate stem cell proliferation, fate, and differentiation in a wide variety of tissues and organs. We also highlight known roles of CHD proteins in human developmental diseases and present current unanswered questions about the pleiotropic effects of CHD protein complexes, their genetic targets, nucleosome sliding functions, and enzymatic effects in cells and tissues.

Introduction

Epigenetic modifier proteins are commonly divided into three classes: chromatin writers (eg, histone methyltransferases and acetylases), erasers (eg, histone demethylases and deacetylases), and readers (eg, chromodomain and tudor domain remodeling proteins). In this review, we focus on a set of chromatin readers and an important family of ATP-dependent helicase-containing DNA-binding proteins called chromodomain helicase DNA-binding (CHD) proteins. We review their structures, functions, and recently discovered roles in stem cells and human diseases. Interestingly, CHD proteins have been identified as critical regulators of cellular processes such as stem cell quiescence, proliferation, and cell fate determination. In addition, they are implicated in a wide variety of human disease processes, including autism, multiple organ system development, and cancer. Finally, we synthesize recent literature indicating that CHD proteins act at enhancer and promoter regions of genes that regulate key developmental processes, suggesting they orchestrate major cellular proliferation and fate decisions. For reference, a summary of CHD proteins, associated mouse and human phenotypes, stem cells, interacting proteins, and target binding sites is provided in Table 1.

Structure and Function of the CHD Superfamily

There are three major superfamilies of ATP-dependent chromatin remodeling enzymes in eukaryotic organisms: SWItch/Sucrose NonFermentable (SWI/SNF), Imitation SWI, and CHD, each of which has a characteristic histone interaction domain [1]. These chromatin remodeling enzymes interpret or read histone modifications through specialized protein domains that vary both between and among the protein families. Upon reading the chromatin state, these enzymes disrupt DNA–histone interactions by sliding nucleosomes either along the DNA strand or by translocating the nucleosome core particle to another DNA strand [2]. Ultimately, this chromatin remodeling function allows for improved or reduced access to DNA by transcription factors and other DNA-binding proteins that influence gene expression. The CHD family of ATP-dependent chromatin remodeling enzymes comprises nine proteins divided into three subfamilies based on domain homology (Fig. 1). All CHD proteins contain two tandem chromatin organization modifier (chromo) domains and two Sucrose NonFermentable2 (SNF2)-like ATP-dependent helicase domains [3,4]. The organization of these domains and how they differ between CHD proteins were recently reviewed [5]. In this study, we review highly important functions of specific CHD proteins and protein domains and focus on the roles of CHD proteins in stem cells and human developmental disorders.

Chromodomains were originally identified in *Drosophila* heterochromatin protein 1 (HP1). HP1 has a single chromodomain that binds nucleosomes to promote closed chromatin states (heterochromatin) and downregulate homeotic genes during development [6–8]. Specifically, the HP1

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TABLE 1. CHROMODOMAIN PROTEINS, ASSOCIATED MOUSE AND HUMAN PHENOTYPES, STEM CELLS, INTERACTING PROTEINS, AND TARGET BINDING SITES

Protein	*Mouse phenotypes*	*Human phenotypes*	*Stem cell type*	*Interacting proteins*	*Binding sites*	*Reference(s)*
CHD1		Prostate cancer	ES cells	Mediator complex	H3K4me3 AT-rich sequences	[11,22,30,31,84]
			iPS cells	NCoR, HDAC1/2		
CHD2	−/− lethal	Epilepsy	Mesenchymal stem cells	H3.3		[39,69,70,77,96,97]
CHD3				NuRD, HDAC1/2, ATR, TRIM27		[69,70,77,98]
CHD4/Mi-2b		Epilepsy	Hematopoietic stem cells	NuRD	H3K4	[26–28,44,46,86,98]
		Uterine cancer	Neural stem cells	Polycomb	H3K9me3	
		Dermatomyositis				
CHD5	−/− viable; males infertile	1p36 deletion	Neural stem cells	NuRD	H3K4 H3K27me3	[12,87,89,99,100]
		Tumor suppressor				
CHD6		ID		RNA Pol II		[73]
CHD7	−/− lethal	CHARGE	ES cells	P300, others	Sox2, Oct4, Nanog Neurod, Rxrg, Rarb, Twist, Sox9	[12,32,51,52,64,101]
			Neural stem cells	SOX2, PBAF		
	+/− CHARGE-like	Autism, ID	Neural crest cells			
CHD8 (Duplin)	−/− lethal	Autism		β-catenin		[82]
		ID		CTCF, CHD7		
CHD9 (CReMM)			Mesenchymal stem cells	GR, PPAR-α	Osteocalcin	[40,41]

