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REVIEW

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Mediator complex: update of key insights into transcriptional regulation of ancestral framework and its role in cardiovascular diseases

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Abstract

Transcriptional regulation plays a pivotal role in coordinating the complex morphogenetic and molecular events involved in heart development and function. In the early stages of cardiovascular diseases (CVDs), the Mediator complex (MED) performs a variety of essential functions. While initial studies focused on correlating MED components with specific CVDs, more recent research has shifted toward a deeper exploration of the MED's role in the early pathogenesis of these diseases. This review highlights the latest findings published between January 2018 and February 2025, with a particular focus on the protein subunits MED1, MED12, MED13, MED13L, MED15, and MED23, and their implications in various cardiovascular pathologies. The MED complex is a crucial regulator of gene transcription, bridging transcription factors and RNA polymerase II. In "-omic" sciences, studying MED functions is essential to understanding molecular interactions that regulate gene expression. Within precision medicine, the MED complex is a key node in gene expression networks. Its study within the -omic framework can provide valuable insights into how molecular interactions shape cellular processes in both health and disease, ultimately enhancing the diagnosis, understanding, and treatment of CVDs through personalized medicine.

Research insights

What is currently known about this topic? (max. 3 highlights)

- Mediator complex subunits regulate gene expression linked to cardiovascular disease progression.
- Defective subunits in the Mediator complex disrupt heart function and promote vascular dysfunction.
- Some subunits, as MED1, MED14 and CDK8, are involved in adipogenesis and lipid metabolism.

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What is the key research question? (formatted as a question)

- What are the specific mechanisms by which individual Mediator complex subunits contribute to onset/progression of cardiovascular diseases?

What is new? (max. 3 highlights)

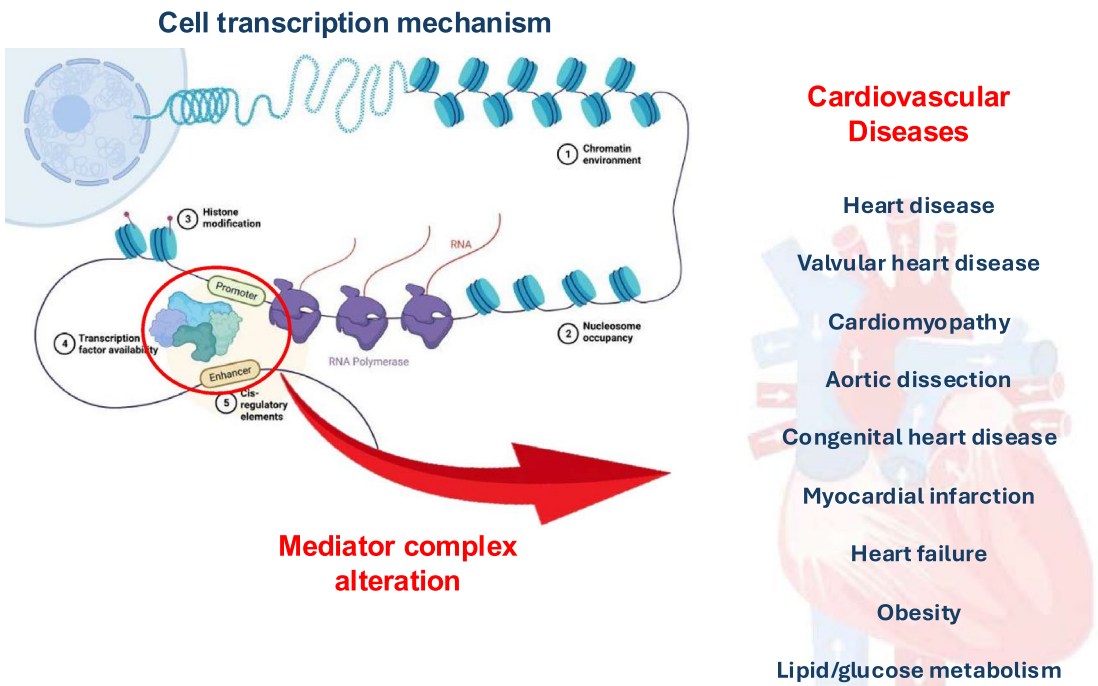
- Recent studies (2018–2024) reveal new insights into specific MED subunits linked to cardiovascular diseases.
- Dysregulation of MED1, MED12, MED13, MED13L, MED15, and MED23 are implicated in the early stages of structural heart abnormalities.
- Growing evidence connects prenatal events to early stage cardiovascular diseases, expanding research focus.

How might this study influence clinical practice? (max. 1 highlight)

- Targeting specific Mediator subunits offers potential therapeutic strategies for cardiovascular diseases.

Keywords Cardiovascular diseases, Epigenetics, Mediator complex, Precision medicine, Transcriptional regulation

