Histone lysine methylation and congenital heart disease: From bench to bedside (Review)

XIN YI[1-3], XUEJUN JIANG[1-3], XIAOYAN LI[1-3] and DING-SHENG JIANG[4-6]

[1]Department of Cardiology, Renmin Hospital of Wuhan University; [2]Cardiovascular Research Institute, Wuhan University; [3]Hubei Key Laboratory of Cardiology, Wuhan, Hubei 430060; [4]Division of Cardiothoracic and Vascular Surgery, [5]Key Laboratory of Organ Transplantation, Ministry of Education, [6]Key Laboratory of Organ Transplantation, Ministry of Health, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

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Abstract. Histone post-translational modifications (PTM) as one of the key epigenetic regulatory mechanisms that plays critical role in various biological processes, including regulating chromatin structure dynamics and gene expression. Histone lysine methyltransferase contributes to the establishment and maintenance of differential histone methylation status, which can recognize histone methylated sites and build an association between these modifications and their downstream processes. Recently, it was found that abnormalities in the histone lysine methylation level or pattern may lead to the occurrence of many types of cardiovascular diseases, such as congenital heart disease (CHD). In order to provide new theoretical basis and targets for the treatment of CHD from the view of developmental biology and genetics, this review discusses and elaborates on the association between histone lysine methylation modifications and CHD.

Contents

Correspondence to: Dr Xuejun Jiang, Department of Cardiology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan, Hubei 430060, P.R. China
E-mail: xjjiang@whu.edu.cn

Dr Ding-Sheng Jiang, Division of Cardiothoracic and Vascular Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, P.R. China
E-mail: jds@tjh.tjmu.edu.cn

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1. Introduction

Congenital heart disease (CHD) involves the anatomical structure abnormality caused by the formation of obstacles or the abnormal development of the heart and great vessels during the period of embryonic development, or a group of congenital malformations with actual or potential influence on heart function arising from the open tunnels which should have self-closed after childbirth. CHD mostly occurs during 2-8 weeks after impregnation, and it is the most common cardiovascular malformation affecting children; it severely affects the health of infants and young children (1-4). At present, CHD is regarded as a multigene disease influenced by the environment and heredity; however, the pathogenesis of the disease and the underlying molecular mechanisms and interations between genes remain unclear (5-8). Heart development is a very complex process, involving the expression of numerous genes at specific time points in the process of embryonic development, and it is regulated by many transcription factors (9,10). The realization of this process is not only determined by gene sequences, but is also largely generated by the transformation of epigenetics. In addition, an increasing number of studies have found that children with CHD have an extremely low occurrence rate of gene mutation, which can only explain a small number of CHD cases, as there is no pathogenic gene transformation for the majority of CHD cases (11-13). Some recent studies have found that 'epigenetics' may very likely participate or play an important role in the occurrence of CHD (14-16).

Epigenetics suggests that DNA sequence undergoes no transformation, but the gene expression occurs by heritable transformation, which is the other heritable material transformations in the cells apart from the heritage information and with stable heredity in the process of cell development and proliferation (17-19). Epigenetics is mainly the reversible and heritable transformation of gene function with the DNA sequences of the nucleus unchanged, and these transformations include DNA

modifications (such as methylation), various kinds of histone modifications (such as methylation, acetylation, ubiquitination and phosphorylation), chromatin remodeling, non-encoding RNA regulation (20-26). In the field of 'epigenetics', by transforming the chromatin structure with the help of related enzymes and interacting with other regulator protein, histone modifications regulate gene expression, and influence occurrence and development of diseases, which is also known as 'the second heritage code', mainly including methylation, acetylation, phosphorylation, ubiquitin, adenosine, small ubiquitin related modification, ADP ribosylation and proline isomerization (21,27,28). Histone methylation is one of the most common histone modifications, and mainly includes arginine methylation and lysine methylation (29-31). Comparatively speaking, histone methylation modification transforms loosen or agglutination state of chromatin mainly through influencing the affinity of histone and DNA, regulates gene expression by influencing the affinity of other transcription factors and structural gene promoters. Thus, it can be seen that histone methylation modification has the gene expression regulatory function similar to the DNA genetic code, and plays an important role in the process of growth and development (32-34).

In recent years, studies have shown that histone lysine methylation is not only closely related to tumor occurrence and development, developmental defects, senile dementia, cardiac hypertrophy and other clinical diseases, but also participates in the occurrence of CHD, influencing the development of heart structure and CHD candidate gene expression (35-45). For this reason, this review aims to summarize the new progress of CHD epigenetic mechanism research from the aspect of histone lysine methylation modification, in order to provide a new scientific basis for the prevention and treatment of CHD.