CHD, chromodomain helicase DNA-binding; ES, embryonic stem; iPS, induced pluripotent stem; CHARGE, Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and development, Genital hypoplasia, and Ear abnormalities, including deafness and vestibular disorders; CReMM, chromatin-related mesenchymal modulator; ID, intellectual disability; NuRD, Nucleosome-Remodeling Deacetylase complex.

chromodomain facilitates protein–protein interactions with the repressive histone modification H3K9me3, leading to the formation of heterochromatin [6,9,10]. It is now understood that the primary common function of chromodomains is binding to methylated histone residues. Indeed, CHD proteins contain a unique variant of the chromodomain containing a methyl-binding cage that facilitates interactions with lysine residue 4 of histone H3 (H3K4) [10,11]. CHD1 chromodomains (Fig. 1) interact with lysine 4 of methylated histone H3 (H3K4me), and CHD5 chromodomains bind to and maintain lysine 27 of trimethylated histone H3 (H3K27me3) [11,12]. Thus, specific CHD chromatin remodeling proteins exhibit unique functions and preferences for repressive or active histone marks, and the methyl-histone-binding chromodomains are essential for maintaining dynamic chromatin structures and proper gene expression.

The helicase–ATPase domains of CHD proteins are highly similar to those observed in the SWItch2/SNF2 superfamily of ATP-dependent chromatin remodeling enzymes [3,13]. The helicase–ATPase domain functions as a bilobed motor, which provides chemical energy and promotes mechanical disruption of DNA–histone contacts. This histone–DNA disruption leads to sliding of core histones along the DNA template or core histone evacuation and deposition onto another DNA strand [14–17]. Additionally, the CHD subfamilies are delineated by the presence of subfamily-specific protein domains (Fig. 1). CHD1 and CHD2 contain DNA-binding domains, which have been shown to be similar in function to SWI3, ADA2, N-COR, and TFIIB (SANT) domains present in CHD6-9 [18]. The SANT domain confers nonspecific DNA binding, particularly to linker DNA between nucleosomes [19–21].

Chromodomains in CHD1 exhibit preferential binding to AT-rich sequences [22]. Compared with wild-type, recombinant CHD1 and CHD2 lacking the DNA-binding domain lose the ability to bind both to DNA and to nucleosomes, demonstrating the critical roles of CHD1 in nucleosome targeting to DNA [18,23]. CHD3, CHD4, and CHD5 lack DNA-binding domains, yet contain two tandem plant homeodomains (PHDs) [24]. PHD domains are zinc finger motifs that facilitate interactions with methylated histone residues and protein cofactors, for example, between CHD3/4 and histone deacetylase 1, which is part of the potent negative transcriptional regulation Nucleosome-Remodeling Deacetylase (NuRD) complex [25]. PHD domains confer specificity to the target histone residues. For example, binding of the two tandem PHD domains in CHD4 to H3K4 (unmodified) and H3K9me3 (but not to H3K4me3) mediates the transcriptional repressive activity of CHD4/NuRD [26–28]. In addition to the chromodomain and helicase domains, CHD6–9 proteins also contain tandem BRahma Kismet (BRK) domains that are also present in *Drosophila* Brahma (*brm*), but the functions of these BRK domains are not understood [29].

CHD Proteins and Embryonic Stem Cells

Regardless of the overall protein domain structure, the function of CHD superfamily proteins is intimately tied to regulation of gene expression through remodeling of nucleosomes. Importantly, emerging trends across the entire

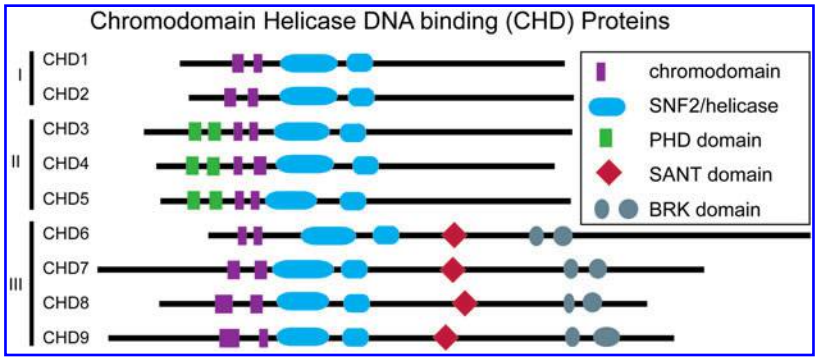

FIG. 1. Cartoon of chromodomain helicase DNA-binding (CHD) proteins and subfamilies. Shown are protein domains with relative positions to the amino (*left*) and carboxy (*right*) termini, not to scale. Adapted with permission from Layman et al. [4].