Graphical abstract



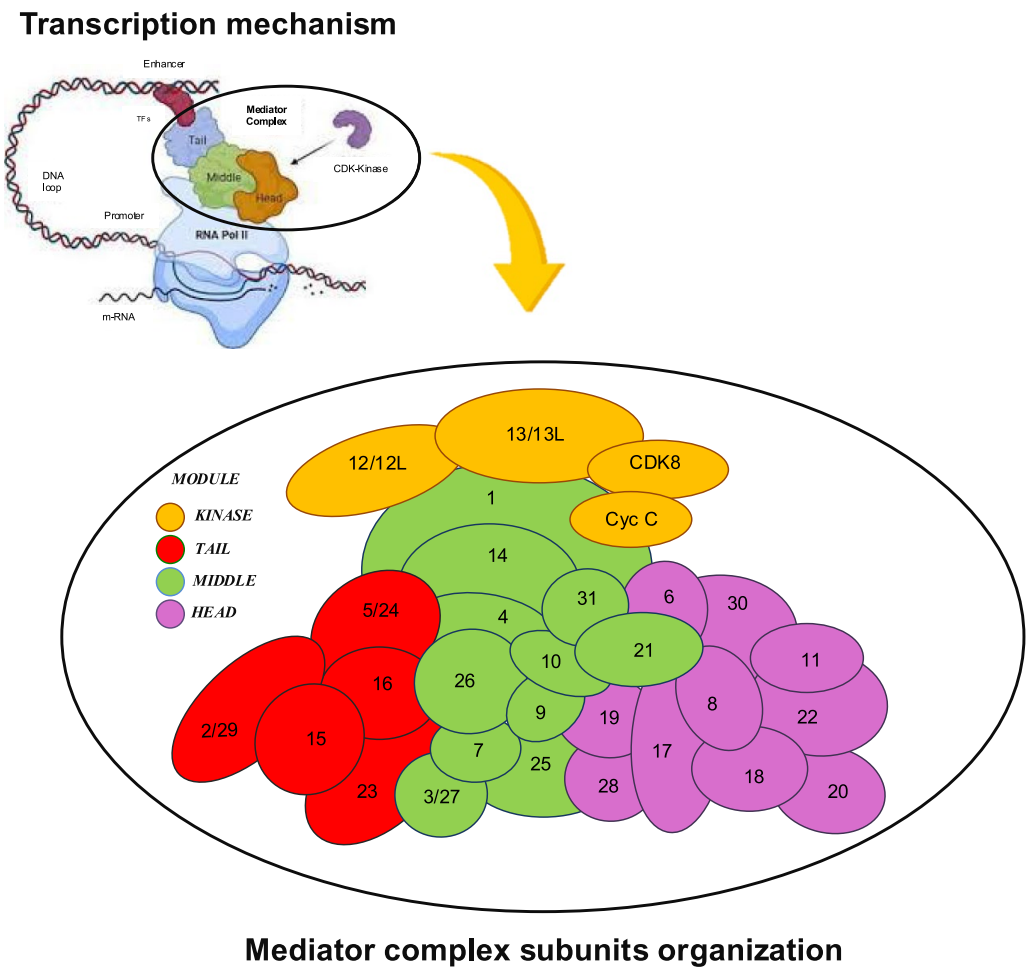


Fig. 1 Visual overview of mediator complex structure. Schematic representation of the Mediator (MED) complex structure, highlighting its overall architecture and the main sub-modules, namely, the Head, Middle, Tail, and Kinase modules. This figure also illustrates the spatial relationships between these modules and the positioning of specific subunits (such as MED1, MED12, MED13, MED15, and MED23), which are discussed in detail throughout the manuscript

Introduction

The Mediator complex (MED) is a multi-subunit assembly essential for the regulation of gene transcription. It serves as a functional bridge between transcription factors and RNA polymerase II, coordinating the expression of genes involved in diverse biological processes. In humans, the complex comprises approximately 25–30 subunits, structurally organized into distinct modules: the head and middle modules (forming the core), the tail module, and the kinase module [1] (Fig. 1). The MED complex plays a pivotal role in cellular functions, such as metabolism, inflammation, and proliferation, and its dysregulation has been increasingly associated with various pathological conditions, including cardiovascular diseases (CVDs) [2, 3]. Emerging evidence links mutations or dysfunctions in specific MED subunits to abnormalities in cardiac development, lipid homeostasis, and vascular remodeling [4, 5]. Notably, recent studies have highlighted how perturbations in MED subunit activity during prenatal development, particularly those affecting MED1, MED12, and MED23, can impair cardiomyocyte differentiation, angiogenesis, and growth factor signaling, thereby increasing susceptibility to congenital heart defects and early onset cardiovascular conditions [6–8]. For example, MED12 mutations have been identified in syndromic disorders with cardiovascular involvement, while loss of MED1 disrupts TGF-β and BMP pathways critical for heart and vessel formation [9–11]. These findings underscore the importance of understanding MED-mediated transcriptional regulation within the developmental origins of CVDs. Prenatal events, such as alterations in MED subunit-mediated signaling pathways,

can influence cardiac formation and vascular stability, predisposing to early cardiovascular disease (CVD). Studies have shown that mutations in MED subunits, such as MED12, lead to congenital defects related to the heart and vasculature, increasing the risk of cardiac malformations and developmental defects [12–15]. Given the modular structure of the MED complex, individual subunits exhibit specialized roles despite operating within a coordinated framework. Among them, MED1, MED12, MED13, MED13L, MED15, and MED23 have emerged as particularly relevant in the context of cardiovascular biology. These subunits are implicated in processes, such as energy metabolism, inflammation, and cell cycle control, all of which are central to the pathogenesis of CVDs. The rationale for focusing on these specific MED subunits lies in their demonstrated involvement in early molecular events leading to cardiac dysfunction, as well as their potential as predictive biomarkers and therapeutic targets in personalized medicine. However, the precise mechanisms through which each subunit contributes to disease remain insufficiently elucidated, representing a critical knowledge gap.

This review aims to provide a comprehensive and up-to-date synthesis of the roles of selected MED subunits in CVDs, focusing on findings published between January 2018 and February 2025. By analyzing the most clinically relevant MED subunits, MED1, MED12, MED13, MED13L, MED15, and MED23, we explore their biological significance, pathogenic mechanisms, and translational potential. Furthermore, Table 1 summarizes all MED subunits currently linked to cardiovascular pathology. A deeper understanding of these molecular regulators is essential for advancing diagnostic strategies and developing novel therapeutic approaches in cardiovascular medicine.

Literature search strategy

A comprehensive literature review was conducted to identify studies published between January 2018 and February 2025 focusing on the role of MED subunits, specifically MED1, MED12, MED13, MED13L, MED15, and MED23, in cardiovascular development and disease pathogenesis. Articles were retrieved from PubMed, Scopus, Web of Science, and EMBASE, using combinations of the following search terms: *"Mediator complex"*, *"MED subunits"*, *"cardiovascular disease"*, *"heart development"*, *"transcriptional regulation"*, *"epigenetics"*, *"precision medicine"*, and "*-omics"*. Only peer-reviewed original research articles, systematic reviews, and meta-analyses were included. As reported in Table 2, overall, the reviewed studies reveal that distinct MED subunits exert highly specialized functions in cardiac and vascular systems, often acting through transcription factor-specific recruitment and epigenetic modulation. Advanced -omic approaches such as ChIP-seq, ATAC-seq, and RNA-seq have been instrumental in mapping the transcriptional networks and enhancer–promoter dynamics coordinated by the MED complex. Notably, MED13 and MED13L show strong relevance to cardiac metabolic regulation and congenital cardiopathies, while MED12 and MED15 are more involved in vascular pathology and immune response regulation. These insights underscore the MED complex's potential as a diagnostic and therapeutic target in the context of precision cardiovascular medicine.

