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Cohesin: an emerging master regulator at the heart of cardiac development

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ABSTRACT **Cohesins are ATPase complexes that play central roles in cellular processes such as chromosome division, DNA repair, and gene expression. Cohesinopathies arise from mutations in cohesin proteins or cohesin complex regulators and encompass a family of related developmental disorders that present with a range of severe birth defects, affect many different physiological systems, and often lead to embryonic fatality. Treatments for cohesinopathies are limited, in large part due to the lack of understanding of cohesin biology. Thus, characterizing the signaling networks that lie upstream and downstream of cohesin-dependent pathways remains clinically relevant. Here, we highlight alterations in cohesins and cohesin regulators that result in cohesinopathies, with a focus on cardiac defects. In addition, we suggest a novel and more unifying view regarding the mechanisms through which cohesinopathy-based heart defects may arise.**

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INTRODUCTION

Cohesinopathies are a family of related multispectrum developmental disorders. While the first identified cohesinopathies were Roberts syndrome (RBS; MIM 268300), also known as SC phocomelia (MIM 269000), and Cornelia de Lange syndrome (CdLS; MIM 122470), cohesinopathies may extend to related developmental abnormalities such as Warsaw Breakage syndrome (WBS; MIM 613398), Mungan syndrome (MGS; MIM 611376), Mullegama–Klein–Martinez syndrome (MKMS; MIM 301022), Juberg–Hayward syndrome (JHS; MIM 216100), developmental epileptic encephalopathy (DEE; MIM 308350), Baller–Gerold syndrome (BGS; MIM 218600), chronic atrial and intestinal dysrhythmia (CAID; MIM616201), Diamond–Blackfan anemia (DBA; MIM 105650), Treacher–Collins syndrome (TCS; MIM 154500), and CHARGE (coloboma, heart defects, atresia choanae, retardation of growth, genital hypoplasia, and ear abnormalities) syndrome (MIM 214800; omim.org).

Cohesinopathic phenotypes can include growth retardation, phocomelia (shortened, flipper-like appendages), malformed and/or missing digits, craniofacial abnormalities and cleft palate, seizures, intellectual disabilities, hearing loss, renal defects, gastrointestinal defects, and in severe cases, spontaneous abortion or stillbirth (omim.org). Of particular interest here are the incidence and range of heart defects in both RBS and CdLS individuals. For instance, postmortem examinations, primarily of RBS fetuses, highlight a wide range of cardiac abnormalities. These include ventricular septal defects, atrial septal defects, patent ductus arteriosus, hypoplastic ascending aortas, interrupted aortic arches, left ventricular outflow tract obstruction, aortic stenosis, and patent foramen ovale (Herrmann *et al.*, 1969; Freeman *et al.*, 1974; Song and Chi, 1996; Paladini *et al.*, 1996; Vega *et al.*, 2006; Goh *et al.*, 2010). CdLS individuals and mouse models of CdLS exhibit high frequencies (up to 50%) of cardiac abnormalities that include atrial septum defects, sick sinus syndrome, ventricular septal defect, pulmonary stenosis, aortic displacement, right ventricular hypertrophy, valvular abnormalities, and patent ductus arteriosus (Kline *et al.*, 2014, 2018; Piche *et al.*, 2019). Zebrafish embryo models of either RBS or CdLS similarly exhibit a suite of cardiac defects that include cardiac edema, reduced or absent left jogging/looping of the heart, loss of blood flow, cardia bifida, septal defects, and ventriculobulbar and atrioventricular valve malformations (Barresi *et al.* 2010; Rhodes *et al.* 2010, Mönnich *et al.* 2011; Muto *et al.*, 2011; Thomas *et al.* 2014; Percival *et al.*, 2015; Schuster *et al.*, 2015, Xu *et al.*, 2015). The extent to which heart defects occur in cohesinopathies highlights the importance of investigating the molecular etiologies of and possible therapies for these disorders, as surgical interventions remain the most common treatment for surviving RBS and CdLS patients.

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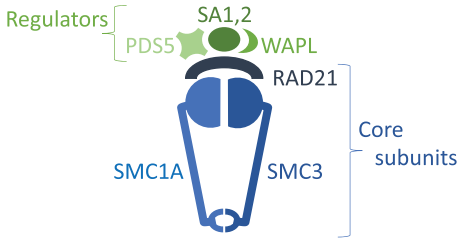

FIGURE 1: Core cohesin subunits (blue) SMC1A and SMC3 contain ATPase globular head domains and associate via hinge/dimerization domains located distally at the end of long antiparallel coiled coils. RAD21 (blue) caps the ATPase heads and in turn recruits auxiliary factors (green) PDS5, WAPL, and either SA1 or SA2. DNA (not shown) is thought to reside with the lumens of SMC coiled coil domains.

Human	Yeast
SMC1A	Smc1
SMC3	Smc3
RAD21	Mcd1/Scc1
SA1 or SA2	Scc3/Irr1
PDS5A or PDS5B/APRIN	Pds5
WAPL	Rad61
Sororin	N/A
ESCO2 or ESCO1	Eco1/Ctf7
NIPBL	Scc2
MAU2	Scc4

TABLE 1: Table of cohesin and cohesin regulator names in humans and yeast. Core subunits in yellow, auxiliary cohesin core-associated complex in blue, other regulators in gray.