CHD family include roles in the maintenance, survival, or proliferation of stem cell populations and in directing cell fate decisions of their progeny (Fig. 2). Embryonic stem (ES) cells comprise a self-renewing and pluripotent cell population from which the majority of mammalian tissues are derived. ES cells can be viewed as a blank slate with an open chromatin environment, becoming progressively more differentiated toward neural, hematopoietic, mesenchymal, and other lineage-specific cells through activation or repression of various genetic pathways. CHD1, the first CHD protein implicated in stem cell function, was shown to participate in Mediator complex regulation of ES cells by maintaining open chromatin [30]. The Mediator complex is a multiprotein complex responsible for preinitiation of gene transcription that binds to CHD1 and recruits it to actively expressed genes [31]. Specifically, CHD1 binds to tracts of the active mark trimethylated histone H3 at the residue lysine 4 (H3K4me3) and excludes the repressive mark H3K27me3 [30]. When CHD1 is deleted in ES cells, chromatin condenses to form heterochromatin and pluripotent differentiation is impaired potentially due to promotion of ectodermal lineage gene expression at the expense of endodermal lineage gene expression [30]. In addition to its role in ES cells, CHD1 influences pluripotency since induction of *CHD1* expression is required for efficient reprograming of mature fibroblasts into induced pluripotent stem (iPS) cells [30]. Together, these studies show that CHD1 is vital for maintaining pluripotency in ES and other stem cells. By extension, CHD1 may also play an important role in establishment of the pluripotent state, but this has yet to be formally tested.

Like CHD1, CHD7 has been implicated in several stem cell populations and appears to be critical for regulating cell fate decisions through modulation of signaling and epigenetic pathways. The mouse *Chd7* gene is highly expressed in ES cells, where it appears to function similarly to CHD1 by associating with signals of active gene expression and open chromatin at enhancer elements of critical stem cell pluripotency genes, including *Sox2*, *Oct4*, and *Nanog* [32]. While it is common for genes to be completely active or inactive in fully differentiated cells, the euchromatic chromatin environment in stem and progenitor cells is poised for either repression or activation [33,34]. Unlike their active and inactive counterparts, poised enhancers and promoters typically display both active and repressive marks [35]. CHD7 preferentially binds active (H3K4me1+, H3K27ac+) and poised (H3K4me1+, H3K27me3+) enhancer elements at ectodermal lineage genes in ES cells [32]. Thus, colocalization of CHD7 with poised genetic elements presents a paradigm whereby CHD7 may play a role in recruiting transcription factors, histone modifiers, and/or other chromatin remodeling proteins in a cell type-specific manner to promote activation or repression of certain classes of genes through resolution of the poised chromatin state.