Clinical potential of MED subunits: towards personalized cardiovascular medicine

In recent years, interest in the MED complex in cardiovascular pathophysiology has grown significantly, due to its central role in transcriptional regulation and its ability to integrate environmental, epigenetic and genetic signals. The subunits MED1, MED12, MED13, MED13L, MED15 and MED23 are emerging as key nodes in gene networks involved in the development and progression of CVDs, revealing potential predictive biomarkers and innovative therapeutic targets (Table 1). This section highlights recent discoveries regarding alterations in MED subunits in specific cardiac pathological conditions. Figure 2 summarizes the MED complex structure and its cardiovascular roles.

MED1

MED1 is a core subunit of the Mediator complex, which is essential for transcriptional regulation. Its loss disrupts the interaction between enhancers and promoters, preventing the recruitment of RNA polymerase II and inducing chromatin remodeling [16]. Knockdown of Med1 in murine models causes severe cardiac dysfunction, with transcriptional deregulation and early death associated with the alteration of several factors. The dysregulation of genes, such as Pgc1α, Pparα, and Errα, lead indeed to cardiac hypertrophy, fibrosis, and contractile dysfunction [8, 9].

At the vascular level, the absence of MED1 in macrophages alters M1/M2 polarization, increasing inflammation through PPARγ [10]. The relationship between MED1 and macrophage polarization is a compelling area of investigation, especially considering its relevance to atherosclerosis, a disease characterized by chronic inflammation and lipid accumulation in arterial walls. Recent studies have demonstrated that MED1 facilitates alternative (M2) macrophage polarization by coactivating PPARγ and promoting the transcription of anti-inflammatory and tissue-repair genes. In contrast, MED1 deficiency skews macrophage polarization toward the pro-inflammatory M1 phenotype, which secretes

Table 1 MED subunits involved in heart and vascular system of CVD

Mediator module	Subunit	Cardiovascular disease implications	References
HEAD	MED6	–	–
	MED8	–	–
	MED11	–	–
	MED17	Congenital heart defects Endothelial dysfunction	[24, 54]
	MED18	Genetic syndromes	[24]
	MED19	Cardiovascular dysfunction Metabolic syndrome	[24]
	MED20	Obesity	[55]
	MED30	Congenital heart defects (Langer–Giedion Type II Syndrome; Cornelia de Lange Syndrome-4)	[24, 56]
	MED31	–	–
MIDDLE	MED1	Cardiac hypertophy Obesity Glucose tolerance Endothelial dysfunction	[8, 24, 57]
	MED4	Obesity Metabolic syndrome	[24]
	MED7	Cardiovascular dysfunction	[24]
	MED9	–	–
	MED10	–	–
	MED21	–	–
TAIL	MED2	–	–
	MED3	–	–
	MED5	–	–
	MED14	Adipogenesis alteration Meatbolic syndrome	[24]
	MED15	Di George syndrome and VCFS (22q11.2 deletion) Cardiac hypertrophy Metabolic disease	[24]
	MED16	–	–
	MED23	Cardiac hypertrophy Adipogenesis alteration Endothelial dysfunction	[24, 43]
	MED24	Cardiac hypertrophy	[16, 24]
	MED25	Cardiac heart defect (Basel-Vanagaite-Smith-Yosef Syndrome; Charcot-Marie-Tooth Disease type 2B2) Metabolic disorders (MODY1)	[58]
KINASE	CDK8	Heart failure Lipid biosynthesis/trafficking	[27, 59]
	MED12	Cardiac heart defect (Ohdo Syndrome; Luijan-Fryns Syndrome)	[26, 27, 29]
	MED12L	–	–
	MED13	Cyanotic congenital heart disease Metabolic syndrome Obesity	[34, 38, 60]
	MED13L	Transposition of the great arteries Conotruncal heart defect in intellectual disability Coarctation of the aorta	[36–38, 61]

cytokines like TNF-α, IL-1β, and IL-6, all implicated in plaque progression and destabilization in atherosclerosis [10]. Given that macrophage phenotype plasticity influences plaque stability, MED1's role in promoting M2 polarization may be protective in atherosclerotic settings. Atherosclerotic lesions with higher M2 macrophage content are typically associated with reduced necrotic core formation and greater fibrous cap integrity, reducing the

Table 2 Summary of key studies on mediator complex subunits and cardiovascular diseases (January 2018–February 2025)

MED subunit	Model/system	-Omic methodologies	Key findings	Cardiovascular relevance
MED1	- Mouse knockout - iPSC-derived cardiomyocytes	- ChIP-seq - RNA-seq	- Loss of MED1 impairs transcription of cardiac-specific genes during development	Essential for cardiac morphogenesis and transcriptional programming
MED12	- Zebrafish - Human aortic tissue	- RNA-seq - Epigenetic profiling	- MED12 regulates TGF-β and Wnt pathways - Mutations linked to aortic aneurysms	Involved in vascular remodeling and aortopathy
MED13	- Cardiomyocyte-specific knockout mice	- Transcriptomics - Proteomics	- Regulates metabolic gene expression - Loss promotes cardiac hypertrophy	Potential target for metabolic reprogramming in heart failure
MED13L	- Human genetic data - CRISPR-Cas9 models	- Whole-exome sequencing - RNA-seq	- Mutations cause congenital heart defects via altered enhancer–promoter looping	Implicated in developmental syndromes with cardiac phenotype
MED15	- Human vascular smooth muscle cells	- ATAC-seq - ChIP-seq	- Acts as a co-regulator of inflammatory genes in atherosclerosis	Links gene–environment interactions to vascular inflammation
MED23	- Knockout mice - Human coronary artery samples	- RNA-seq - Histone ChIP	- Modulates gene expression downstream of MAPK pathway - Associated with vascular tone and endothelial function	May influence blood pressure regulation and endothelial stability