2. Histone methylation

Histone methylation involves the methylation occurring at histone H3 and the N-terminal of H4 arginine (Arg) or lysine (Lys) residues, catalyzed by histone methyltransferase. The function of histone methylation is mainly reflected in heterochromatin forming, genomic imprinting, X chromosome inactivation and transcriptional control (46-52). Apart from histone methyltransferase, the histone demethylase is also found (53,54). At first, it was considered that the histone methylation effect was stable and irreversible; however, the existence of methyltransferase renders the process of histone methylation more dynamical.

Modification sites of histone methylation. Histone methylation can occur on of Lys and Arg histone residues. Lysine residues can be single, double and triple methylated, while arginine residues can be single and double methylated (55-57). This varying degree of methylation largely increases the complexity of histone modifications and regulator gene expressions (29,58). Methylation action sites are in the N atoms at the side chains of Lys and Arg. Lys locus 4, 9, 27, 36 and 79 of histone H3 (H3K4, H3K9, H3K27, H3K36 and H3K79), Lys locus 20 of histone H4 (H4K20), Arg locus 2, 17, 26 of histone H3 (H3R2, H3R17 and H3R26) and Arg locus 3 of histone H4 (H4R3) are the common loci of methylation (Fig. 1). Studies have shown that histone Arg methylation is a comparatively dynamical mark, and is related to gene activation; however, Arg methylation lacking H3 and H4 is related to gene silencing (59-61). On the contrary, Lys methylation seems to be a stable mark of gene expression regulation. For example, H3K4 methylation is related to gene activation, while H3K9 and H3K27 methylation are related to gene silencing (38,62-66). In addition, H4K20 methylation is related to gene silencing, H3K36 and H3K79 are related to gene activation (67-72).

Related enzymes of histone methylation. Arginine methylation occurs at the equal locus of histone H3R2/R17/R26 and H4R3, and plays a promoting effect on gene expression (60). When the methylation process occurs, histone arginine methyltransferase or protein arginine methyltransferase (PRMT), as the collaborative activity factor, is recruited into the promoter region of the target gene and thus activates gene expression (73-75). The PRMT of catalyzing histone arginine methyltransferase includes two categories: the first type of PRMT being catalyzed to form single methylation arginine and unsymmetrical double methylation arginine, and the second type of PRMT being catalyzed to form single methylation arginine and symmetrical double methylation arginine (76,77). The family of PRMT includes PRMTl, PRMT3, RMTI/HMT, PRMT4/CAMRl and PRMT5. K4, K9, K27, K36, K79 of histone H3 and K20 of H4 all can be methylated. The methylation level is regulated and executed by a type of methyltransferase with SET structural domain with highly conserved nucleus and the pre-SET and post-SET structural domain with abundant cysteine sequence (31,78,79). The denomination of SET structural domain is constituted with 3 initial letters of 3 genes from expressing SET structural domain found at the earliest, which are Su(var)3-9, E(z) and Trx (80). Furthermore, histone demethylase can catalyze histone lysine to demethylation, and then affect the level of methylation. At present, the demethylase of histone mainly has two types: lysine specific demethylase (LSD1) and Jmjc domain-containing histone demethylase (JHDM) (81,82).

3. Histone lysine methylation and heart development

Epigenetic modification, including methylation and acetylization plays an important role in the regulation of gene expression. Studies have indicated that histone methylation can reduce or increase its affinity for charged DNA, loosen or tighten the chromatin structure to affect the accessibility and interactions between transcriptional factors and DNA templates, ultimately promote or inhibit gene expression (83,84). Recent evidence supports a prominent role for histone methylation in normal and aberrant heart development (85-87). A recent study demonstrated that changes in histone methylation levels in histone H3 that binds with critical promoter parts of the ssTnI gene can cause the corresponding changes in ssTnI gene expression, which indicated that histone methylation was involved in the regulation of myofibril gene expression in the heart during development (88). Additionally, Hand2 and Irx4 transcription factors have been shown to be reduced in SMYD1-deficient mice, suggesting that SMYD1-mediated histone methylation is necessary for the expression of these essential cardiac transcription factors (89). Hence, these findings illustrate the pervasive roles of histone methylation in the process of heart development.

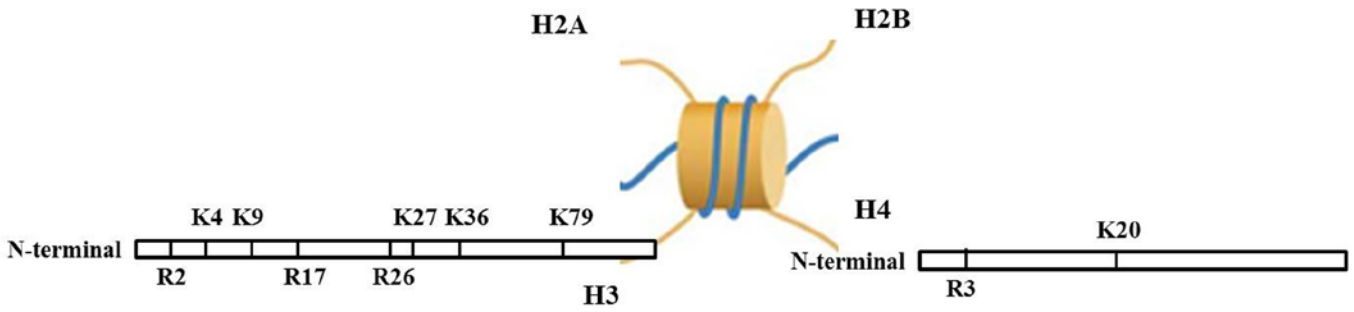

Figure 1. The common methylation action sites in H3 and H4.