Cohesin complexes and effectors

Cohesins are DNA-binding ATPase ring-like complexes (Figure 1). Cohesin structure and putative functions of cohesin and its regulators are reviewed in depth elsewhere (Rudra and Skibbens, 2013b; Jeppsson *et al.*, 2014; Marston, 2014; Skibbens, 2019). Briefly, the cohesin complex in part contains ATPase subunits SMC1A and SMC3 (structural maintenance of chromosomes 1A and 3), in which SMC1,3 ATPase globular heads extend from elongated coiled coil domains that associate at their distal tips. RAD21 (radiation-sensitive 21 homolog protein) is positioned atop of the two SMC1,3 ATPase domains, forming a trinary ringlike structure (Skibbens, 2016). An auxiliary complex that contains SA1 or SA2 (stromal antigen proteins 1 and 2), PDS5A or PDS5B/APRIN (precocious dissociation of sisters A and B), and WAPL (wings apart-like) associates stably with the core ringlike structure by binding RAD21 (Figure 1 and Table 1; Rudra and Skibbens, 2013b; Jeppsson *et al.*, 2014; Marston, 2014; Nichols and Corces, 2018; Skibbens, 2019; Marko *et al.*, 2019; Davidson *et al.*, 2019; Kim *et al.*, 2019; Banigan and Mirny, 2020; Golfier *et al.*, 2020; Mayerova *et al.*, 2020; Higashi *et al.*, 2021; Matityahu and Onn, 2021). While SA and PDS5 are both required to maintain sister chromatid tethering and cohesin-dependent changes in DNA architectures (described below), WAPL instead helps drive cohesin release from DNA (Figure 2). Conversely, cohesin deposition onto DNA requires the effector heterodimer comprising NIPBL (nipped-B-like protein) and MAU2 (maternal effect uncoordinated; Figure 2; Rollins *et al.*, 1999, 2004; Ciosk *et al.*, 2000). Once bound to DNA, NIPBL and MAU2 typically dissociate from cohesins. Breaking the cycle of cohesin deposition/release from DNA is a second effector factor, the acetyltransferase ESCO2 (establishment of sister chromatid cohesion 2, also named EFO2 for establishment factor ortholog 2), which modifies SMC3 (Bellows *et al.*, 2003; Hou and Zou, 2005; Kueng *et al.*, 2006; Zhang *et al.*, 2008a; Rolef Ben-Shahar *et al.*, 2008; Ünal *et al.*, 2008). SMC3 acetylation blocks WAPL-dependent cohesin release, converting cohesins into a stable DNA-bound state (Figure 2). In response to DNA damage, however, ESCO2 can instead acetylate RAD21, which similarly stabilizes cohesin binding to DNA (reviewed in Mfarej and Skibbens, 2020a). ESCO1/EFO1, a paralog of ESCO2, also regulates cohesin dynamics, but primarily functions during the G1 portion of the cell cycle (Skibbens *et al.*, 1999; Toth *et al.*, 1999; Ivanov *et al.*, 2002; Bellows *et al.*, 2003; Hou and Zou, 2005; Kueng *et al.*, 2006; Zhang *et al.*, 2008a; Rolef Ben-Shahar *et al.*, 2008; Ünal *et al.*, 2008; Sutani *et al.*, 2009; Rowland *et al.*, 2009; Minamino *et al.*, 2015; Alomer *et al.*, 2017). As described below, the interplay of these factors provides a diverse array of DNA architectures that impact almost all facets of DNA metabolism (Rollins *et al.*, 1999, 2004; Gillis *et al.*, 2004; Krantz *et al.*, 2004; Tonkin *et al.*, 2004; Hou and Zou, 2005; Schüle *et al.*, 2005; Vega *et al.*, 2005; Musio *et al.*, 2006; Deardorff *et al.*, 2007, 2012; Horsfield *et al.*, 2007; Gordillo *et al.*, 2008; Stedman *et al.*, 2008; Kawauchi *et al.*, 2009; Dorsett, 2010; Rhodes *et al.*, 2010; Bose *et al.*, 2012; Gimigliano *et al.*, 2012; Dorsett and Merkenschlager, 2013; Pistocchi *et al.*, 2013; Remeseiro *et al.*, 2013; Yan *et al.*, 2013; Marsman *et al.*, 2014; Minor *et al.*, 2014; Muto *et al.*, 2014; Mannini *et al.*, 2015; Schuster *et al.*, 2015; Yuan *et al.*, 2015; Banerji *et al.*, 2016, 2017; Fazio *et al.*, 2016; Boudaoud *et al.*, 2017; Muto and Schilling, 2017; Gu *et al.*, 2021; Weiss *et al.*, 2021).

Cohesin is a pleiotropic regulator of genome biology

Cohesin and cohesin effectors are involved in a wide range of biological processes. The first and best-understood function of cohesin is to tether together the products of DNA replication, termed sister chromatid cohesion (SCC). During S phase, cohesins are loaded, via transient association of NIPBL-MAU2 (yeast Scc2, Scc4), onto each nascent sister chromatid as they emerge from the DNA replication fork (Skibbens *et al.*, 1999; Ciosk *et al.*, 2000; Lengronne *et al.*, 2006; Moldovan *et al.*, 2006; Rudra and Skibbens, 2013a; Nasmyth, 2017; Murayama *et al.*, 2018; Zheng *et al.*, 2018). ESCO2 (yeast Eco1/Ctf7—hereafter ESCO2/Eco1) is recruited to the fork via PCNA, MCM, and other DNA replication factors (Skibbens *et al.*, 1999; Moldovan *et al.*, 2006; Ivanov *et al.*, 2018; Minamino *et al.*, 2018; Yoshimura *et al.*, 2021). Once recruited, ESCO2 acetylates SMC3 subunits on each of the newly deposited cohesins (Ünal *et al.*, 2008; Rolef Ben-Shahar *et al.*, 2008; Zhang *et al.*, 2008b). SMC3 acetylation precludes WAPL-dependent dissociative activity, thereby converting cohesins to a tethering competent dimeric or oligomeric state (Zhang *et al.*, 2008b; Cattoglio *et al.*, 2019; Shi *et al.*, 2020; Kulemzina *et al.*, 2012; Tong and Skibbens, 2015; Eng *et al.*, 2015; Xiang and Koshland, 2021). In this way, the establishment of cohesion is intimately coupled to DNA replication. The maintenance of cohesion identifies the products of DNA replication as sister chromatids until mitosis. At anaphase onset, RAD21 (Mcd1/Scc1 in yeast) is degraded, allowing sister chromatids to move apart and into the newly forming daughter cells, thus ensuring high-fidelity chromosome segregation (Figure 2; Guacci *et al.*, 1997; Michaelis *et al.*, 1997; Uhlmann and Nasmyth, 1998; Ciosk *et al.*, 1998; Uhlmann *et al.*, 1999).