risk of plaque rupture and thrombotic events. Furthermore, MED1 modulates the BMP and TGF-β pathways, implicated in the development of pulmonary hypertension and vascular stability [8]. MED1 has been shown to play a key role in cellular proliferation and differentiation processes, particularly in smooth muscle and endothelial cell lineages. In animal models, MED1 deletion leads to neo-endometrial hyperplasia and increased vascular smooth muscle cell (VSMC) activation, both of which mirror crucial pathophysiological processes observed in atherosclerosis. For instance, neo-endometrial hyperplasia involves uncontrolled cellular proliferation, akin to the VSMC proliferation and migration seen during intimal thickening in atherosclerotic plaques. Similarly, VSMC activation contributes to vascular remodeling by altering the structural and functional properties of the arterial wall [17, 18].

These parallels suggest that MED1 regulates transcriptional programs critical for vascular homeostasis and that its dysregulation may contribute to a pro-atherogenic environment. Therefore, findings from reproductive or vascular remodeling models provide mechanistic insights that are highly relevant to cardiovascular disease, strengthening the rationale for investigating MED1 as a modulator of atherosclerosis and vascular inflammation. Global gene expression analyses in Med1 knockout models have revealed upregulation of genes associated with fibrosis, hypertrophy, and myocardial damage, resulting in death within 4 weeks in mice [11]. Given its function in cardiomyocytes and macrophages, MED1 represents a potential early biomarker and a promising therapeutic target for cardiovascular diseases, including ventricular hypertrophy and atherosclerosis.

In preclinical studies, its deletion during pregnancy caused ventricular dilation and fatal heart failure [19]. For further details on the pathologies in which MED1 is involved, see Table 1.

Emerging therapeutic strategies include:

- RNA interference (RNAi) or antisense oligonucleotides (ASO) to selectively reduce Med1 expression in inflammatory contexts.
- CRISPR/Cas9 gene editing to correct deleterious mutations in Med1 or modulate specific enhancers related to its regulation.
- Small molecule modulators to interfere with the interaction between MED1 and nuclear receptors (e.g., PPARγ).
- Mimetic peptides or interface inhibitors to hinder the assembly of the Mediator complex in pathological contexts.

In parallel, innovative diagnostic approaches such as 2-deoxyglucose PET combined with glutamine metabolism tracers are being validated to discriminate M1/M2 macrophages in vivo, providing non-invasive tools to monitor MED1 involvement in vascular inflammation [20]. This is relevant, because MED1 plays a role in macrophage polarization, which influences vascular inflammation. Using these imaging methods, researchers may be able to non-invasively track MED1-related shifts in macrophage phenotype, offering a potential tool for both