4. Related enzymes of histone lysine methylation and congenital heart disease

CHD is the most common type of birth defect, manifesting as obstacles in the process of embryonic heart or blood vessel development, which may result in the morphology, structure, function and metabolic abnormalities of heart and blood vessels (2,3,5). According to the statistics, CHD has become the first reason for birth defects and the main cause of perinatal death and death in children (2). The causes of CHD are not yet completely clear; however, most scholars consider that many types of CHD are caused by a single gene mutation and chromosome aberration, and most types of CHD belong to complex genetic diseases, which are caused by the interaction between genetic factors and environmental factors (90,91). Studies have shown that histone lysine methylation modification as part of the epigenetic regulation, is involved in the development of heart and blood vessels, which is also one of the causes of CHD (92,93). The level of histone lysine methylation is determined by the balance of histone methylation and demethylation, which is a process by which methyl groups are transferred onto or removed from the amino acids of histone proteins. Histone methyltransferase and histone demethylase catalyze histone methylation and demethylation, respectively. In most cases, under the action of the methylation and demethylation, the histone tails relax or surround, which can loosen or inhibit DNA of transcription factors so as to turn the genes in DNA 'off' and 'on', resulting in the normal or aberrant expression of related genes and leading to abnormal heart development. To understand the research progress of histone lysine methylation and CHD, we summarize the known histone lysine modifying enzymes which regulates CHD in Table I.

H3K4 methylation and CHD

Trithotax group (TrxG) proteins. During heart development, several cardiac progenitor pools give rise to diverse cell lineages, such as cardiomyocytes, vascular smooth muscle cells, fibroblasts that form the connective tissues and endothelial cells of the endocardium. The heart expresses many epigenetic factors, including both histone modifying proteins and chromatin remodelers. Among the epigenetic factors, TrxG proteins are special family of chromatin factors that regulate developmental gene expression in the heart (94). TrxG proteins function in multi-subunit complexes, three TrxG complexes, the MLL complex, the BRM/BAF complex and a supercomplex, and have been purified in mammalian cells (95). TrxG proteins are evolutionarily conserved H3K4 methyltransferases that maintain the transactivation states of lineage-specific genes during embryonic development. Multiple TrxG genes are normally expressed in the mouse heart. Due to the essential function of TrxG genes, constitutive knockouts of key TrxG genes often result in lethality during early embryogenesis before cardiac phenotypes can be analyzed. The differentiation of mouse embryonic stem cells (ESCs) toward mesodermal and endodermal lineages is severely altered and, in particular, the cardiac lineage differentiation of ESCs is completely abolished in the absence of MLL2, a TrxG member. Moreover, the expression of core cardiac transcription factors and the levels of H3K4 trimethylation of these cardiac-specific promoters are significantly decreased by the loss of MLL2 (96). Taken together, these results reveal a critical role for MLL2 in the proliferation and cardiac lineage differentiation of mouse ESCs, and provide critical insight not only into the novel role of the TrxG protein in cardiac development, but also into their clinical significance in related CHD.

SMYDs. SET and myeloid, nervy and DEAF-1 (MYND) domain-containing proteins (SMYDs), including SMYD1-5, have two functional protein domains, SET (mediates histone lysine methylation activity) and MYND (mediates the protein-protein interaction and binds to DNA motifs) domains (80). SET-MYND-domain 1 (SMYD1/BOP) encodes an evolutionary conserved histone methyltransferase containing a split SET domain interrupted by a MYND domain, which includes two members SMYD1a and SMYD1b, can catalyze H3K4 methylation (97). The expression of SMYD1 is restricted to skeletal and cardiac muscles in humans, fish, chickens and mice. There is evidence to indicate that SMYD1 plays important roles in cardiac differentiation, development and function (98). The global knockdown of SMYD1a and SMYD1b in zebrafish has been shown to result in the disruption of myofibril formation and an absence of beating of the heart. Molecular and cellular experiments showed that myofibers in embryos in which SMYD1 was knocked down appeared as immature myofibers with centrally located nuclei and disorganized myofibrils, indicating that SMYD1 played a critical role in myofibers maturation and contraction (97). Conventional null SMYD1 mice die *in utero* around embryonic day 10.5 (E10.5) due to heart defects, including disrupted maturation of ventricular cardiomyocytes and malformation of the right ventricle (99). However, Diehl *et al* recently reported that SET and MYND domain containing 2 (SMYD2), is capable of H3K4 methylation when bound to Hsp90a and acts on non-histone targets by

Table I. Known histone lysine modifying enzymes involved in congenital heart diseases.