A second role for ESCO2 and cohesins is to promote chromosome condensation. Condensation occurs during prophase, early

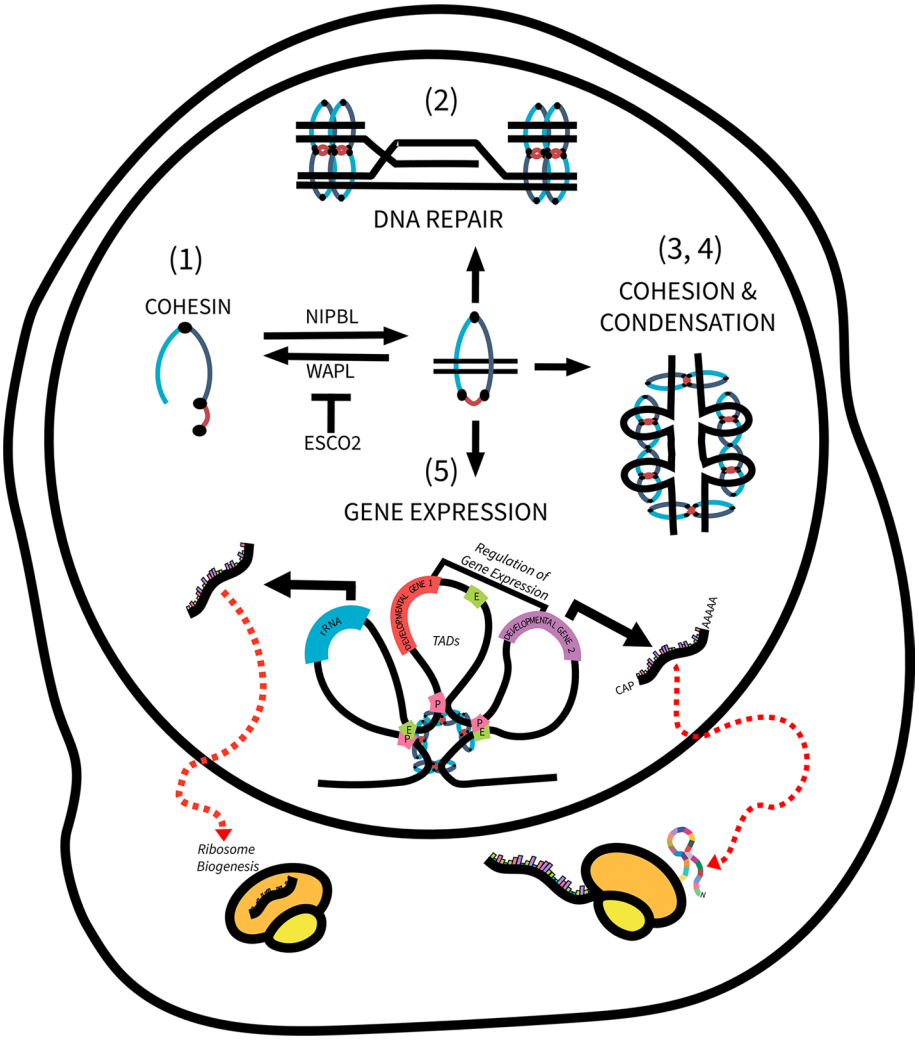

FIGURE 2: Cohesins regulate central processes that promote genome structure and function. Cohesin binds to DNA in an NIPBL-dependent manner and releases from DNA via the WAPL release factor (step 1). The ESCO2 acetyltransferase promotes stable binding of cohesin to DNA, converting cohesin into a WAPL-refractory state (step 1). Once bound to DNA, cohesin regulates a variety of cellular processes, including cohesion, which drives DNA repair through homologous recombination (step 2), sister chromatid cohesion (step 3), chromosome condensation (step 4), and regulation of gene expression (step 5). Cohesin-dependent gene expression occurs through formation of topologically associated domains (TADs), chromatin looping, and rRNA transcription to promote RNA biogenesis (lower portion of figure). Evidence implies that all of these processes contribute to the etiologies of cohesinopathies.

during mitosis, packaging chromosomes into discrete units that can be segregated faithfully during anaphase (Figure 2). Mutation of *ESCO2/ECO1*, or most cohesin subunit genes, results in significant chromosome condensation defects (Guacci *et al.*, 1997; Skibbens *et al.*, 1999; Hartman *et al.*, 2000; Gard *et al.*, 2009; Orgil *et al.*, 2015). Notably, ESCO2/Eco1 activities are limited to S phase (Skibbens *et al.*, 1999), becoming a substrate for ubiquitination-based proteolysis at the end of S phase (Lyons and Morgan, 2011; Lyons *et al.*, 2013). Thus, ESCO2/Eco1-dependent acetylation of cohesins during S phase appears to license mitotic condensation reactions that occur much later in the cell cycle (Guacci *et al.*, 1997; Skibbens *et al.*, 1999; Toth *et al.*, 1999; Ivanov *et al.*, 2002; Rolef Ben-Shahar *et al.*, 2008; Ünal *et al.*, 2008). The role that cohesins play in condensation remains unclear, but they may act indirectly, for instance, by licensing (recruitment or activation) condensins. Condensins are closely related SMC-type complexes that are central to chromatin compaction during mitosis (Guacci *et al.*, 1997; Lavoie *et al.*, 2002, 2004; Gard *et al.*, 2009; Ding *et al.*, 2018). Notably, mutation or knockdown of *WAPL/RAD61* instead results in hypercondensed chromosomes, likely due to persistent and increased levels of chromatin-bound cohesins (Lopez-Serra *et al.*, 2013; Shen and Skibbens, 2017, 2020).

Reinforcing cohesion between sister chromatids ensures a ready template if DNA double-strand breaks occur. Thus, a third role for cohesin and ESCO2/Eco1 is to produce a special form of cohesion that occurs outside of S phase, termed damage-induced cohesion (DIC). In this case, DNA damage induces a new wave (post–S phase) of ESCO2/Eco1 expression, which in turn acetylates RAD21 (yeast Mcd1/Scc1) to promote close spatiotemporal positioning of sister chromatids. This DIC pathway promotes strand-invasion reactions and is critical for error-free DNA repair via homologous recombination (Figure 2; Ström *et al.*, 2004, 2007; Ünal *et al.*, 2004, 2007; Ström and Sjögren, 2007; Mfarej and Skibbens, 2020b, 2022).

A fourth role of cohesins involves several mechanisms that impact gene expression (Skibbens *et al.*, 2010; Bose *et al.*, 2012; Xu *et al.*, 2013; Lu *et al.*, 2014; Xu *et al.*, 2016; Banerji *et al.*, 2016, 2017). During the G1 portion of the cell cycle, cohesins extrude DNA to form large loops, or topologically associated domains (TADs), that can span megabases of DNA (Figure 2). As opposed to cohesion-dependent loading reactions that occur during the S phase, in which NIPBL and MAU2 rapidly dissociate, loop extrusion appears to occur in response to continued NIPBL–MAU2 association. The extent of DNA extrusion by cohesins, and thus loop size, appears limited in part by ESCO1,2 and genome organization factors such as CTCF and Mediator (Wendt *et al.*, 2008; Hadjur *et al.*, 2009; Kagey *et al.*, 2010; Vos *et al.*, 2021). Once terminated, cohesins remain at the DNA loop base (*cis* interactions), but can also cross-link loops across different chromosomes (*trans* interactions) to produce large TADs that may contain hundreds of genes. Genes contained within individual TADs can be induced or repressed by chromatin-modifying complexes, producing spatially defined and unique transcriptional domains (Figure 2; Hansen, 2020; Rao *et al.*, 2014; Merkenschlager and Nora, 2016; Wutz *et al.*, 2017; Gassler *et al.*, 2017; Rowley and Corces, 2018; Davidson *et al.*, 2019; Kim *et al.*, 2019). In contrast to large TADs, small-scale cohesin-dependent looping can bring into registration DNA regulatory elements such as enhancers, insulators, and promoters, through which individual genes or gene clusters can be regulated (Figure 2). Several examples, described below, support TAD and gene-specific transcriptional regulation by cohesins.