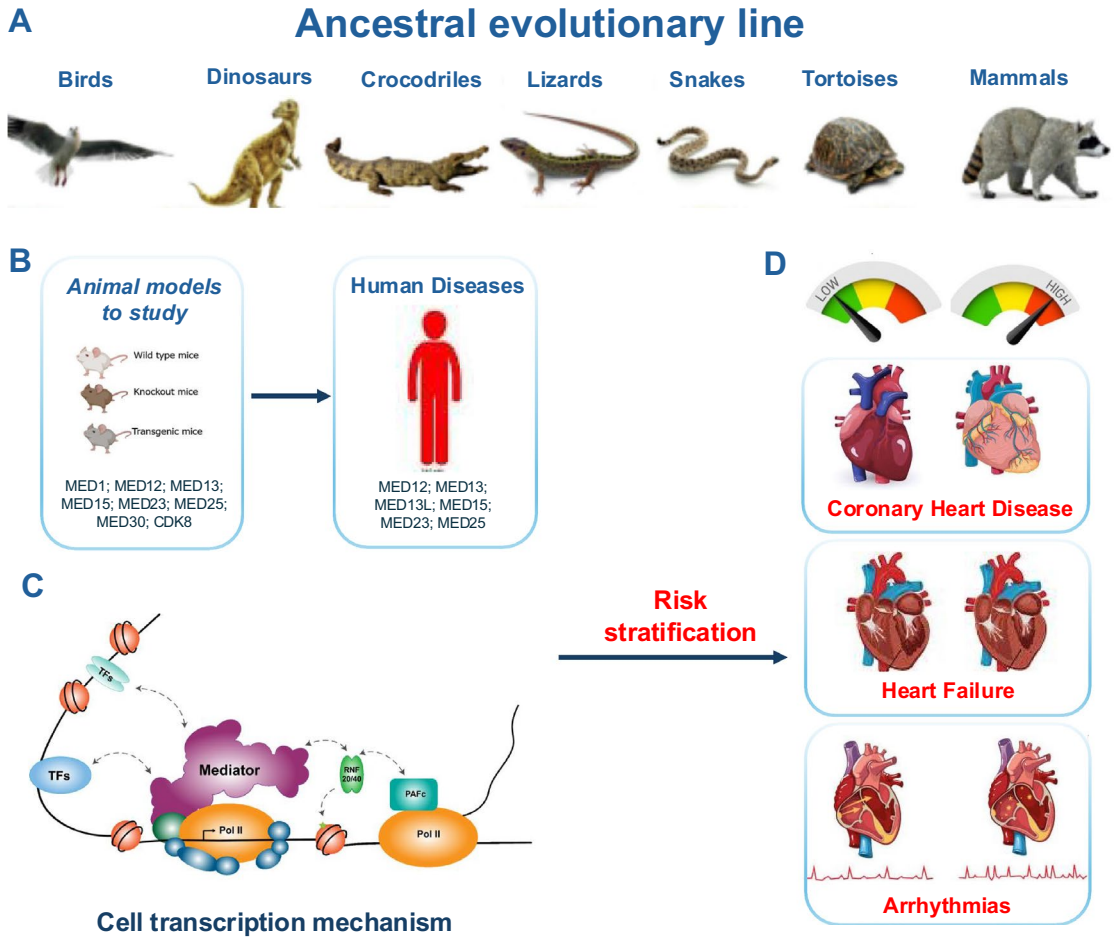


Fig. 2 Overview of the mediator complex. **A** MED is evolutionarily conserved because it regulates gene transcription, a fundamental and essential process for cellular function, growth, and development across all species. Its conservation reflects its critical role in maintaining cellular homeostasis and organismal survival. **B** In both animals and humans, numerous MED subunits have been identified as playing crucial roles in the pathogenesis of various diseases. However, only a few of these subunits have been found to be altered during prenatal development. **C** MED complex is integral to all physiological and pathological molecular pathways, serving as a key component of the eukaryotic transcriptional machinery. **D** This panel highlights the major cardiovascular diseases in which MED subunits are implicated. In detail, color gradients are intended to be conceptual

studying disease mechanisms and monitoring therapeutic responses in cardiovascular conditions.

Finally, recent studies have highlighted that Med1 in macrophages regulates ROS production and STAT1/NF-κB activation, contributing to endometrial hypertrophy and smooth muscle cell migration [21]. Therefore, modulating MED1 activity could offer new ways to reprogram the immune response and prevent pathological vascular remodeling, paving the way for personalized therapies in the treatment of cardiovascular diseases [22, 23].

MED12

MED12, a core component of the CDK8 kinase module within the Mediator the complex, is plays a key role in transcriptional repression by modulating the activity of RNA polymerase II. It is essential for proper cardiac development, particularly through its regulation of pathways such as those belonging to the Wnt/β-catenin and Nanog which are critical for cardiomyocyte proliferation and differentiation [16, 24]. Studies in mouse models have demonstrated that MED12 dysfunction impairs gene expression involved cardiac morphogenesis, cell migration, and inflammatory responses, contributing to congenital heart defects [25]. Hemizygous mutations in MED12 have been associated with the X-linked Ohdo syndrome and other syndromic phenotypes involving congenital heart defects, as reported in Table 1 [26]. Notably, a G > A transition in exon 9 of MED12, identified by whole-exome sequencing (WES)

in a family with dilated cardiomyopathy (DCM), represents a novel mechanistic insight. Computational modeling suggests that this nucleotide substitution impairs CDK8 binding, which in turn reduces its kinase activity and disrupts the regulation of calcium-handling genes in cardiomyocytes, critical elements for cardiac contractility [27]. MED12 is also implicated in aortic pathology. Its downregulation in the aortas of patients with aortic dissection (AD) has been associated with impaired proliferation of vascular smooth muscle cells and enhanced cellular senescence. Mechanistically, this is linked to the inhibition of the TGFβ1 signaling pathway [16], positioning MED12 as a potential therapeutic target for aortic disease prevention [28].

To better integrate clinical relevance, a prenatal diagnostic case is particularly illustrative. In a female fetus presenting with increased nuchal translucency, skeletal anomalies, and cardiac outflow tract defects, WES revealed a de novo heterozygous MED12 loss-of-function variant [29]. This variant was consistent with Hardikar syndrome (HS), a rare congenital disorder characterized by a spectrum of malformations, including cleft lip and/or palate, biliary tract anomalies, intestinal malrotation, and congenital cardiac defects [30, 31]. The syndrome is primarily observed in females and is often associated with de novo mutations in the MED12 gene. This case underscores the importance of MED12 in early cardiac development and highlights the potential of early genetic testing for prenatal diagnosis and management.

Given the multifaceted role of MED12 in cardiac and vascular development, therapeutic strategies may include:

- Targeting CDK8/MED12 activity with selective inhibitors, currently under investigation in oncology, which may be repurposed to modulate pathological transcription in cardiovascular diseases.
- Gene-editing approaches (e.g., CRISPR–Cas9) to correct pathogenic MED12 variants in cardiac tissues.
- RNA-based therapies or antisense oligonucleotides to modulate MED12 transcript levels in affected tissues.
- Small molecule enhancers of TGFβ1 signaling in cases, where MED12 downregulation leads to vascular defects.

Furthermore, MED12 expression profiles may serve as biomarkers for the early diagnosis of congenital malformations and for stratifying risk in individuals predisposed to DCM or AD. Integration of MED12 into precision medicine frameworks could significantly improve diagnosis, prognosis, and therapeutic targeting in patients with genetically driven cardiovascular conditions.

MED13

MED13 is an essential component of the cyclin-dependent kinase 8 (CDK8) module of the Mediator complex and plays a crucial role in transcriptional regulation in cardiac and metabolic tissues [16]. Like MED12, genetic variants and dysregulation of MED13 have been associated with various forms of cardiomyopathy and metabolic syndrome (see Table 1) [16, 24]. MED13 exerts cardioprotective effects by modulating transcription of metabolic and anti-hypertrophic genes. It has been especially implicated in congenital heart defects, such as cyanotic heart disease and hypertrophic cardiomyopathy (HCM), as well as in cardiomyopathies secondary to metabolic dysfunction [32]. In cardiomyocytes, MED13 regulates transcriptional programs essential for cardiac energy metabolism, mitochondrial function, and muscle integrity. A key mechanistic feature of MED13 is its tissue-specific overexpression during cardiac hypertrophy, which has been shown to be regulated by microRNA-208a (miR-208a). miR-208a is encoded within the Myh6 gene, which itself is highly expressed in cardiac tissue. Under conditions of cardiac stress or hypertrophy, miR-208a levels rise and suppress its direct target Thrap1, a negative regulator of MED13, thereby indirectly promoting MED13 overexpression in the heart [33]. This selective derepression of MED13 results in enhanced transcription of genes involved in oxidative metabolism and mitochondrial biogenesis, allowing the hypertrophic heart to meet increased energetic demands [34]. Notably, cardiac-specific overexpression of MED13 in mouse models has been shown to extend beyond the heart, modulating systemic metabolism by improving lipid utilization in white adipose tissue and the liver, reducing fat accumulation and increasing insulin sensitivity [32, 35]. In contrast, cardiac deletion of MED13 results in metabolic dysregulation, including glucose intolerance and hepatic steatosis [12]. These effects are believed to be mediated via unidentified circulating endocrine factors, named cardiokines, regulated by MED13. At the molecular level, MED13 influences gene expression by interacting with nuclear receptors and transcription factors, such as NURR1 and MEF2, modulating pathways involved in glucose uptake, fatty acid oxidation, and mitochondrial dynamics [16, 24]. In skeletal muscle, for instance, loss of MED13 activates a compensatory metabolic program enhancing glycogen storage through GLUT4 (Slc2a4), hexokinase II (HK2), and PGC-1α, suggesting opposing roles depending on the tissue context.