	Abnormal pattern	Species	Related cardiac phenotype
Modifiers of H3K4			
Trithotax group proteins			
MLL2	Deficiency	Mice	Embryonic lethal
	Deficiency	Mouse embryonic stem cells	Abnormal proliferation and cardiac lineage differentiation
	Mutation	Humans	Atrial/ventricular septal defects, aortic coarctation
SMYDs			
SMYD1	Deficiency	Zebrafish	Immature myofibers, non-beating heart
	Deficiency	Mice	Embryonic lethal, hypoplastic right ventricle
SMYD3	Deficiency	Zebrafish	Pericardial edema, abnormal expression of heart-chamber markers
T-box transcription factors			
TBX1	Mutation	Humans	DiGeorge syndrome, double outlet right ventricle, ventricular septal defect
TBX2	Mutation	Humans	Ventricular septal defects
TBX3	Mutation	Mice, humans	Cardiac conduction dysplasia
TBX5	Deficiency	Mice	Defective epicardial and coronary blood vessel formation
	Mutation	Humans	Holt-Oram syndrome
TBX18	Deficiency	Mice	Defective epicardium and coronary vessels
TBX20	Mutation/ deficiency	Mice	Failed heart looping, defective chamber differentiation, cardiomyopathy, arrhythmias
	Mutation	Humans	Septal defects, valvulogenesis defects, cardiomyopathy
DPF3	Mutation or deletion	Zebrafish	Incomplete cardiac looping, defective ventricular contractility and muscular fibers
PTIP	Deficiency	Mice	Abnormal cardiac conduction system, ventricular arrhythmia
SETD7	Deficiency	Zebrafish	Developmental heart edema
LSD1	Deficiency	Mice	Ventricular septal defects, salt-sensitive hypertension
BCOR	Mutation	Humans	Oculo-facio-cardio-dental (OFCD) syndrome
Modifiers of H3K9			
G9a and GLP	Deficiency	Mice	Embryonic lethality, atrioventricular septal defects
EHMT1	Mutation/ deficiency	Humans	Chromosome 9q subtelomere deletion syndrome with atrial/ventriculap septal defect
Blimp-1/PRDM	Deficiency	Mice	Ventricular septal defect and persistent arterial trunk
Jarid2	Mutation/ deficiency	Mice	Ventricular/atrial septal defect, double-outlet right ventricle, dilated atria
Modifiers of H3K27			
Polycomb group proteins			
PRC1	Mutation/ deficiency	Mice	Bone dysplasia and heart development defects
Ezh2	Mutation/ deficiency	Mice	Double outlet right ventricle, persistent truncus arteriosus, ventricular septal defects, atrial septal defects, atrioventricular canal defects and enlarged aortic valves, postnatal myocardial pathology
UTX	Deficiency	Mice	Embryonic lethality, reduced somite counts, heart malformation
	Deficiency	Mouse embryonic stem cells	Failed to develop heart-like rhythmic contractions
Jmjd3	Deficiency	Mice	Embryonic lethality
	Deficiency	Mouse embryonic stem cells	Impaired mesoderm and subsequent endothelial and cardiac differentiation
Modifiers of H3K36			
NSD1	Mutation/ deficiency	Humans	Sotos syndrome
WHSC1	Deficiency	Mice	Perinatal lethal, atrial and ventricular septal defects
	Mutation	Humans	Wolf-Hirschhorn sydrome
Jmjd5	Deficiency	Mice	Embryonic lethal
Modifiers of H3K79			
DOT1L	Deficiency	Mice	Embryonic lethal, yolk sac angiogenesis defects, cardiac dilatation, cardiomyocyte death, systolic dysfunction, conduction abnormalities
Modifiers of H4K20			
NSD1	Mutation/ deficiency	Humans	Sotos syndrome, ventricular/atrial septal defect, patent ductus arteriosus

inhibiting the functional activity of p53 via methylation of p53, lysine 370, which was differentially expressed during cardiac development with highest expression in the neonatal heart (100). To elucidate the functional role of SMYD2 in the heart, they generated knockout mice harboring a cardiomyocyte-specific deletion of SMYD2 and performed histological, functional and molecular experiments. Unexpectedly, cardiac deletion of SMYD2 was dispensable for proper morphological and functional development of the murine heart (100). H3K4 methyltransferase SMYD3 is highly expressed within developing zebrafish heart and knockdown of it led to severe defects such as pericardial edema and abnormal expression of three heart-chamber markers in cardiac morphogenesis (101). These results indicate that SMYD3 plays an important role in heart development and its proper functioning is essential for normal heart morphogenesis during development.

