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The Molecular Genetics Mechanisms of Congenital Heart Disease (CHD)

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Abstract: As a common birth defect, the incidence rate of congenital heart disease (CHD) remains high, which brings heavy burden to families and society. Further exploration of molecular genetic mechanism can provide key basis and new ideas for revealing the cause of CHD, achieving accurate diagnosis and effective treatment. In recent years, the molecular genetic mechanisms of congenital heart disease have been continuously studied. On the one hand, multiple pathogenic genes have been discovered, including protein coding genes, non coding RNA genes, etc., and their mutations or abnormal expression are closely related to the occurrence of diseases; On the other hand, the role of gene regulatory networks and epigenetic modifications in it is gradually becoming clear, opening up new horizons for a comprehensive analysis of the pathogenesis of congenital heart disease. However, there is still much unknown about the role of the interaction between epigenetic modifications and environmental factors in the occurrence of congenital heart disease. This article reviews the roles of genetic and epigenetic mechanisms in the occurrence of congenital heart disease, in order to provide a basis for further exploration of early diagnosis and personalized treatment of congenital heart disease.

Keywords: Congenital heart disease, genetic mechanism, epigenetic mechanisms.

1. Introduction

Congenital heart disease (CHD) is the most common type of congenital malformation, accounting for approximately 28% of all congenital malformations. It refers to anatomical abnormalities caused by obstacles or developmental abnormalities in the formation of the heart and large blood vessels during embryonic development, or the failure to close channels that should automatically close after birth (in normal fetuses). The incidence rate of congenital heart disease accounts for 0.4%~1% of live infants. A small number of congenital heart diseases have the opportunity to self heal before the age of 5, and there are also a small number of patients with mild deformities that have no significant impact on circulatory function and do not require any treatment, but most patients require surgical treatment to correct the deformities. With the rapid development of medical technology, surgical outcomes have greatly improved. Most patients, if treated with timely surgery, can recover to normal like normal people, without affecting their growth and development, and can meet the needs of ordinary work, study, and life.

The CHD spectrum is particularly broad, including hundreds of specific subtypes. Some patients may have multiple malformations at the same time, and the symptoms vary greatly. The lightest cases

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can be asymptomatic for life, while the most severe cases may present with severe symptoms such as hypoxia, shock, and even premature death at birth. According to the combination of hemodynamics and pathophysiological changes, it can be divided into cyanotic or non cyanotic types, and can also be divided into three categories based on the presence or absence of shunting: non shunting type (such as pulmonary artery stenosis, aortic constriction), left to right shunting type (such as atrial septal defect, ventricular septal defect, patent ductus arteriosus), and right to left shunting type (such as Tetralogy of Fallot, major vessel displacement) [1].

The specific etiology of CHD is currently unclear, and it is the result of genetic and environmental factors and their interactions. Genetic factors have a significant impact on CHD, with chromosomal abnormalities, gene mutations, copy number variation, non-coding RNA, DNA methylation, and histone modifications playing important roles in its occurrence [2]. In addition, abnormalities in certain stages of embryonic development can also lead to poor cardiac structural development, ultimately resulting in CHD. This article provides a comprehensive analysis of the relationship between chromosomal abnormalities, gene mutations, copy number variations, epigenetic modifications, and the occurrence of congenital heart disease, in order to provide a basis for further exploration of early diagnosis and personalized treatment of congenital heart disease.

2. Genetic Mechanism

2.1. Gene Mutations

Gene mutations are one of the main causes of CHD, and the discovery of CHD gene mutations has been accelerated with the completion of human genome sequencing. The genes associated with CHD include transcription factors (TFs) and pathway genes, with gene deletions or mutations being the most common abnormalities.

GATA4, NKX2.5, and ZIC3 play important roles in the formation of cardiac structures and are important TFs. After the NKX2.5 gene mutation, protein transcription is interrupted, and important functional regions after the mutation site cannot be transcribed normally; Mutations in the GATA4 gene lead to changes in protein structure, reduced transcriptional activity, impaired ability to introduce cells into the nucleus, affecting transcriptional activation, and ultimately resulting in abnormal cardiac structure; The protein function encoded by ZIC3 depends not only on its localization in the nucleus, but also on its ability to subsequently activate target genes, and the zinc finger domain plays an important role in these functions. Li Qingman et al. conducted a screening study on NKX2.5, GATA4, and ZIC3 gene mutations in 210 patients with sporadic congenital simple heart disease in Hainan Province [3]. The research results showed that the three TFs mentioned in this article may have novel gene mutations that play an important role in cardiac function. Further animal experiments are needed to explore the genetic mechanisms underlying CHD caused by genetic mutations.