These findings underscore the pleiotropic and tissue-specific functions of MED13, making it an attractive therapeutic target not only in cardiovascular diseases such as hypertrophy and heart failure but also in metabolic disorders like obesity and insulin resistance. Future interventions might include small molecule modulators, RNA-based therapies targeting miR-208a, or CRISPR–Cas9-mediated editing to modulate MED13 expression in a tissue-selective manner, optimizing energy homeostasis and protecting against cardiovascular and metabolic complications.

MED13L

MED13L, instead, is crucial for neurocardiac development and could have implications in genetic dilated cardiomyopathy [36, 37]. Specifically, MED13L has been implicated in congenital heart defects, most notably isolated transposition of the great arteries (TGA), where gene disruptions and missense variants have been identified in multiple patients (Table 1) [24]. In addition, a duplication of the MED13L Med13L gene has been associated with aortic coarctation. Pathogenic variants in Med13L have been linked to autosomal dominant MED13L syndrome, characterized by global developmental delay and cardiac malformations. Two heterozygous variants in exon 7 of Med13L were found to cause the retention of a 73-bp portion of the intron, leading to a frameshift and premature translation termination, consistent with haploinsufficiency [36]. These findings provide insight into the genetic underpinnings of Med13L syndrome and its associated cardiac abnormalities. Recent studies have also shown that mutations or altered expression of Med13L are associated with DCM, as reported in Table 1 [37, 38].

The role of cardiac MED13L protein in regulating nuclear receptor signaling is particularly noteworthy, as this pathway governs the transcription of genes involved in modulating both cardiac and systemic energy homeostasis [38]. This makes Med13L a promising therapeutic target for addressing metabolic disorders and specific CVDs. Given the critical role of both Med13 and Med13L in regulating cardiac metabolism and function, future research should focus on identifying therapeutic strategies to modulate their activity. Targeting the pathways regulated by these subunits, such as NRs signaling and RNA modification processes, could provide novel treatments for cardiomyopathies, congenital heart defects, and energy-related cardiac diseases. Gene-editing technologies or small molecules that correct or compensate for Med13 or Med13L mutations could have significant therapeutic potential, particularly in preventing or treating conditions like DCM and congenital heart defects.

In addition, exploring the potential of Med13 and Med13L as biomarkers for early diagnosis of heart failure, congenital heart disease, and metabolic disorders could improve patient outcomes by enabling earlier, more precise interventions. Given their involvement in energy homeostasis and gene regulation, these subunits could also serve as targets for precision medicine approaches, tailoring treatments based on the specific genetic and molecular profiles of patients. With ongoing advancements in genomic medicine, the role of Med13 and Med13L as therapeutic targets is an exciting frontier in CVD research.

MED15

The role of MED15 in CVDs remains incompletely understood, but accumulating evidence suggests its involvement in the regulation of key pathways related to lipid metabolism, inflammation, and oxidative stress, processes central to the development of atherosclerosis [24]. MED15 appears to influence cholesterol and triglyceride homeostasis, both of which are essential for maintaining vascular health. Specifically, MED15 contributes to cardiovascular pathophysiology, influencing the sterol regulatory element-binding proteins (SREBP) pathway in lipid metabolism, the NF-κB signaling pathway in inflammation, and the NRF2-mediated antioxidant response in oxidative stress regulation [39, 40]. Dysregulation in lipid metabolism is a critical factor in the formation of atherosclerotic plaques, which can lead to coronary artery disease (CAD) and other cardiovascular pathologies (see Table 1) [16]. One of the most significant mechanisms by which MED15 influences CVDs is through its regulation of inflammatory gene expression. Chronic vascular inflammation is a hallmark of atherosclerosis, and MED15 has been implicated in modulating the expression of inflammatory cytokines and adhesion molecules. These factors promote the recruitment of immune cells to the vessel wall, accelerating plaque formation and the progression of atherosclerotic lesions [16]. In addition, MED15's role in cellular responses to oxidative stress, further emphasizes its importance in endothelial dysfunction. Oxidative stress is a major contributor to endothelial injury, which plays a crucial role in the initiation of atherosclerosis and vascular remodeling [6]. Through the modulation of oxidative stress pathways, MED15 may help maintain vascular homeostasis, potentially preventing or mitigating the progression of atherosclerosis. Recent case studies have highlighted the potential clinical relevance of MED15 in congenital heart defects. A primigravid woman's fetus, with a 22q11.21 microdeletion, encompassing the MED15 gene, presented with aortic stenosis and renal anomalies, which ultimately led to neonatal death at 1 month of age. This

case underscores the importance of considering the 22q11.2 deletion syndrome, in diagnosing congenital heart defects and related anomalies, including those that may be linked to MED15 dysfunction [41]. Although the prevalence of MED15 mutations, such as those associated with the 22q11.2 microdeletion, appears to be low, targeted genetic screening in patients with suggestive phenotypes may facilitate earlier diagnosis and personalized clinical management of congenital heart defects [42]. This finding indicates that MED15's impact is not limited to metabolic and inflammatory pathways but also extends to developmental processes, particularly those involved in heart and vascular formation.