Models for cohesinopathies

Understanding how mutations in cohesin and cohesin regulators give rise to cohesinopathies remains complex. For instance, RBS was originally posited to occur due to mitotic failure and proliferative stem cell loss (Mönnich *et al.*, 2011; Gordillo *et al.*, 2008; Morita *et al.*, 2012; Whelan *et al.*, 2012; Percival *et al.*, 2015). This mitotic failure model only gained traction due to early studies finding that yeast cell *eco1* mutants and RBS cells (*ESCO2* mutated) both exhibit SCC defects (Skibbens *et al.*, 1999; Hou and Zou, 2005; Vega *et al.*, 2005). Notably, mitotic defects do not underlie CdLS, which exhibits a suite of phenotypes similar to those of RBS (Mönnich *et al.*, 2011; Banerji *et al.*, 2016; Dorsett and Krantz, 2009). Instead, transcriptional dysregulation mechanisms for both RBS and CdLS are now well established (Xu *et al.*, 2013; Lu *et al.*, 2014; Xu *et al.*, 2016; Banerji *et al.*, 2016, 2017).

This emerging model for RBS is predicated on compelling evidence that ESCO2 (and cohesins) regulates gene transcription programs that are critical for normal development in a number of model systems. For example, *Drosophila* studies of wing development were the first to reveal dysregulation of *cut* and *ultrabithorax* genes by nipped B (NIPBL/Scc2) mutation (Rollins *et al.*, 1999, 2004). Evidence from zebrafish further revealed that defects in bone regeneration, obtained upon either Esco2 or cohesin subunit knockdowns, are coincident with reduced expression of *connexin43* (*cx43*; Banerji *et al.*, 2016, 2017). *cx43* encodes a gap junction protein that, among other things, regulates bone growth and joint formation (Iovine *et al.*, 2005; Hoptak-Solga *et al.*, 2008). Notably, exogenous expression of *cx43* partially rescues the bone growth defects that otherwise arise due to Esco2 or cohesin knockdown (Banerji *et al.*, 2016, 2017). More recent evidence reveals that Esco2 and cohesin also regulate expression of DNA damage-binding protein 1 (*ddb1*; Sanchez *et al.*, 2022). Ddb1 is a key subunit of CRL4 E3 ligase complex that is in part composed of Ddb1, Cullin4 (CUL4), and Ddb1–CUL4–associated factors (DCAFs) complex. CRL4-dependent ubiquitination provides for well-defined cessations of sequential developmental programs so that CRL4 gene mutations result in a wide array of birth defects. Notably, CRL4 is targeted by the highly teratogenic drug thalidomide (Ito *et al.*, 2010). Formally, this raises the possibility that Esco2-cohesin-dependent dysregulation of CRL4 (via *ddb1*) in RBS and CdLS maladies is coupled to the teratogenic effects of thalidomide poisoning. This model is supported by findings that exogenous expression of *ddb1* rescues many of the phenotypes that otherwise arise upon SMC3 knockdown in zebrafish embryos (Sanchez *et al.*, 2022). While speculative in that this recent study awaits independent corroboration, the link between RBS/CdLS genetic mutations and pharmacological pathways such as CRL4/thalidomide may provide new avenues for strategies to reduce birth defect severity. Finally, defects in cohesin-dependent transcription of rRNA genes and ribosome biogenesis are also well documented (Skibbens *et al.*, 2010; Bose *et al.*, 2012; (Bose *et al.*, 2012; Xu *et al.*, 2015; Herdman *et al.*, 2017; Gu *et al.*, 2021). rRNA is critical for ribosome biogenesis and protein synthesis (Figure 2). In turn, reduced ribosome function, downstream of reduced rRNA levels, results in numerous developmental maladies that include CHARGE, Treacher–Collins syndrome, and Blackfan anemia (Choesmel *et al.*, 2007; Nakhoul *et al.*, 2014; Vincent *et al.*, 2016; Merkuri and Fish, 2019). Notably, the severity of phenotypes that arise from cohesin mutation in zebrafish embryos are reduced by increasing translation rates, which in part bypasses ribosome deficiencies (Bose *et al.*, 2012; Xu *et al.*, 2013, 2015; Yuen *et al.*, 2016; Xu *et al.*, 2016; Mfarej and Skibbens, 2020a).

An emerging body of evidence also implicates oxidative stress and DNA damage (possibly upstream of gene expression defects) as contributing to RBS phenotypes (Mfarej and Skibbens, 2020a). Recent findings indeed document that RBS and CdLS cell models exhibit heightened genotoxic agent sensitivity and dysregulated intracellular redox states (Berg and Francke, 1993; Ren *et al.*, 2005; Vrouwe *et al.*, 2007; Gordillo *et al.*, 2008; Xu *et al.*, 2013; Perkins *et al.*, 2016, 2019; Cukrov *et al.*, 2018; McKay *et al.*, 2019; Olley *et al.*, 2021; Mfarej and Skibbens 2022). Consistent with a role for redox stress in cohesinopathies, the up-regulation of Eco1 during the DNA damage response relies on the transcription factor yeast AP-1 5 (Yap5). Yap5 responds to stressors (such as elevated iron levels) and in turn regulates cell oxidative states (Pimentel *et al.*, 2012; Mfarej and Skibbens, 2020b). In fact, simply mutating either cohesin genes or cohesin regulator genes is sufficient to produce elevated levels of reactive oxygen species. Notably, genotoxic phenotypes that occur in response to cohesin or *ECO1* gene mutation can be ameliorated by exposure to antioxidants such as N-acetylcysteine or riboceine (Cukrov *et al.*, 2018; Mfarej and Skibbens, 2022). In light of this, it may not be surprising that mutation of DNA repair pathways results in a suite of birth defects that overlap with those in RBS and CdLS individuals (Mfarej and Skibbens, 2020a).