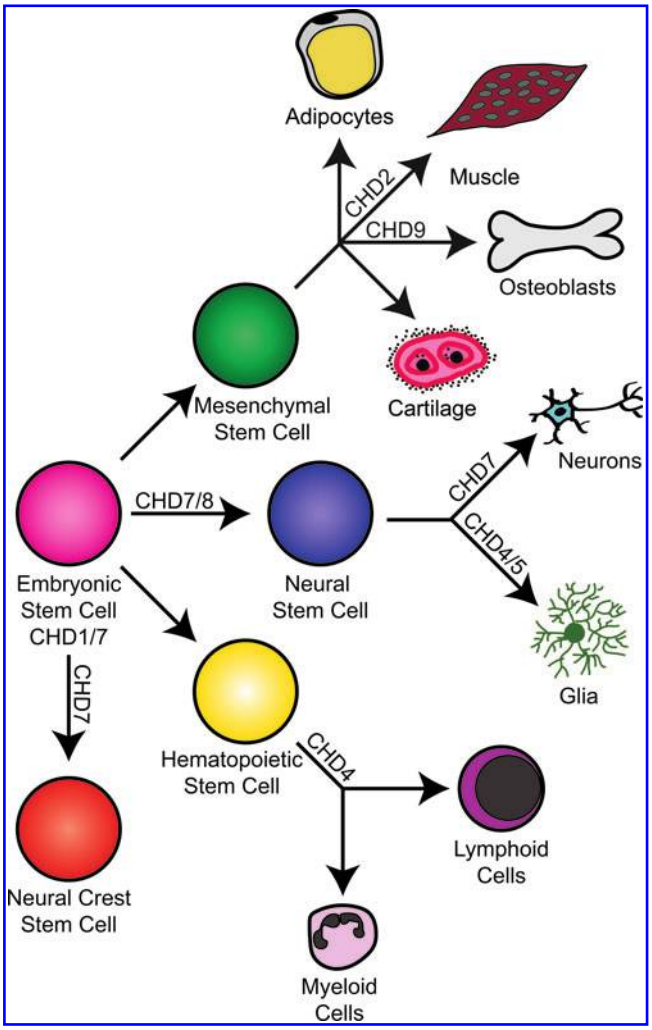

FIG. 2. CHD proteins function in a variety of stem cell types. Shown, in colored circles, are the various stem cell types and their associated CHD proteins, along with differentiated cell lineages to which they contribute. Specific functions (activation, inhibition) are omitted for simplicity or, in some cases, because this information is not yet available.

CHD Proteins and Mesenchymal Stem Cells

Recent studies have provided evidence that CHD proteins also regulate mesenchymal development (Fig. 2). Mesenchymal stem cells are multipotent mesoderm-derived cells that give rise to myoblasts (muscle), adipocytes (fat), osteoblasts (bone), and chondrocytes (cartilage) [36–38]. The differentiation of mesenchymal stem cells into four distinct lineages is regulated by several different CHD proteins. Induction of myogenic cell fates requires the recruitment by CHD2 of a chromatin destabilizing histone variant, histone H3.3, to muscle differentiation genes, which then facilitates binding and gene activation by the transcription factor MyoD [39]. Interestingly, CHD9, also known as chromatin-related mesenchymal modulator, binds to and promotes the expression of osteocalcin (bone gamma-carboxyglutamate), one of the major genes responsible for promoting bone development [40,41]. Collectively, these observations emphasize the importance of CHD family proteins in mesenchymal cell fate decisions and highlight the basic principle that these proteins can have diverse and potentially nonredundant functions within the same stem cell type.

CHD Proteins and Hematopoietic Stem Cells

In addition to their roles in promoting development of mesenchymal derivatives, one CHD protein (CHD4) has been implicated in hematopoietic lineages (Fig. 2). The diverse cell types present in blood are derived from common hematopoietic stem cell progenitors that reside in the bone marrow and adopt one of two potential lineages: myeloid and lymphoid [42,43]. Myeloid lineage cells give rise to red blood cells, platelet-producing megakaryocytes, and granulocyte immune cells [42,43]. Lymphoid lineage cells give rise to the agranulocytic natural killer, T-, and B-cells that also contribute to the innate and adaptive immune responses [42,43]. CHD4, also known as Mi-2β, is an NuRD complex component that has been shown to promote self-renewal and multilineage differentiation of hematopoietic stem cells [44]. Importantly, loss of the *Chd4* gene in mouse bone marrow leads to an abundance of erythroid progenitors and red blood cells and to loss of lymphoid and remaining myeloid lineage cell types [44]. Further examination of CHD4 activity in the regulation of hematopoietic stem cells may provide novel insights into mechanisms of human diseases such as cancers affecting lymphoid lineage cells, including leukemia and lymphoma. Functions for other CHD proteins in hematopoietic cell types have not yet been reported.