The Notch pathway is involved in pathways such as the ventricular tube, cardiac conduction system, and ventricle. This pathway plays an important regulatory role in the development of the atrioventricular canal (AVC), outflow tract (OFT), aortic valve, and ventricle in mammalian hearts. It can promote myocardial cell regeneration, participate in cardiac vascular construction, and repair myocardium by negatively regulating the transformation of myocardial fibroblasts into myofibroblasts. The Notch pathway is composed of Notch receptors, Notch ligands, CSL (CBF-1, Suppressor of Hairless, Lag) DNA binding proteins, other regulatory molecules, and effectors. There are four types of Notch receptors in mammals; There are five types of Notch ligands, and abnormalities in these pathways and mutations in the Notch gene can lead to the occurrence of CHD. Ackah et al. found that in non syndromic autosomal dominant human lineages, Notch1 mutations can cause a series of developmental aortic valve abnormalities and severe valve calcification. The

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transcript of Notch1 is active in developing mouse aortic valves, and the hair related transcription inhibitory factor (Hrt) family activated by the Notch1 pathway interacts with the transcription factor Runx2 to inhibit Runx2 transcriptional activity [4]. Runx2 is closely related to aortic valve calcification and is a core transcriptional regulator of osteoblasts.

Genetic mutations are an important cause of CHD. Mutations in cardiac structural protein genes, pathway genes, and transcription factor genes can disrupt normal heart development, leading to abnormal cell proliferation and differentiation, structural formation disorders, and underdeveloped conduction systems, ultimately resulting in congenital heart disease.

2.2. Copy Number Variation

Copy number variation (CNV) refers to a change in the copy number of DNA fragments in the genome, including an increase or decrease. This type of mutation typically occurs in genomic fragments of 1kb or more, mainly manifested as submicroscopic level duplications or deletions, and is a common form of structural differences in the genome. CNV seq technology refers to the whole genome low depth CNV sequencing of sample DNA based on high-throughput sequencing technology, which has the advantages of wide detection range, high positive detection rate, and high throughput [5]. Through CNV seq testing, the genetic causes of fetal CHD can be screened. The common cause is chromosomal microdeletions, such as 7q11.23 microdeletion and 22q11.2 microdeletion

Zhou, et al. diagnosed 12 cases of 7q11.23 microdeletion and 8 cases of 7q11.23 microduplication through chorionic villus puncture, amniocentesis, and umbilical cord blood puncture in 47749 elderly pregnant women [6]. Finally, ultrasound testing revealed 10 cases of ultrasound abnormalities in 12 fetuses with 7q11.23 microdeletion, including 4 cases of cardiovascular system abnormalities; Among the 8 cases of 7q11.23 microduplication, 6 cases showed ultrasound abnormalities, including 2 cases of cardiovascular system abnormalities, indicating that cardiovascular system abnormalities and growth and development delay are the most common clinical manifestations of prenatal 7q11.23 microduplication syndrome. Urinary and cardiovascular system abnormalities are the more common clinical phenotypes of 7q11.23 microduplication syndrome.

Zou Yue et al. selected 78 pregnant women with suspected fetal cardiac developmental abnormalities from July 2018 to March 2020 at Jilin Maternal and Child Health Hospital as subjects [7]. Among them, 35 fetuses were diagnosed with cardiac developmental abnormalities, 14 fetuses were found to have 22q11.2 microdeletion, and 1 fetus with normal cardiac development had 22q11.2 microdeletion, indicating a close relationship between 22q11.2 microdeletion and fetal cardiac developmental abnormalities.

Abnormal copy number can cause CHD. It alters the copy number of chromosome fragments and disrupts gene balance. Due to the dose effect of genes, the regulation and expression of gene networks are disrupted, affecting the role of genes related to heart development, ultimately leading to abnormalities in heart structure and function and causing disease.

2.3. Aneuploid

Chromosomal abnormalities include chromosomal numerical abnormalities (aneuploidy) and chromosomal structural abnormalities (deletion, duplication, inversion, translocation). Chromosomal aneuploidy was the first recognized genetic factor that can lead to CHD and is still considered the main cause of CHD to this day.

Common chromosomal abnormalities include trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), and sex chromosome abnormalities (Turner syndrome). Chai, et al. found through their study of 39 cases of Down syndrome treated from February 2013 to February 2018 that over 40% of

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patients had CHD, demonstrating a certain correlation between CHD and Trisomy 21 syndrome [8]; Li, et al. conducted ultrasound diagnosis on 56 cases of trisomy 18 syndrome from January 2014 to March 2020, and found that 37 cases (69.81%) had fetal cardiac structural abnormalities [9]; Zou Qing conducted a clinical study on 44 Turner syndrome patients using magnetic resonance imaging from October 2019 to February 2021, and found that the abnormal myocardial contraction function and left ventricular morphology and function in Turner patients are related to aortic lesions [10].