CARDIAC ABNORMALITIES IN COHESINOPATHIES: WHICH FACTORS ARE TO BLAME?

Congenital heart defects are the most common source of perinatal lethality. Cardiac defects also contribute to early mortality in individuals with cohesinopathies (Parker *et al.*, 2010; de Koninck *et al.*, 2020). In fact, cardiac defects are associated with cohesinopathic-type maladies such as Warsaw breakage syndrome, Mungan syndrome, Mullegama–Klein–Martinez syndrome, Baller–Gerold syndrome, and related disorders (Diamond–Blackfan anemia and CHARGE syndrome; omim.org). Thus, cohesins appear centrally positioned as key regulators of heart development. Zebrafish and mouse embryos provide relevant models through which mutations in genes that encode for ESCO2/Esco2, NIPBL/Nipbl, and cohesin subunits, and that give rise to heart malformations, cardiac edema, and other defects, can be studied (Kawauchi *et al.*, 2009; Rhodes *et al.*, 2010; Mönnich *et al.*, 2011; Remeseiro *et al.*, 2013; Xu *et al.*, 2013; Percival *et al.*, 2015; Schuster *et al.*, 2015; Singh and Gerton, 2015; Xu *et al.*, 2015; Santos *et al.*, 2016; Cukrov *et al.*, 2018; Liu *et al.*, 2021; Kamel *et al.*, 2022; Sanchez *et al.*, 2022).

Mouse models of CdLS are particularly informative, as well as perplexing. Using *Nipbl* as an example, only 20% of heterozygous mice survive 3 wk past birth. Intriguingly, survivor tissues contain roughly 70% of NIPBL protein levels, indicative of a compensatory pathway which otherwise might render mice inviable (Kawauchi *et al.*, 2009). These findings suggest *Nipbl* haploinsufficiency, so subsequent phenotypic analyses are based in part on specimens in which additional genetic complexities may be required to support viability. Regardless, roughly 30-60% of *Nipbl* ± survivor mice exhibit heart abnormalities (such as atrial septal defects), along with numerous other skeletal and craniofacial deformities (Kawauchi *et al.*, 2009, 2016; Santos *et al.*, 2016). Heart defects predominate in CdLS individuals—why is there such poor penetrance of heart defects in mouse models? The coupling of heterozygous *Nipbl* and *Nkx2* (and early determinant of cardiac development—see below) in mice is particularly informative. *Nkx2* heterozygous mice typically form normal hearts. Double heterozygotic *Nkx2* and *Nipbl* mice, however, exhibit significantly increased (over 80%) incidence of heart defects (Santos *et al.*, 2016). These findings suggest that the penetrance of heart defects in *Nipbl* ± mice depends in part on synergistic

participation of other genes. Mice heterozygous for either *Rad21*, *Smc3*, or *Smc1a* at first blush appear to tell a different story. Collectively, mice heterozygous for these genes exhibit a suite of phenotypes that include aberrant stem cell renewals through IFN, HOXa and Lgr5 signaling pathways (Deng *et al.*, 2022; Fisher *et al.*, 2017; Chen *et al.*, 2019; Xu *et al.*, 2014), myeloid-based hematopoiesis dysregulation (Viny *et al.*, 2015; Wang *et al.*, 2019), accelerated lymphoma progression via loss of plasma cell terminal differentiation (Rivas *et al.*, 2021a, 2021b), DNA damage response deficiencies (Xu *et al.*, 2010), meiosis defects and decreased spermatogenesis (Biswas *et al.*, 2018), and a change in over 78,000 Rad21-binding *cis*-regulatory modules (Faure *et al.*, 2012). Notably, heart/cardiovascular defects are not reported in any of these studies—but neither are normal hearts documented or commented upon. Certainly, organ development is not necessarily affected equally across species, depending on the amount of gene product needed for function. Moreover, there are clear instances of different gene essentiality and phenotypic penetrance between mice and humans (Bartha *et al.*, 2018). Future studies on this specific line of inquiry may thus provide exciting new insights into heart development.

Tissue changes that occur during heart and vasculature system developments are well characterized. Briefly, linear heart tube remodeling gives rise to an arched structure, trabeculations that generate distinct chambers, "electrification" to produce a conduction system, and finally additional cell proliferations required to form atrial and ventricle septa (reviewed in Brand 2003; Buijtendijk *et al.*, 2020; Tan and Lewandowski, 2020; Kemmler *et al.*, 2021; Martin and Waxman 2021). Not surprisingly, the perturbation of numerous mechanisms can give rise to cardiovascular defects or disease. Possibilities include alterations during organogenesis that stem from death and/or migration defects of early progenitor stem cell populations, transcriptional dysregulation of cardiovascular morphogenic genes, and increased levels of reactive oxygen species (Muto *et al.*, 2011; Schuster *et al.*, 2015; Santos *et al.*, 2016; Cukrov *et al.*, 2018; de Koninck *et al.*, 2020; Mfarej and Skibbens, 2020b). These mechanisms are not mutually exclusive, so different combinations may give rise to a wide variety of heart defects. Here, we concentrate on cohesinopathic cardiac defects observed primarily in mice and zebrafish embryos.

Transcriptional dysregulation mechanisms of cohesinopathic cardiac abnormalities

A simple model for cohesinopathic cardiac defects that might interfere with heart development is that cohesin pathway mutations simply alter the expression of genes critical for heart development. *ESCO2/esco2* mutation, for instance, alters the expression of numerous genes (*DDB1/ddb1*, *CX43/cx43*, *RUNX1/ runx1*, etc.) critical for both cardiovascular development and early steps in stem cell generation (Horsfield *et al.*, 2007; Banerji *et al.*, 2016, 2017; Sanchez *et al.*, 2022; Guo *et al.*, 2018). NIPBL/Nipbl knockdown in mice and zebrafish embryos similarly reduces expression of numerous cardiac morphogenic factors (*Tbx5/tbx5*, *Nkx2.5/nkx2.5*, *Hand1/2/hand1,2* and *GATA4/5/gata4,5*) described below (Muto *et al.*, 2011, 2014; Santos *et al.*, 2016). The impact of cohesins on transcription also extends to WNT and WNT effectors such as the *OCT4, NANOG*, and *SOX17* cardiomyocyte differentiation factors (Figure 3; Kagey *et al.*, 2010; Muto *et al.*, 2011; Nitzsche *et al.*, 2011; Zhang *et al.*, 2013; Pistocchi *et al.*, 2013; Schuster *et al.*, 2015; Abboud *et al.*, 2015; Chin *et al.*, 2020). In mice embryos, the WNT-dependent β-catenin intracellular signal transducer orchestrates paracrine signaling from the endoderm to the mesoderm. Once established, mesodermal signaling promotes cardiomyogenesis (Liu *et al.*, 2007; Stefanovic *et al.*, 2009; Afouda and Hoppler, 2011).