T-box (TBX) transcription factors. TBX transcription factors share a highly conserved DNA-binding domain and play critical roles in embryonic development (102). Six members of TBX family (TBX1, TBX18 and TBX20 of the TBX1 subfamily, and TBX2, TBX3 and TBX5 of the TBX2 subfamily) are required for the cardiac morphogenesis in mammals (103). TBX1 interacts with H3K4 methyltransferase to enhance its H3K4 monomethylation status through T-box, regulates expression of related genes by epigenetic patterns (104). TBX1 mutation can lead to DiGeorge syndrome (DGS), which is the most common microdeletion syndrome, and is characterized by congenital cardiac, craniofacial and immune system abnormalities (105). Additionally, Pan *et al* reported that a novel heterozygous TBX1 mutation, p.Q277X, was identified in an index patient with double outlet right ventricle and ventricular septal defect (106). TBX2 gene is expressed in the myocardium of the atrioventricular canal, outflow tract and inflow tract and plays a critical role in heart chamber formation (107). The genomic deletion and duplication of TBX2 gene have been found to be associated with ventricular septal defects (108). The evolutionary conserved TBX3 gene encodes T-box transcription factors and locus forms a CTCF independent autonomous regulatory domain with multiple combinatorial regulatory elements, which plays crucial roles in the development and homeostasis of the cardiac conduction system in humans and mice (109). Previous studies have found that TBX5 is expressed in the proepicardial organ or septum transversum, which is required for the normal development of proepicardium/proepicardial organ cells, as well as proper epicardial formation and maturation (110). Additionally, TBX5 deficiency delays epicardiac cell attachment to the myocardium and impairs production of epicardial-derived cells and their migration into the myocardium, and results in abnormal coronary vasculogenesis and murine ischemic cardiomyopathy (111). Clinical studies have shown that Holt-Oram syndrome is caused by mutations in TBX5, which is a human inherited disorder and manifests as left pericardium agenesis and anomalous coronary arteries along with ventricular septal defects (112-114). These findings all demonstrate that TBX5 is essential for epicardial development in hearts and establishment of the coronary vasculature. Similar to TBX5, TBX18 is also highly expressed in proepicardial cells and proepicardium, TBX18-deficient proepicardium produces an epicardium and coronary vasculature with structural and functional defects, and that remodeling of the disorganized subepicardial plexus in TBX18-deficient hearts produced a mature coronary artery network with fewer distributing conduit vessels and smaller lumen profiles, which indicates that TBX18 plays critical role in coronary development (115). However, TBX20 is necessary in heart development by regulating cardiomyocyte proliferation and regional specification and formation of cardiac chambers and valves; TBX20 mutations in mice can result in the failure of heart looping, developmental arrest, and the lack of chamber differentiation, and loss of TBX20 in mice leads to cardiomyopathy with associated arrhythmias and death (116,117). More seriously, mutations in human TBX20 result in cardiac malformations including septal defects, double outlet right ventricle and cardiomyopathy (118,119). These findings provide novel insight into the molecular mechanism underlying CHD and suggest potential implications for the development of novel preventive and therapeutic strategies for CHD.

DPF3. DPF3 is a member of the highly conserved d4 protein family, which is characterized by a double PHD finger in the C-terminal and has two splice variants DPF3a and DPF3b in human and mice (120). In the process of embryonic development, DPF3 is expressed both in heart and somites of mouse, chicken and zebrafish, which is important epigenetic regulation factor for heart and muscle development by associated with the BAF chromatin remodeling complex and binds methylated lysine residues of H3K4 (121). Previous studies have found that DPF3 mutation or deletion leads to incomplete cardiac looping, attenuated ventricular contractility and disassembled muscular fibers caused by the transcriptional deregulation of structural and regulatory proteins in the heart, which all demonstrate that DPF3 is responsible for cardiac development imbalance, ventricular septal defect and other cardiac disorders (121).

Pax transactivation domain interacting protein (PTIP). PTIP is an essential cofactor for H3K4me by KMT2C/D, which is encoded by the Paxip1 gene and is essential for embryonic development in mice and flies (122-124). As a critical component of the KMT2C/D complex, the loss of PTIP leads to reduced levels of H3K4me3 in whole embryos, ESCs and *Drosophila* larvae (125,126). Stein *et al* demonstrated that temporal and tissue-specific deletion of PTIP reduces H3K4 methylation level and alters the transcriptional program in nondividing cardiomyocytes. It is suggested that a role for KMT2 complexes not just in establishing active chromatin domains but also in the maintenance of the differentiated state over time. Furthermore, the loss of PTIP-mediated H3K4me results in significant changes in the physiology of the cardiomyocytes, suggesting that PTIP deletion is the direct cause of premature ventricular beats, a harbinger of lethal ventricular arrhythmias in nondividing cardiomyocytes (42,127).