Aneuploid is an important pathogenic factor for CHD, as they result in incomplete chromosome numbers and disrupt genomic stability. Due to chromosomal imbalance, it interferes with the normal expression and regulation of genes, affects key processes of heart development, alters gene dosage, and ultimately leads to structural abnormalities and functional disorders of the heart, resulting in diseases.

3. Epigenetic Mechanisms

3.1. DNA Methylation

DNA methylation refers to the transfer of methyl groups to specific bases in the DNA sequence through covalent bonding under the action of DNA methyltransferase, thereby altering genetic expression without altering the DNA sequence. DNA methylation is an epigenetic modification that mainly refers to the addition of methyl groups to specific regions of DNA molecules under the action of DNA methyltransferase (DNMT), usually on the cytosine (C) residues of CpG islands, mainly occurring at the cytosine 5 carbon position of CpG dinucleotides, forming 5-methylcytosine (5-mC). In addition, DNA methylation also includes small amounts of N6 methylpurine (N6 mA) and 7-methylguanine (7-mG). CpG islands are regions in DNA sequences rich in cytosine guanine (CpG) dinucleotides. During the methylation process, the methyl group (- CH3) is covalently attached to the fifth carbon atom of cytosine, forming 5-methylcytosine (5-mC). This chemical modification will not alter the base sequence of DNA, but will affect gene expression. DNA methylation is crucial in many biological processes. During embryonic development, it contributes to cell differentiation and regulation of tissue-specific gene expression. For example, during the differentiation of embryonic stem cells into nerve cells, the DNA methylation pattern undergoes dynamic changes, activating some nerve cell specific genes while inhibiting some genes related to stem cell pluripotency.

Research has shown that in the early stages of heart development, the proliferation and differentiation of myocardial cells are key processes. Changes in DNA methylation can affect the proliferation ability of myocardial cells. For example, certain cell cycle regulatory genes are regulated by DNA methylation, and abnormal methylation may lead to dysregulated expression of these genes. When the expression of genes regulating the cell cycle is abnormal, myocardial cells may not be able to proliferate normally, resulting in insufficient myocardial tissue during heart development. Meanwhile, abnormal DNA methylation can also interfere with the normal differentiation process of genes related to myocardial cell differentiation. For example, preventing cardiac myocytes from differentiating into mature cell types with specific functions, such as atrial or ventricular myocytes, can lead to structural and functional abnormalities in the heart. Lu Ying [11] found through DNA sequencing of 210 cardiovascular disease (CVD) patients from 8 residential areas in Suzhou that the methylation of the NPPB gene promoter is positively correlated with the risk of CVD; DNA methylation binding proteins have been shown to play a bridging role in DNA methylation mediated gene silencing [12], and abnormal DNA methylation is closely related to the occurrence of human diseases. Among them, DNA methylation binding proteins are important regulatory factors of cardiac fibroblasts and have important relationships with heart failure, cardiac fibrosis, arrhythmia, etc.

DNA methylation is closely related to CHD. It adds methyl groups to specific gene regions to regulate gene expression. Abnormal DNA methylation can alter the activity of genes related to cardiac

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development, disrupt normal expression balance, inhibit their expression, affect myocardial cell differentiation and cardiac structure formation, ultimately leading to CHD.

3.2. Histone Modification

Histone modification refers to various covalent chemical modifications that occur on amino acid residues of histones. Histones are the core components of chromatin, including the major histone types H2A, H2B, H3, and H4, which form octamers. DNA wraps around these octamers to form nucleosomes, which are the basic structural units of chromatin. Histone modifications can occur at multiple sites of histones, including the N-terminal tail and the histone core region. These modifications can alter the structure and function of chromatin, thereby affecting gene expression.

Histone modifications mainly include methylation and acetylation. Histone methylation is a process that can cause structural changes in chromosomes and regulate gene expression through other transcription factors. This is determined by the site of methylation (lysine or arginine) and the degree of methylation (mono-or poly methylation). Histone methylation is catalyzed by histone methyltransferases (HMTs), which are divided into two families: histone lysine methyltransferases (HKMTs) and histone arginine methyltransferases (HRMTs). Their roles in regulating gene expression can be completely opposite, with some activating gene transcription and others inhibiting it. The state of histone methylation modification is mainly achieved through the synergistic regulation of histone methyltransferases and histone demethylases. Wang Ziwei found that knocking out the histone demethylase KDM5A in mice resulted in delayed cardiac development and incomplete myocardial compaction, proving that knocking out the histone demethylase KDM5A inhibited the proliferation and differentiation of mouse cardiomyocytes, indicating that histone methylation can lead to CHD [13].