CHD Proteins and Neural Stem Cells

Neural stem cells play a vital role in the development and maintenance of the central nervous system and in sensory organs by producing neurons and supporting cells such as glia and oligodendrocytes. CHD4, CHD5, and CHD7 play pivotal roles in the function and differentiation of neural stem cell niches in the subventricular zone (SVZ) of the forebrain and dentate gyrus of the hippocampus through cooperation with major epigenetic modifiers, transcription factors, and signaling pathways. During cortical neurogenesis, CHD4 is expressed in murine SVZ neural progenitor cells and interacts with the Polycomb Repressive Complex 2 (PRC2), specifically with the H3K27 methyltransferase enzyme, Enhancer of Zeste 2 [45,46]. The CHD4/PRC2 complex directly binds to the promoter of the glial fibrillary acidic protein (GFAP) gene (*Gfap*), represses its expression, and prevents glial differentiation [46]. Through inhibition of the *Gfap* locus, CHD4 and PRC2 promote neuronal differentiation during the neurogenic period (between embryonic days 11 and 18 in mice) [46]. In addition to these roles for CHD4 in neural stem cells, a recent study demonstrated that CHD4 and other NuRD complex proteins actively repress genes that inhibit neuronal differentiation in the cerebellum [47]. Thus, individual CHD proteins have important roles in stem cell and differentiated cell populations, guiding decision making and developmental progression at multiple stages.

Similar to CHD4, CHD5 also interacts with the PRC2 and specifically associates with the repressive histone modification H3K27me3 in neural stem cells [12]. CHD5 is highly expressed in neural progenitor and neuroblast cells of the SVZ and subgranular zone (SGZ) of the hippocampus, which produces neurons that are important for learning and memory [12]. Reduced *Chd5* expression in the developing cortex also leads to a significant loss of migratory neuroblasts [12], and *Chd5*-deficient neural stem cells exhibit downregulation of genes responsible for neuronal migration and maturation [12]. Taken together, these studies demonstrate that CHD4 and CHD5 are critical for the inhibition of glial differentiation during key neurogenic phases of mammalian brain development and suggest that chromatin remodeling is vital and dynamic during brain development.

CHD7 is another CHD protein that is enriched in and critical for proper function of neural stem cells. *Chd7* is highly expressed in the SGZ of the hippocampus and the SVZ of adult mice, where it colocalizes with markers of neural stem cells (GFAP), neural progenitor cells (marked by the transcription factor ASCL1), and neuroblasts (marked by Doublecortin or DCX) [48,49]. Longitudinal studies in mice with temporally induced conditional deletion of *Chd7* in adult SVZ neural stem cells show that *Chd7* deficiency leads to a reduction in mature dopaminergic and GABAergic olfactory bulb interneurons and reduced expression of the proneural genes, *Sox4* and *Sox11* [49]. In the SGZ of the hippocampus, conditional knockout of *Chd7* also leads to a reduction in neurogenesis, which can be rescued through exercise [49]. In a recent study, *Chd7* was also shown to promote quiescence and maintenance of adult hippocampal neural stem cell populations [50]. Considering that *Chd7* also promotes neural stem cell progenitor proliferation in the developing olfactory and otic placodes [51,52], these studies provide convincing evidence that CHD7 is essential for stem cell function in a variety of tissues. However, the precise mechanisms by which CHD7 regulates stem cell proliferation, quiescence, fate, or differentiation, which binding partners and genomic targets it associates with, and whether these mechanisms vary between developmental and postnatal stages remain to be determined. It is also not clear whether differences in CHD7-mediated mechanisms of neural development differ across the various neural stem cell populations in the SVZ, SGZ, and sensory organs.

CHD Proteins in Human Disease

CHD7 and CHARGE syndrome

CHARGE syndrome (Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and development, Genital

hypoplasia, and Ear abnormalities, including deafness and vestibular disorders) is a multiple congenital anomaly condition that occurs in approximately 1 in 10,000 live births [53]. Heterozygous mutations in *CHD7* are found in over 90% of individuals with CHARGE syndrome, suggesting that it is a monogenic disorder with variable expressivity [54–56]. To date, there are no definitive genotype/phenotype correlations, likely due to the tremendous diversity of *CHD7* nonsense, missense, deletion, and truncation mutations and the highly variable expressivity of CHARGE features, even between members of the same family who have the same mutation [56]. In vitro biochemical assays with recombinant CHD7 protein have confirmed that CHD7 is an ATP-dependent chromatin remodeling enzyme capable of modulating DNA–histone interactions [57]. Interestingly, when point mutations in the chromodomains from individuals with CHARGE are introduced into recombinant CHD7, its ATP-dependent chromatin remodeling enzymatic activity is reduced in a mutation-specific manner [57]. These studies provide additional evidence for haploinsufficiency as the major mechanism of CHARGE features. However, additional functions of other CHD7 protein domains may still be discovered and these new cellular functions, if they exist, may help explain the wide variability in clinical features in individuals with *CHD7* mutations.