These insights into the involvement of MED15 in both congenital and acquired cardiovascular conditions emphasize the need for further research to delineate its precise molecular mechanisms. Understanding how MED15 regulates lipid metabolism, inflammatory responses, and oxidative stress could pave the way for new therapeutic interventions, especially in the context of atherosclerosis and other CVDs associated with lipid dysregulation and chronic inflammation. Looking ahead, MED15 could emerge as a critical therapeutic target, particularly in the early stages of CVDs, where lipid metabolism and inflammation are key drivers of disease progression. Targeted therapies aimed at modulating MED15 activity, or its downstream pathways may help alleviate endothelial dysfunction and the progression of atherosclerosis. For instance, small molecule modulators or gene-editing strategies could be developed to either enhance or inhibit MED15 function, depending on the therapeutic need. Such approaches could be particularly effective in treating metabolic disorders like dyslipidemia, which contribute to atherosclerosis. Furthermore, genetic screening for MED15 mutations, particularly those associated with the 22q11.2 microdeletion syndrome, could aid in early diagnosis and more precise management of congenital heart defects. This would enable timely intervention and potentially improve patient outcomes, especially in individuals predisposed to both congenital and acquired cardiovascular diseases.

In preclinical models, MED15 interference has been shown to alter the inflammatory response in endothelial cells exposed to pro-inflammatory cytokines. These findings suggest that aberrant expression of MED15 may predict endothelial vulnerability and plaque instability, making it a potential biomarker for early stage atherosclerosis or vascular dysfunction. The ability to track changes in MED15 expression could provide clinicians with a valuable tool for identifying individuals at high risk for CVDs, especially those with subclinical atherosclerotic lesions.

In conclusion, MED15's involvement in lipid metabolism, inflammation, and oxidative stress highlights its potential as a novel therapeutic target in CVDs. Further research is essential to elucidate the full scope of its regulatory roles in cardiovascular health and to explore its clinical applicability in the diagnosis and treatment of atherosclerosis and related cardiovascular disorders. Through a better understanding of MED15's function, novel targeted therapies could be developed, offering more effective treatments and improving long-term outcomes for patients with cardiovascular diseases.

MED23

MED23 has been implicated in the regulation of mitogenic responses and vascular homeostasis [24, 43]. Mice with endothelial deletion of MED23 develop hypertension and endothelial dysfunction, indicating a protective role of this subunit in vascular physiology [44]. Moreover, MED23 interacts with the ERK–MAPK pathway, a crucial signaling cascade in vascular proliferation and adaptation, positioning it as a potential therapeutic target for conditions like resistant hypertension or vascular hyperplasia [45]. Studies have also highlighted its contribution to angiogenesis and the preservation of vascular integrity. In mouse models, deletion of Med23 in endothelial cells leads to embryonic lethality, intracranial hemorrhages, and dilated vessels, underscoring its essential role in vessel stability [46]. The loss of Med23 impairs vasculogenesis and disrupts angiogenesis, expecially in regions of high expression, such as the head and retina.

In vitro experiments confirm that the absence of MED23 in human endothelial cells causes similar angiogenic defects, MED23's cell-autonomous role in blood vessel formation and stability. A key mechanisms through which MED23 supports vascular health is the regulation of angiopoietin-2 (Ang2), a factor that destabilizes the vascular network and induces inflammation. MED23 deficiency leads to increased Ang2 levels, which weakens vessel stability and impairs angiogenic tubules formation [43]. Importantly, inhibiting Ang2 has been shown to partially mitigate these defects, suggesting that MED23 helps maintain vascular integrity by suppressing Ang2 signaling. This mechanism highlights the critical role of MED23 in regulating the balance between angiogenesis and vascular stability. To further expand on the mechanism by which MED23 regulates Ang2 expression, it is likely that MED23 modulates the transcriptional activity of genes involved in angiogenesis through its interaction with other transcription factors or signaling pathways, such as the NF-kB or PI3K–Akt pathways, which are known to be involved in inflammatory responses and endothelial function. By controlling the expression of these genes, MED23 ensures proper

vascular development and prevents excessive vascular permeability [43].

Given its central role in vascular integrity, MED23 could be an attractive target for therapeutic strategies aimed at addressing CVDs associated with vascular instability, such as aneurysms, vascular malformations, and diabetic retinopathy (Table 1). Targeting Med23 or modulating its activity may offer novel approaches to enhance angiogenesis and stabilize blood vessels in patients with compromised vascular function.

Potential therapeutic approach targeting the MED23–Ang2 axis could include the development of small molecules or gene therapies that specifically enhance MED23 activity in endothelial cells. Such interventions could stimulate angiogenesis in ischemic tissues, aiding in the repair of damaged blood vessels or promoting tissue regeneration following events like heart attack or stroke.

Alternatively, targeting the downstream effects of MED23, particularly its regulation of Ang2, could provide a strategy for stabilizing the vasculature in conditions characterized by excessive vascular permeability or instability. Inhibition of Ang2, in combination with Med23 modulation, may improve endothelial function and prevent the progression of CVDs driven by blood vessel fragility, such as atherosclerosis.

Moreover, MED23's role in regulating vascular stability in specialized tissues, such as the retina and brain, opens the possibility of targeted therapies for conditions like diabetic retinopathy or cerebrovascular diseases. Given its ability to modulate both angiogenesis and inflammation, MED23 could also serve as a key target in managing inflammatory-driven vascular diseases.

In conclusion, MED23 represents a promising therapeutic target for the treatment of vascular diseases. By harnessing its ability to regulate angiogenesis and vascular stability, future treatments could offer significant improvements for patients suffering from conditions, such as aneurysms, ischemic heart disease, and vascular malformations. Further research into the molecular pathways regulated by MED23 will be crucial for advancing these therapeutic possibilities.

Conclusion

The mediator (MED) complex is a multisubunit, evolutionarily conserved assembly that plays a central role in transcriptional regulation across species. Emerging evidence has highlighted the distinct contributions of several subunits, such as MED1, MED12, MED13, MED13L, MED15, and MED23, in cardiovascular development and disease (Fig. 2). Dysregulation of these subunits with a spectrum of cardiovascular conditions, including structural heart defects, vascular inflammation, and metabolic syndromes.