Transcription factors control many facets of heart development, including identity of cardiac chambers, terminal differentiation in cardio myocytes, and establishment of patterning boundaries (Olson, 2006; Srivastava, 2006). TBX5 (T-box transcription factor 5) is a potent transcription activator that interacts with zinc-finger protein GATA4 (GATA binding protein 4) and NKX2.5 (NK2 homeobox 5). GATA factors, including GATA4, control the onset of cardiac differentiation (Zhao *et al.*, 2008), while all three factors (TBX5, GATA4, and NKX2.5) are required for proper heart development (Hiroi *et al.*, 2001; Lickert *et al.*, 2004; Mori *et al.*, 2006; Lou *et al.*, 2011; Stelmle and Moskowitz, 2017). In fact, coexpression of *GATA4*, *NKX2.5*, and *TBX5* is sufficient to differentiate embryonic carcinoma cells into cardiac-like myocytes (Ieda *et al.*, 2010; Afouda and Hoppler, 2011; Qian *et al.*, 2012). Other transcription factors, such as the basic helix loop helix (bHLH) transcription factors HAND1/2 (Heart and Neural Crest Derivatives Expressed 1 and 2) and SALL4 (Spalt Like Transcription Factor 4), either augment TBX5 transcription directly or function downstream of TBX5 (Stelmle and Moskowitz, 2017). Not surprisingly, mutations in either HAND1/2 or SALL4 similarly result in heart and/or chamber differentiation defects (Srivastava *et al.*, 1997; Firulli *et al.*, 1998; Kohlhase *et al.*, 2003; Koshiba-Takeuchi et al., 2006; Stelmle and Moskowitz, 2017). Downstream of transcriptional regulation, intercellular communication also is critical for proper heart development. For instance, channel proteins connexin 40 and 43 (CX40/GJA5 and CX43/GJA1, respectively) mediate gap junction intercellular communication (GJIC) that is essential for proper cardiac development and function (Figure 3). Mutations in either *CX40/Cx40/cx40* or *CX43/Cx43/cx43,* both of which are transcriptionally dependent on cohesins (Figure 3), result in a variety of cardiac phenotypes that include both morphological malformations (septal and looping abnormalities) and functional defects (arrhythmias and cardiomyopathies; Huang *et al.*, 1998; Lo and Wessels, 1998; Alcoléa *et al.*, 1999; Dasgupta *et al.*, 1999; Lo *et al.*, 1999; Nishii *et al.*, 2001; Li *et al.*, 2002; Sohl and Willecke, 2003; Severs *et al.*, 2004, 2006; Duffy *et al.*, 2006; Delmar and Makita, 2012; Salameh *et al.*, 2013; Ahir and Pratten, 2014; Molica *et al.*, 2014; Boengler and Schulz, 2017; Hyland *et al.*, 2021).

Intersection of thalidomide, CRL4, and cohesinopathic cardiac development models

Recent lines of evidence now point to roles for both thalidomide and CRL4 E3 ubiquitin ligase in cardiovasculature development. The complexity of the impact of CRL4 and thalidomide on cardiac development may best be examined through the pathway centered on the TBX5. Balanced TBX5 protein levels are critical for proper heart development: TBX5 haploinsufficiency results in Holt–Oram syndrome (bradycardia and/or cardiac fibrillation, defects in atrial/ventricular septal formation, cardiac conduction, etc.), while either elevated expression or autosomal dominant TBX5 mutations produce embryonic lethal heart defects (omim.org/entry/142900).

Cohesin and ESCO2-dependent regulation of CRL4, as well as thalidomide effects, appear to impact cardiac development by additional mechanisms. On one hand, thalidomide binds TBX5 directly (Figure 3), and specifically within the T-box domain required for DNA binding (Khalil *et al.*, 2017). Thus, thalidomide inhibits TBX5-dependent deployment of cardiovascular transcription programs. Thalidomide also disrupts TBX5-HAND2 interactions (but not, for instance, TBX5-GATA4 binding), augmenting the adverse effect on heart development (Khalil *et al.*, 2017). On the other hand, thalidomide impacts heart development through CRL4 function. In the absence of thalidomide, CRL4 ubiquitinates G-protein receptor kinase