In individuals with CHARGE syndrome, *CHD7* haploinsufficiency causes dysfunction in sensory processes and impaired hearing, vision, balance, and olfaction. To more fully understand the role of *CHD7* in development and its impact on sensory processes, mouse models have been created and carefully analyzed. In our laboratory, a *Chd7* gene trap null allele was generated through insertion of the *lacZ* reporter into the *Chd7* allele, creating a functionally null allele with β-galactosidase reporter activity [58]. Interestingly, *Chd7* null mouse embryos do not survive past embryonic day 10.5, presumably from respiratory and cardiovascular defects, while *Chd7* heterozygous mice display many of the same defects observed in CHARGE [58]. Similarly, there have been no humans identified with homozygous mutations in *CHD7*, suggesting that complete loss of *CHD7* (and perhaps other *CHD* genes) is embryonically lethal.

Chd7 is widely expressed in mammalian tissues, most notably in those affected in CHARGE syndrome, including the heart, inner ear, eye, olfactory epithelium, and brain [4,58]. In each organ thus far analyzed, *Chd7* expression has been predictive of tissue or cellular defects in mutant mice. In the inner ear, *Chd7* heterozygous mice display hypoplasia or aplasia of the lateral and posterior semicircular canals and innervation defects of the vestibular sensory epithelium [52,59]. Conditional knockout of *Chd7* causes complete aplasia of vestibular and cochlear structures, reductions in fibroblast growth factor signaling, and decreased proliferation with reduced otic neural progenitors and reduced expression of proneural genes such as *Ngn1* and *Neurod1* [52]. These data indicate that CHD7 may function in some sensory tissues similarly as it does in brain neural stem cells, through regulation of critical molecular pathways that activate neurogenesis and inhibit gliogenesis.

Hyposmia and anosmia, reduction or loss of the sense of smell, are two of the most highly penetrant phenotypes observed in individuals with CHARGE. Olfactory deficits are commonly accompanied by hypoplasia or aplasia of the olfactory bulbs in the brain [55,60–62]. It was discovered, through electrophysiological and behavioral assays, that *Chd7* heterozygous mice display complete anosmia, lack of odor discrimination, and olfactory bulb hypoplasia [61,63]. *Chd7* is highly expressed in olfactory epithelial neural stem and progenitor cells, as demonstrated by colocalization with Ascl1 and Neurod1 [61]. In mice, loss of *Chd7* correlates with a marked decrease in olfactory epithelial neural stem cell proliferation, a subsequent reduction in olfactory sensory neurons, and impaired recovery from damage [61]. Interestingly, *Chd7* heterozygous mutant mice also show decreased dopaminergic tyrosine hydroxylase-positive interneurons in the olfactory bulb, which could be due to impaired efferent signals from the olfactory epithelium or a defect in olfactory bulb neurogenesis from the SVZ neural stem cell niche [61]. Thus, olfactory processing depends on CHD7 function not only in the peripheral olfactory epithelium but also in central nervous system-derived neurogenic niches.

Coimmunoprecipitation and chromatin immunoprecipitation studies have also shown that in neural stem cells, CHD7 physically interacts with SOX2 at genes that are associated with human diseases, including Alagille syndrome (caused by mutations in *JAG1*, a Notch signaling ligand), Feingold syndrome (caused by mutations in *MYCN*, a bHLH transcription factor), and Pallister–Hall syndrome (caused by mutations in *GLI3*, a mediator of Sonic hedgehog signaling) [64]. Several phenotypes observed in these syndromes are also common in CHARGE syndrome, including genital abnormalities (Pallister–Hall and *SOX2* deficiency), tracheoesophageal defects (Alagille, Feingold, and *SOX2* deficiency), pituitary and endocrine dysfunction (Pallister–Hall and *SOX2* deficiency), and semicircular canal hypoplasia (Alagille). CHD7 binding to SOX2 is intriguing due to the extensive overlap in expression and function of these two proteins and their contributions to development of ectodermal lineages affected in CHARGE, including the brain, retina, and neural crest-derived cells, that populate the heart and craniofacial tissues [65]. Together, these observations suggest that CHD7 activity and protein–protein interactions may be important for stem cell differentiation and cell fate decisions in a wide variety of tissues and cell types.