Recent studies emphasize the importance of these MED subunits in modulating critical gene networks involved in cardiac metabolism, vascular integrity and systemic energy balance. This growing body of research suggests that targeted manipulation of individual Mediator subunits could a novel therapeutic avenue for preventing or treating CVDs. Understanding how these subunits coordinate transcriptional responses in cardiomyocytes, endothelial cells, and immune cells may lead to the identification of precise molecular targets.

Looking forward, several key research directions are needed to unlock the full therapeutic potential of the Mediator complex in CVDs:

- Subunit-specific functional mapping. Detailed mechanistic studies are required to define the tissue-specific roles of individual MED subunits in cardiovascular physiology and pathology.
- Temporal and spatial expression profiling. Investigating how MED subunit expression patterns vary across developmental stages and disease progression could help identify critical windows for therapeutic intervention.
- Integration of multi-omics Data. Combining transcriptomics, epigenomics, and proteomics with CRISPR-based gene perturbation studies can reveal how MED subunits orchestrate complex regulatory networks in the heart and vasculature.
- Development of precision therapies. Designing small molecules, antisense oligonucleotides, or gene therapies that selectively modulate the activity of dysregulated MED subunits may enable tailored treatment of conditions like heart failure, atherosclerosis, and cardiomyopathies.
- Identification of MED-based biomarkers. Defining MED subunit-specific mutations, expression signatures, or post-translational modifications in patient samples may facilitate early diagnosis, risk prediction, and treatment monitoring.

In summary, the Mediator represents a promising yet underexplored frontier in cardiovascular biology. Continued investigation into the subunit-specific roles and regulatory mechanisms of this complex will be crucial for the development of next-generation therapeutics that address the root molecular causes of CVDs and improve long-term outcomes for patients.

Methodological limitations in the study of MED subunits: current challenges in -omic sciences

Despite significant progress in -omic sciences (transcriptomics, epigenomics, proteomics and lipidomics) in the study of MED subunits, there are important limitations

that affect the robustness and transferability of the obtained results.

First, reproducibility is a crucial challenge. Many -omic studies show variability related to technical factors, such as analytical platforms, normalization methods, statistical thresholds, and biological factors, including intra- and inter-individual heterogeneity, pathological state of the tissue. The absence of standardized protocols and poor harmonization between data sets hinder the definition of coherent molecular signatures linked to specific MED subunits [47, 48].

Second, the dependence on the tissue context should be emphasized. MED subunits exert highly specific functions, modulating the transcriptome in a cell type- and microenvironment-dependent manner. However, many -omic analyses are based on bulk tissues, which masks cellular complexity and prevents distinguishing the role of MED subunits in specific cell populations (e.g., cardiomyocytes vs. fibroblasts or immune cells). Emerging technologies, such as single-cell RNA-seq and spatial transcriptomics, are filling this gap, but their use in the cardiovascular context remains limited [49–51].

Finally, there is limited translation from animal models to humans. Mouse models have provided valuable insights into the function of MED subunits, but evolutionary divergence in enhancer–promoter sequences and MED composition may limit the transferability of results. Furthermore, many human CVD-related mutations are heterozygous or missense, while experimental models are often based on total knockouts that do not reflect human pathology [36, 52, 53].

To address these challenges, it is essential to integrate -omics data with human clinical and genomic data sets, adopt more representative experimental models, such as patient-derived human iPSCs, and develop predictive algorithms based on machine learning. Only through this integrated approach will it be possible to fully exploit the potential of MED subunits in personalized cardiovascular medicine.

Future perspectives and clinical transferability

The use of multi-omic technologies (transcriptomics, epigenomics, proteomics) and artificial intelligence is accelerating the identification of MED subunit expression patterns associated with distinct cardiovascular phenotypes. The combination of MED1, MED13 and MED23 expression levels with clinical markers could improve risk stratification, prediction of the evolution of diseases such as cardiomyopathy or pulmonary hypertension and early identification of patients eligible for targeted therapies.

Therapeutically, intervention on the subunits of the MED complex could occur through small molecules capable of modulating their activity or interaction with transcription factors; epigenetic approaches to re-establish a correct transcriptional pattern, gene editing to correct loss-of-function mutations; or RNA-based therapies, such as siRNA or antisense oligonucleotides, to selectively inhibit dysfunctional subunits. The main challenge remains tissue selectivity and long-term safety. However, the convergence of genetics, translational pharmacology and precision medicine makes the clinical potential of targeting MED subunits concrete as a new therapeutic strategy in CVD.

Glossary: Key concepts on the mediator complex and transcriptional regulation

Mediator complex	A multiprotein complex evolutionarily conserved across species that acts as a bridge between DNA-bound transcription factors and RNA polymerase II. It regulates gene transcription by modulating polymerase activity and integrating intracellular signals.
MED subunits	The subunits of the Mediator complex (e.g., MED1, MED12, and MED23) have specific and often tissue-dependent functions. They can act as activators or repressors of gene transcription depending on the biological context.
Transcriptional regulation	The process of controlling the transcription of DNA into RNA. It involves interactions between enhancers, transcription factors, Mediator, and RNA polymerase II to initiate or modulate gene expression.
Transcription factors	Proteins that bind to specific DNA sequences (regulatory motifs) and recruit the Mediator complex to activate or repress target genes.
RNA polymerase II (Pol II)	The enzyme responsible for synthesizing messenger RNA (mRNA) in

	protein-coding genes. Mediator regulates its recruitment and activity.
Enhancers and promoters	Regulatory regions of DNA. Enhancers increase gene expression even when located far from the target gene, while promoters are located near the transcription start site and serve as the binding site for the transcriptional machinery.
Transcriptional cofactors	Proteins such as mediator that do not bind directly to DNA but facilitate communication between transcription factors and the transcriptional machinery.
Cardiovascular diseases (CVDs)	Pathological conditions affecting the heart and blood vessels. Aberrant transcriptional regulation of genes involved in metabolism, inflammation, and cardiac development can contribute to their onset.

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Declarations

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