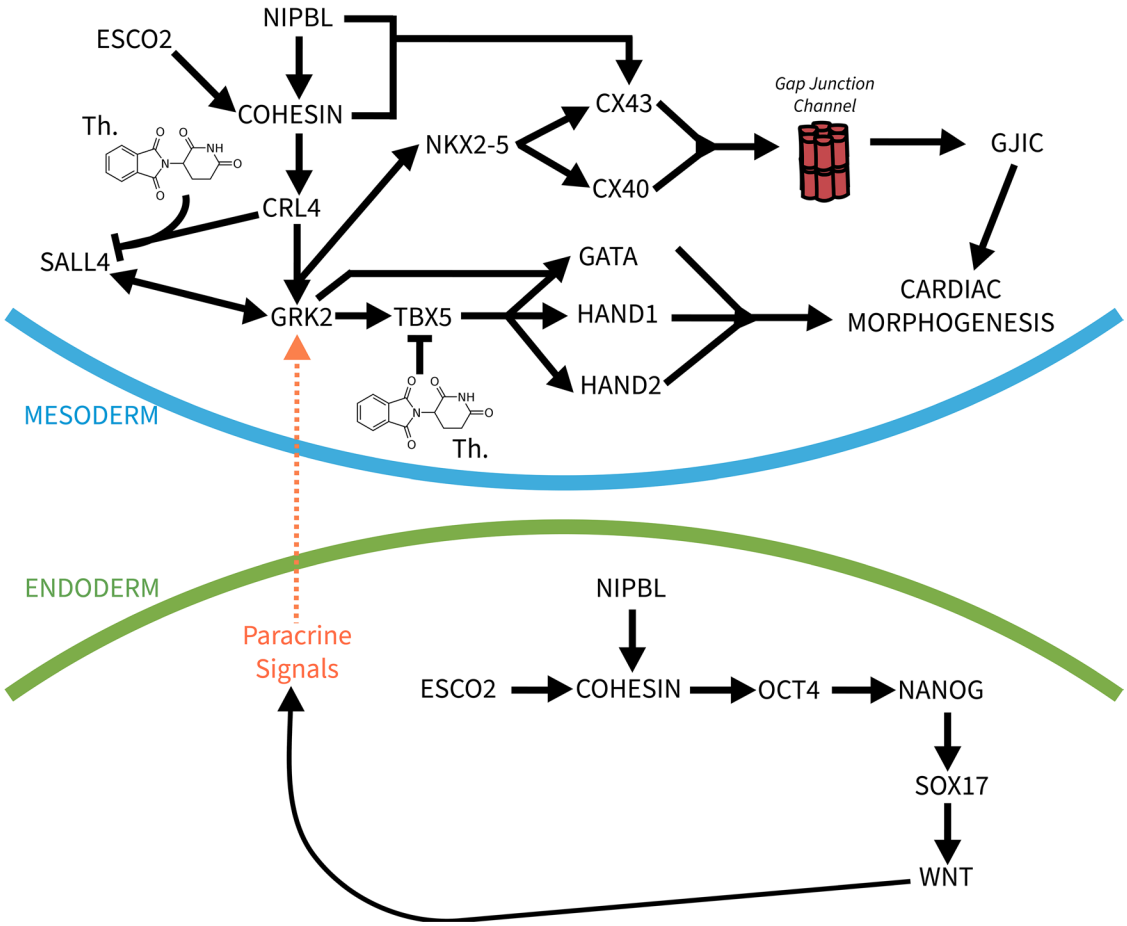

FIGURE 3: Models that describe how cohesins may function as master regulators in embryonic stages of cardiac development. Cohesin-dependent signaling occurs in the mesoderm to promote cardiac morphogenesis, whereby CRL4 and SALL4 funnel through TBX5 to mobilize heart development. In turn, TBX5 regulates two outputs that promote heart development: induced transcription of cardiac morphogenesis genes and transcription of factors required for gap junction intercellular communication (GJIC). Separately, WNT signaling in the endoderm occurs through the differentiation factors OCT4, NANOG, and SOX17. WNT outputs induce paracrine mechanisms that reinforce signaling to TX5 upstream of cardiac morphogenic programs. Lewis structure labeled with "Th." indicates the effect of thalidomide on the above factors.

2 (GRK2/Grk2), the turnover of which is critical for proper heart development in mice and zebrafish (Philipp *et al.*, 2014; Zha *et al.*, 2016). GRK2 also regulates GATA gene-dependent transcription, expanding CRL4-dependent effects on developmental pathways (Franco *et al.*, 2018). Thalidomide, however, redirects CRL4 to ubiquitinate SALL4 (Donovan *et al.*, 2018; Matyskiela *et al.*, 2018), leading to increased GRK2 levels and decreased SALL4 levels—the latter of which likely impact TBX5 function (Figure 3). Interestingly, thalidomide patient genome analysis shows a correlation between severity of cardiac defects and both *TBX5* or *SALL4* allele variations (Gomes et al., 2019). While these findings suggest that thalidomide and CRL4 influence TBX5 and cardiac effectors through mechanisms separate from those of cohesin/ESCO2 described above, the convergent outcomes highlight the importance of the way in which these pathways interact and may be pharmacologically ameliorated (Figure 3).

Cohesin-based cardiac connections via connexins?

Proper deployment of cardiac developmental programs hinges on cell–cell communication, which is mediated by the gap junction proteins Cx40 and Cx43. Specifically, *CX43* mutations result in oculodentodigital dysplasia (ODDD), which, in addition to limb, digit, and craniofacial/eye malformations, includes irregularities in heart structure and function (Debeer *et al.*, 2005; Flenniken *et al.*, 2005; McLachlan *et al.*, 2005, 2008; Shibayama *et al.*, 2005; Vasconcellos *et al.*, 2005; Gong *et al.*, 2006; Kelly *et al.*, 2006; de la Parra and Zenteno, 2007; Himi et al., 2009; Paznekas *et al.*, 2009; Gabriel *et al.*, 2011; Huang *et al.*, 2013; Jamsheer *et al.*, 2014; Laird, 2014; Kelly *et al.*, 2016; Merrifield and Laird, 2016; Porntaveetus *et al.*, 2017; Pace *et al.*, 2019; Wang *et al.*, 2019). Esco2 and/or cohesin knockdown in zebrafish fins results in both downregulated *cx43* mRNA levels and reduced bone segment regeneration (Banerji *et al.*, 2016, 2017), thereby implicating cohesin in regulation of GJIC. Based on findings that cohesins bind the upstream promoter region of *cx43*, Esco2 likely modifies cohesins to affect chromatin looping and promote *cx43* transcription. Knockdown of either Esco2 or cohesin (Smc3) also reduces mRNA levels of *semaphorin3d*, a factor downstream of CX43/Cx43 and critical for proper skeletal and heart development (Jin *et al.*, 2006; Sato *et al.*, 2006; Sanchez-Castro *et al.*, 2015; Banerji *et al.*, 2016, 2017; Lupu *et al.*, 2020). This indicates that cohesin regulation of *CX43* and GJIC communication is an additional mechanism required for proper heart development and one that, when mutated, contributes to cohesinopathic phenotypes (Figure 3). In addition,

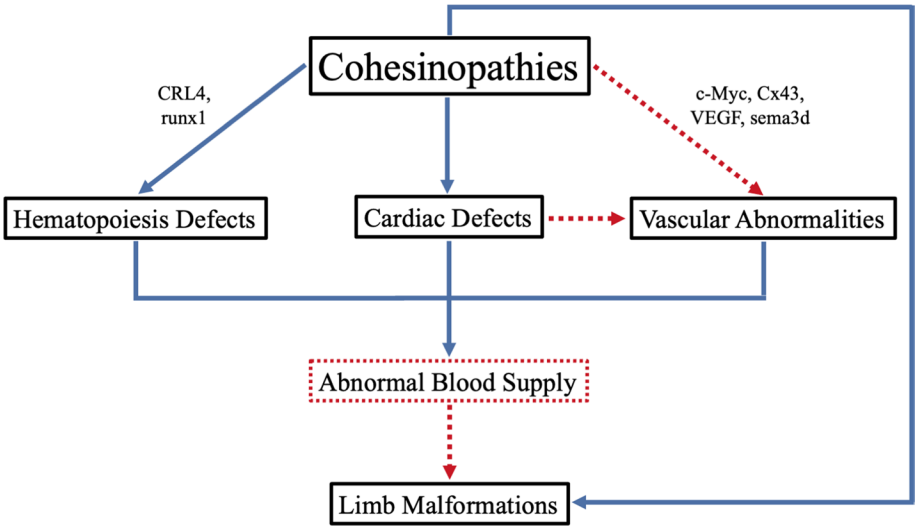

FIGURE 4: Model that describes how cardiac defects may give rise to the birth defects typically observed in cohesinopathies. Prior data substantiate a role for cohesin in both hematopoiesis defects due to CRL4 and RUNX1 dysregulation and cardiac defects. However, another possibility is that other known cohesin targets (e.g., c-Myc, CX43, VEGF, and SEMA3d) contribute to vascular abnormalities in parallel. In turn, these three affected pathways may result in abnormalities in the genesis and delivery of blood tissue. In turn, defective blood tissue function may play an important role in limb malformations that are hallmark birth defects in cohesinopathies, possibly reflecting an interconnected model that unifies the etiologies of cohesinopathy birth defects.