Histone acetylation refers to the process in which histone acetyltransferases (HATs) transfer acetyl groups to lysine residues in histones, thereby activating gene transcription. This process neutralizes the positive charge of histones, making the chromatin structure looser and promoting gene transcription and expression. Histone acetylation is in a dynamic equilibrium state in the nucleus, and is regulated by histone deacetylase (HDAC) to remove acetyl groups and regulate gene expression. This dynamic balance precisely regulates gene transcription and expression in cells, and is an important mechanism for cells to control gene expression, protein activity, or physiological processes. Research has shown that HDAC3 plays an important role in CVDs such as CHD, coronary heart disease, and heart failure [14].

Histone modification plays an important role in CHD by chemically modifying histones to alter chromatin structure. Abnormal histone modifications can interfere with the accessibility and expression regulation of cardiac developmental genes. Abnormal histone methylation sites or degrees may silence or overexpress key genes, disrupt the proliferation and differentiation process of myocardial cells, and ultimately lead to congenital heart disease

3.3. Non-coding RNA

Non coding RNA (ncRNA) refers to RNA that does not encode proteins. In traditional concepts, the central principle of gene expression mainly focuses on the process of DNA transcription into messenger RNA (mRNA), which is then translated into proteins. Non coding RNA does not directly participate in protein coding, but plays a critical role in many biological processes. The non coding RNAs involved in regulation include small interfering RNA (siRNA), microRNA (miRNA), long non coding RNA (lncRNA), and circular RNA (circRNA).

The length of siRNA is usually 20-25 nucleotides. It is a double stranded RNA molecule whose main function is to silence gene expression through RNA interference (RNAi) mechanism. SiRNA

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can bind to an RNA induced silencing complex (RISC) within cells. The nuclease component in RISC can use siRNA as a template to recognize and cleave complementary mRNA sequences, thereby preventing the translation process of mRNA and achieving the goal of regulating gene expression. Zhang Fan [15] used RNAi technology to selectively silence some key CHD genes in mice, which can reduce the expression level of CHD genes in mice to the same level as normal mice, indicating that siRNA has an absolute effect on CHD.

MiRNA is generally around 20-25 nucleotides in length and is a type of endogenous single stranded non coding RNA. MiRNAs mainly function through complementary pairing with target mRNA, but unlike siRNA, miRNAs are usually not fully complementary paired. MiRNA can bind to the 3 '- untranslated region (3'-UTR) of target mRNA, inhibiting mRNA translation or promoting its degradation. Yang Weiwei et al. [16] demonstrated through amniocentesis miRNA sequencing of 30 pregnant women diagnosed with CHD fetuses by ultrasound that changes in miRNA expression levels are associated with human CVDs, including CHD.

LncRNA is an RNA that exceeds 200 nucleotides in length and can function at the transcriptional level. During the development of the heart, lncRNA may regulate gene transcription by binding to DNA. LncRNA is a key molecule regulating CVD and is involved in the occurrence and development of almost all CVDs. The study found that 29 LncRNAs were significantly regulated by angiotensin II, and the expression of Lnc-Ang362 of angiotensin II increased, which can increase the response of vascular smooth muscle cells to angiotensin II. LneRNA transcripts related to myocardial infarction, myosin heavy chain related RNA transcripts, INK4 antisense LncRNA, etc. played an important role in coronary atherosclerotic heart disease, chronic heart failure, atrial fibrillation and other diseases [17].

CircRNA is a special type of non coding RNA characterized by a closed circular structure. CircRNA does not have 5 'and 3' termini and mainly functions by adsorbing miRNA, competing with miRNA for binding, thereby indirectly affecting the expression of miRNA target genes. According to research, cardiac development is finely regulated by multiple pathways, such as Wnt/β-catenin, Notch, and others. CircRNA can interfere with signal transmission and transduction by interacting with key molecules in the pathway. CircRNA binds to the β-catenin protein in the Wnt pathway, preventing its interaction with other signaling molecules and preventing the normal activation of the Wnt pathway, which affects the proliferation and differentiation of cardiomyocytes and leads to congenital heart disease [18].

Non coding RNA is a key influencing factor of CHD, which can regulate gene expression after transcription. Non coding RNA can interfere with cardiac development in various ways, affecting the synthesis of myocardial cell related proteins, altering cardiac pathways, and ultimately leading to congenital heart disease.

4. Conclusion

This article reviews the role of genetic and epigenetic mechanisms in CHD, and analyzes them from six aspects: gene mutation, copy number variation, aneuploidy, DNA methylation, histone modification and non-coding RNA. The most important mechanism is that some genes involved in heart development mutate, leading to abnormal transcription process, and eventually lead to abnormal heart development in infants, leading to CHD. The main purpose of this article is to analyze the pathogenic mechanisms of various types of CHD, in order to deeply reveal the root causes of the disease, assist in accurate diagnosis, and screen for risks in advance through genetic testing and other means. Provide targets for innovative therapeutic strategies, such as targeted gene repair or regulation of epigenetic markers. It can also promote the development of genetic counseling, reduce the incidence of diseases, and improve the health prospects of patients and families.

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