CHD proteins in autism spectrum disorder, intellectual disability, and epilepsy

Application of cytogenetic and next-generation sequencing technologies to large cohorts of individuals with autism spectrum disorder (ASD), intellectual disability (ID), and/or epilepsy has uncovered de novo and inherited heterozygous frameshift, nonsense, or copy dosage mutations in several *CHD* genes, including *CHD2*, *CHD6*, *CHD7*, and *CHD8* [66–74]. For *CHD2*, *CHD6*, and *CHD7*, mutations identified thus far are nonrecurrent (present in only individual cases), private mutations that account for a small fraction of ASD/ID/epilepsy cases. In contrast to the rare isolated mutations in these three *CHD* genes, 13 different recurrent alleles of *CHD8* have been observed in individuals with ASD/ID in association with macrocephaly and gastrointestinal disturbance [66,70,75–78]. In cultured cells, CHD8 has been

shown to bind CHD7 and to both bind and regulate p53 and inhibit its proapoptotic effects during development; thus, it is surprising that loss of CHD8 is not associated with broader phenotypic effects in humans [79–82]. Knockdown of *Chd8* by shRNA does not alter the morphology or neural ectodermal markers of neural progenitors derived from human iPS cells, but does significantly impair their gene expression [74]. A very recent study also showed that CHD7 binds to and represses p53, suggesting some CHD proteins (at least those in the third subclass) may share common downstream mechanisms, interacting factors, and target genes [83]. Thus, CHD7 and CHD8 not only share common mechanistic pathways but also make unique contributions to developmental events in a wide variety of tissues and cell types.

Similar to *CHD7* and *CHD8* in ASD, *CHD2* mutations have been observed in individuals with epilepsy [66–68]. This raises the likelihood that the spectrum of human mutations in *CHD* genes could be much broader than previously suspected. Given the complexities of CHD target genes and interacting partners, a major research goal is to clarify the exact mechanisms by which loss of CHD protein function disrupts neural stem cell and/or neuronal/glial development, and to determine exactly how this disruption results in the complex developmental abnormalities in CHARGE syndrome and the cognitive and behavioral profiles observed in ASD/ID and epilepsy. Such research could uncover common underlying mechanisms that may also potentially be targeted by therapies that directly or indirectly modulate chromatin. Treatments might then be directed toward altering the structure and/or function of synapses, dendrites, axons, and signaling pathways that are critical for proper progenitor, neuronal, and glial development.

CHD proteins in cancer and other disease processes

In addition to the varied developmental roles for CHD proteins in human biology, there are several other conditions where CHD proteins have been implicated either through genetic screens or analysis of tissue transcriptomic or biochemical data. CHD1 was identified as frequently deleted in the homozygous form in prostate cancer [84] and likely contributes to cellular invasiveness [85]. CHD4/Mi-2β has been found to be deleted in a high percentage (17%) of endometrial cancers and is implicated as an autoantigen in the inflammatory disorder dermatomyositis [86]. CHD5 is unique among CHD proteins, in that it is highly enriched in the nervous system and testis, and has been found to act as a tumor suppressor in a wide variety of cancers, including neuroblastoma, breast, ovarian, prostate, colon, and lung cancer, and has been shown to regulate spermatogenesis [87–89]. Notably, *CHD6* mutations have been identified in bladder [90] and colon cancers [91], consistent with roles for CHD proteins in DNA damage repair and response pathways [92]. Analysis of gastric and colorectal cancers has revealed mutations or altered expression of several CHD proteins—CHD1, CHD2, CHD3, CHD4, CHD7, CHD8, and CHD9—providing further evidence of the broad roles for chromatin remodeling in cancer pathogenesis [93]. Somewhat surprisingly, scoliosis is also linked to disruptions or sequence variants in CHD proteins, including CHD2 [94] and CHD7 [95]. Together, these disease associations highlight the wide variety of cells, tissues, and pathophysiological processes that depend upon proper ATP-dependent chromatin dynamics for normal function.

Conclusions

In this study, we have summarized CHD proteins and recent evidence supporting their involvement in a variety of stem cell types. Studies aimed at identifying CHD protein-binding partners, target sites in the genome, and associated disease mechanisms are active areas of research. CHD proteins are emerging as critical contributors to health and disease, with major functions during development of the brain, eye, ear, heart, and skeletal systems. Future work dedicated to uncovering the mechanisms whereby CHD proteins mediate these effects are likely to reveal even more interesting clues about this complex and intriguing class of ATP-dependent chromatin remodelers.

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Author Disclosure Statement

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