SET domain containing protein 7 (SETD7). SETD7 also termed as SET7/9, is another type of histone lysine methyltransferase and only has SET domain for methyltransferase activity, but not MYND domain, which is initially discovered as a specific methyltransferase for nonmethylated H3K4. Tao *et al* found that the knockdown of SETD7 showed the defects in skeletal muscle formation and myofibril structures in a zebrafish developmental model (128). To examine the function of SETD7 in heart development, Kim *et al* firstly demonstrated that SETD7 was highly expressed in developing zebrafish heart and knockdown of it led to severe defects in cardiac morphogenesis such as developmental heart edema.

Furthermore, the double knockdown of SMYD3 and SETD7 caused synergistic defects in heart development. Similar to the knockdown effect, the overexpression of SETD7 also caused the heart morphogenesis defects in zebrafish (85). These results indicate that the histone modifying enzyme, SETD7, plays an important role during heart development and its proper functioning is essential for normal heart morphogenesis during development.

Lysine-specific demethylase 1 (LSD1). LSD1 (also known as AOF2/KDM1A), is a member of a group of enzymes with lysine specific demethylase activity. LSD1 performs enzymatic activity toward di- and monomethyl H3K4 and H3K9 respectively; the specificity for H3K9 arises when LSD1 binds to the androgen receptor, resulting in a shift of its activity from H3K4 (129). LSD1 interacts with proteins mostly through the tower domain, an extended helical structure. Furthmore, there is evidence to indicate that LSD1-interacting proteins can regulate the activity and specificity of LSD1 in developmental processes (130,131). Nicholson *et al* found that mice homozygous for a hypomorphic LSD1 allele exhibit a failure to survive after birth perinatally due to heart defects, with the majority of animals suffering from ventricular septal defects (132). Therefore, the above-mentioned studies thereby illuminate a novel role for LSD1 in the development of the mammalian heart.

BCL-6 corepressor (BCOR). It was found that BCOR inhibited gene transcription by interacting with BCL-6, and BCOR mutation resulted in abnormal activation of AP-2a, which was a key factor that mediated the differentiation of bone marrow mesenchymal stem cells (MSCs) (133). Fan *et al* also pointed out that BCOR recruited a histone demethylase JHDM1B to the target gene promoter, resulting in the demethylation of H3K4me3 and H3K36me2 and transcription repression of genes; however, BCL-6 mutation may impair the recruitment of JHDM1B to chromatin, resulted in increased methylation levels of H3K4 and H3K36 (133). Abnormal histone methylation due to BCOR mutation may affect BCL-6 binding to the AP-2a promoter, causing aberrant activation of gene and resulting in the in occurrence of oculo-facio-cardio-dental (OFCD) syndrome, which is a rare genetic disorder characterized by teeth with extremely long roots, and craniofacial, eye and congenital cardiac abnormalities include septal defect and mitral valve defect abnormalities (133-135). On the whole, it was identified that BCOR mutation affected heart development and AP-2α played a role in congenial heart defects associated with OFCD patients, and indicated that BCOR may be a novel target for diagnostic and treatment strategies of OFCD syndrome.

H3K9 methylation and CHD

G9a and GLP. G9a and GLP are known as major H3K9 mono- and di-methyltransferases and contribute to transcriptional silencing, which play critical biological roles in various cells and tissues. For example, G9a and GLP are indispensable for mouse early development; G9a or GLP knockout mice exhibit embryonic lethality around E9.5 due to severe growth defects (38,136,137). In order to clarify the roles of G9a and GLP in cardiac development, Inagawa *et al* analyzed the phenotypes of cardiomyocyte specific GLP knockout and G9a knockdown mice, it was shown that the H3K9me2 level decreased markedly in the nuclei of the cardiomyocytes of these mice, and the mice exhibited neonatal lethality and severe cardiac defects characterized by atrioventricular septal defects (138). These data indicated that G9a and GLP were required for H3K9me2 in cardiomyocytes and performed an essential role in normal morphogenesis of the atrioventricular septum through regulation of the size of the atrioventricular cushion.

Euchromatin histone methyl transferase 1 (EHMT1). EHMT1 is located on chromosome 9 and encodes Eu-HMTase1, which is a type of methyltransferase found in the region of the chromatin region. EHMT1 could specifically modify H3K9 methylation and thus inhibit the activity of related genes. Some studies have found EHMT1 mutation or deletion is the main cause of chromosome 9q subtelomere deletion syndrome (9qSTDS), approximately half of affected individuals have congenital heart defects primarily characterized by atrial septal defect or ventricular septal defect (139,140).

Blimp-1/PRDM. The PR/SET domain zinc-finger transcriptional repressor Blimp-1/PRDM is initially cloned as a negative regulator of key transcription factors expression and encoded by PRDM1, which contains PR/SET domain in N-terminal and C2H2 zinc finger structure in C-terminal, and thus plays essential roles in primordial germ cell specification, placental, heart, and forelimb development, plasma cell differentiation, and T-cell homeostasis through regulating DNA binding, nuclear input and recruitment of histone modifying enzymes (141). Blimp-1/PRDM causes H3K4 methylation by recruiting of histone modifying enzymes, which inhibits relevant genes expression and thus regulates the development of embryos. In the development of embryos, Blimp-1/PRDM deficiency caused serious cardiac defects including ventricular septal defect and persistent arterial trunk (141,142).