cx40 transcription is regulated not only directly via cohesins, but indirectly through CRL4 and downstream targets of CRL4 such as TBX5, SALL4, and NKX2.5 (Figure 3; Bruneau *et al.*, 2001; Kasahara *et al.*, 2001; Wakimoto *et al.*, 2002, 2003; Linhares *et al.*, 2004; Koshiba-Takeuchi *et al.*, 2006). Thus, *cx40* is likely to be one of many dysregulated genes in cohesinopathies.

The mechanism of GJIC dysregulation in cohesinopathies may be simple in concept but complex in reality. For instance, *cx43* mRNA levels are up-regulated as a result of Esco2 knockdown yet down-regulated as a result of *rad21* mutation during zebrafish embryogenesis (Rhodes *et al.*, 2010; Mönnich *et al.*, 2011; Schuster *et al.*, 2015). These results suggest that connexins, and many other gene products, are differentially affected depending on the nature of the cohesin pathway deficiency (for instance, reduced cohesin acetylation compared with reduced cohesin levels). One interpretation of these findings is that abolishing cohesin acetylation, while retaining cohesin and cohesin binding to DNA, affects transcriptional profiles differently from abolishing cohesins completely. An alternate possibility is that ESCO2 fulfills complex transcriptional roles independent of cohesin acetylation. In fact, numerous noncohesin factors are targeted by ESCO2/Eco1-dependent acetylation (PCNA, MPS3, Rad30; Moldovan *et al.*, 2006; Ghosh *et al.*, 2012; Billon *et al.*, 2017, Chen *et al.*, 2017). Regardless of the mechanism, dysregulation of gap junction levels or function can produce cardiomyopathies, arrhythmias, heart malformations, and/or ischemia (Severs, 1994, 2004, 2008; Gros and Jongsma, 1996; Thomas *et al.*, 1998; van der Velden and Jongsma, 2002; Dhein, 2006; van Rijen *et al.*, 2006; Chaldoupi *et al.*, 2009; Delmar and Makita, 2012; Kato *et al.*, 2012; Salameh *et al.*, 2013; Ahir and Pratten, 2014; Gemel *et al.*, 2014; Molica *et al.*, 2014; Lambiase and Tinker, 2015; Michela *et al.*, 2015; Boengler and Schulz, 2017; Leybaert *et al.*, 2017; Delmar *et al.*, 2018; Zu *et al.*, 2018; Hyland *et al.*, 2021), all of which are likely to contribute to cohesinopathic lethality.

LARGER IMPLICATIONS FOR COHESIN-BASED HEART DEFECTS

The heart is the first organ to develop and provides the blood supply that supports metabolism throughout the entire embryo. This suggests that cardiac defects present in cohesinopathic maladies are likely to enhance systemwide developmental abnormalities. In support of this prediction, cohesin and ESCO2 are known regulators of a number of vasculogenic and angiogenic factors that include CX43, c-Myc transcription factor, VEGF, and SEMA3d (Jin *et al.*, 2006; Sato *et al.*, 2006; Rhodes *et al.*, 2010; Mönnich *et al.*, 2011; Muto *et al.*, 2011; McEwan *et al.*, 2012; Pimentel *et al.*, 2012; Pocrnich *et al.*, 2012; Wuestefeld *et al.*, 2012; Wang and Simons, 2014; Nimlamool *et al.*, 2015; Sanchez-Castro *et al.*, 2015; Banerji *et al.*, 2016, 2017; Hamm *et al.*, 2016; Santos *et al.*, 2016; Lupu *et al.*, 2020; Hyland *et al.*, 2021). Moreover, numerous reports document that cohesins regulate the hematopoietic differentiation transcription factor runx1 (Horsfield *et al.*, 2007; Marsman *et al.*, 2014; Mullenders *et al.*, 2015; Viny *et al.*, 2019; de Koninck *et al.*, 2020; Ketharnathan *et al.*, 2020). In combination, these findings imply that production and circulation of blood are severely abrogated in cohesinopathies and likely contribute to cohesinopathic lethality (Figure 4). Findings in thalidomide studies, for instance, raise the possibility that cardiac defects, vasculature abnormalities, and abnormal hematopoiesis may be sufficient to produce limb malformations, independent of dysregulation of limb development transcription programs (Figure 4; D'Amato *et al.*, 1994; Therapontos *et al.*, 2009). Cohesin pathway mutation effects, however, are not limited to heart abnormalities, as numerous lines of evidence reveal that ESCO2 is also aberrantly expressed in RBS as well as in various cancers (Ryu *et al.*, 2007; van der Lelij *et al.*, 2009; Lu *et al.*, 2010; Chen *et al.*, 2018; Guo *et al.*, 2018; Wang and Liu, 2020; Zhu *et al.*, 2020).

FUTURE DIRECTIONS

Given the numerous mechanisms that may, singly or in combination, produce severe birth defects, how should researchers pursue cohesinopathic etiologies? One avenue is to focus on dysregulated genes. There is strong evidence that transcriptional dysregulations give rise to organ malformations, so that genetic engineering (gene editing/expression, KD of dysregulated transcripts, etc.) or immunomodulatory molecules that redirect CRL function may provide remedies that can ameliorate the severity of those abnormalities. Other insights may be derived from comparing mechanisms of known disorders that phenocopy cohesinopathies. For instance, similarities between cohesinopathies and other developmental maladies such as TE, Holt–Oram syndrome, Duane radial ray syndrome, and ODDD may provide important insights into shared pathways and mechanisms. Similarities in developmental disorders rarely arise due to simple coincidence—ignoring nature's cues can only delay our understanding of molecular pathogenesis.

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