Jarid2. Jarid2, also termed as Jumonji (jmj), the founding member of the Jumonji family, all of which contain the JmjC domain that generally confers histone demethylase activities, which can catalyze H3K9 methylation and function as a transcriptional repressor and to interact with other nuclear factors. Lee *et al* found that the Jarid2 homozygous mouse embryos show heart malformations, including ventricular septal defect, noncompaction of the ventricular wall, double-outlet right ventricle, and dilated atria; furthermore, expression of Jarid2 in the interventricular septum, ventricular wall and outflow tract, which is correlated well with the locations of defects observed in the hearts of mutant mice. These results indicate that Jarid2 plays an important role in embryonic heart development (143). At the molecular level, Kim *et al* demonstrated that Jarid2 can inhibit the proliferation of cardiomyocytes, and inhibit the expression of atrial natriuretic peptide (ANP) by repressing the interaction with transcription factor Nkx2.5 and GATA4 (144). Other studies have also found that mutations or deletions of Jarid2 could increase H3K9 and H3K36 methylation level, resulting in the abnormal expression of development-related genes and thus inducing atrial septal defect or ventricular septal defect and other cardiac defects (145,146).

H3K27 methylation and CHD

Polycomb group proteins. Polycomb group proteins are key regulators of gene expression during development and differentiation, silencing genes via regulation of the chromatin structure, which act in complexes that have specific catalytic

functions important for transcriptional repression. In mammals, 2 major Polycomb group complexes exist: polycomb repressive complex 1 (PRC1) and PRC2. Whereas PRC1 ubiquitinates histone H2A on Lys119,1 PRC2 catalyzes dimethylation and trimethylation of H3K27, generating H3K27me2/3 (147). Weston *et al* pointed out that Rae28 protein, the core component of PRC1, which made PRC1 bind to H3K27me3 and then formed chromatin tight structure to prevent the occurrence of transcription. Rae28 mutation or deletion mice tend to perform bone dysplasia and heart development defects (148). However, Ezh2, the major histone methyltransferase of PRC2, trimethylates H3K27 and is essential for embryonic development (149). Delgado-Olguín *et al* have shown that Ezh2 stabilizes cardiac gene expression and prevents cardiac pathology, but Ezh2 deletion in cardiac progenitors causes postnatal myocardial pathology and destabilizes cardiac gene expression, which suggests that Ezh2 is essential for stable postnatal heart gene expression and homeostasis (150). Furthermore, Chen *et al* demonstrated that a variety of cardiovascular structural malformations were observed in the Ezh2 mutant mice, including double outlet right ventricle, persistent truncus arteriosus, membranous and muscular ventricular septal defects, atrial septal defects, atrioventricular canal defects and enlarged aortic valves, which defined an indispensible role of Ezh2 in normal cardiovascular development (151).

Ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX). Histone demethylase UTX, also known as KDM6A, that specifically targets the repressive H3K27me3 modification plays an important role in the activation of 'bivalent' genes in response to specific developmental cues. Welstead *et al* showed that UTX-deficient embryos had reduced somite counts, neural tube closure defects and heart malformation that presented between E9.5 and E13.5 (152). Other studies have also found that UTX-deficient ESCs failed to develop heart-like rhythmic contractions under a cardiac differentiation condition; UTX deficient mice exhibited severe defects in heart development and embryonic lethality; these data establish that UTX is required for heart development acts as a critical switch to activate the cardiac developmental program (153,154).

Jumonji domain-containing protein 3 (Jmjd3). Jmjd3 (KDM6B), another H3K27 demethylase, functions redundantly with UTX. Jmjd3 is induced and participates in Hox gene expression during development, neuronal differentiation and inflammation, and recent data suggest that Jmjd3 inhibits reprogramming by inducing cellular senescence (155). Jmjd3 deficient mice showed embryonic lethality before E6.5, suggesting a crucial role of Jmjd3 in early embryonic development (156,157). The ablation of Jmjd3 in mouse ESCs impaired mesoderm and subsequent endothelial and cardiac differentiation. These results clarify that Jmjd3 is necessary for mesoderm differentiation and cardiovascular lineage commitment (158).

H3K36 methylation and CHD

Nuclear receptor SET domain containing gene 1 (NSD1). NSD1 is a structure containing the SET domain proteins, with specific H3K36 and H4K20 methyltransferase activity, which is associated with Sotos syndrome by haploinsufficiency (159,160). A very frequent feature among Sotos syndrome patients with intragenic mutations was the presence of congenital heart defects or heart conduction defects, including isolated atrial septal defect, atrial septal defect in association with other structural abnormalities (patent ductus arteriosus; aortic valve dysplasia; ventricular septal defect and aortic coarctation) (161). This evidence indicates that NSD1 may be a cause of a higher prevalence of congenital heart defect in Sotos syndrome patients, which may be a novel target of diagnosis and treatment strategy for Sotos syndrome.

Wolf-Hirschhorn syndrome candidate 1 (*WHSC1).* WHSC1 contains AWS-SET-PostSET domain structure with methyltransferase activity, is encoded by Wolf-Hirschhorn syndrome related regional gene, is homologous with H3K36 specific methyltransferase Set2 in yeast, which can make H3K36 mono- di-, tri-methylated. WHSC1 regulates the expression of related genes through interaction with other transcription factors such as Nkx2.5, in embryonic heart, WHSC1 is found to interact with Nkx2.5 to repress Pdgfra expression (162). Loss of WHSC1 resulted in reduction of H3K36me3 at the Pdgfra locus and upregulation of Pdgfra. Loss-of-WHSC1 mice are perinatal lethal with significant growth retardation and die within 10 days after birth. Deletion of a critical region of human chromosome 4q16.3 containing WSHC1 gene is associated with craniofacial malformations, growth retardation, learning disability and congenital heart defects. WHSC1-null mice display a variety of atrial and ventricular septal defects that manifest those in Wolf-Hirschhorn sydrome patients (163).

Jumonji C domain-containing 5 (Jmjd5). Jmjd5 is a histone demethylase that specifically removes methyl moieties from dimethylated H3K36 and exerts a pro-proliferative effect on a large of cells. Strong Jmjd5 expression was observed only in the yolk sac at E8.5, Jmjd5 was robustly expressed in E10.5 embryos at several sites, including the heart and eye, which indicated that Jmjd5 may play an important role in heart and eye development. Jmjd5 deficiency mice embryos showed delayed development already at E8.5, embryonic lethal around E10 and were actively resorbed at E10.5 (164,165). Collectively, these data indicate that Jmjd5 is essential during embryonal development including heart development.

H3K79 methylation and CHD. H3K79 methylation is related to gene activation and DNA damage repair. Histone methylation occurs at H3K79 is catalyzed by yeast disruptor of telomeric silencing (DOT1) and its mammalian homolog, DOT1L. DOT1 is a kind of evolutionary highly conservative histone methyltransferase, which does not contain the SET domain structure, can be specific to different methylation levels in the H3K79. Compared with other histone lysine methylation, in yeast, DOT1 activity is positively regulated during transcription elongation through Rad6-Bre1 mono-ubiquitination of H2B (166). Recently, loss-of-function experiments revealed a critical role of DOT1L during mouse embryogenesis, as germline Dot1L knockout caused lethality at E10.5 with growth impairment, yolk sac angiogenesis defects, and cardiac dilation (167). In addition, cardiac-specific knockout of DOT1L resulted in increased mortality rate with chamber dilation, increased cardiomyocyte cell death, systolic dysfunction and conduction abnormalities (168). These phenotypes mimic those exhibited in patients with dilated cardiomyopathy. Interestingly, Nguyen *et al* demonstrated that DOT1L is downregulated in idiopathic DCM patient samples compared with normal controls (168). Therefore, the above studies not only establish

a critical role for DOT1L-mediated H3K79 methylation in cardiomyocyte function, but also open new avenues for the diagnosis and treatment of CHD.

H4K20 methylation and CHD. H4K20 can be catalyzed to different forms of monomethylation, dimethylation and trimethylation, PR-SET7 can only single methylate H4K20, but double and triple methylation of H4K20 are catalyzed by two other methyltransferases SUV4-20h1 and SUV4-20h2 (169). It is shown that H4K20 methylation is related to transcription silence, H4K20me3 plays a vital role in the regulation of DNA damage but not directly regulates the expression of genes (170). In addition, Tatton-Brown and Rahman have found that NSD1 is a protein containing the SET domain structure, which with specific H4K20 and H3K36 methyltransferase activity (171). NSD1 mutation or deficiency is the main cause of Sotos syndrome which with a high incidence of CHD characterized by ventricular septal defect, atrial septal defects and patent ductus arteriosus (159,160).

5. Conclusion and prospection

Histone modification is the important content of epigenetics, which is not only showed as directly regulating gene expressions, but also influencing gene activity through DNA modification because of its intimate touching with DNA. However, single histone modification usually cannot come into effect individually, and it determines together the gene expression of genome through collaborative effect of multiple histone modifications; but, yet so far, about the mechanism of histone modification, especially the specific mechanism of regulation of histone modification is not quite clear. Therefore, although the histone lysine methylation modification is related to CHD, further intensive research is still needed to illuminate relationship at the level of molecule. At the same time, besides the genetic factors of CHD pathogenesis, there still exist outer environmental factors, so that the complexity of diagnosing and treatment of diseases has been increased. However, it is clear that the comprehensive and meticulous investigation of histone lysine methylation modifications may provide new insight and understaning into the exploration of CHD pathogenesis and targeted prevention.

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