A REVIEW ON CARDIOVASCULAR DEVELOPMENT AND EPIGENETICS

By

Name: Nafisa Alam Srity

ID: 18346071

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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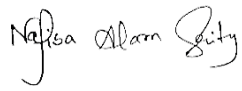

Nafisa Alam Srity
ID: 18346071

Approval

The thesis titled "Cardiovascular development and epigenetics" submitted by Nafisa Alam Srity (18346071) of Summer 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Luluel Maknun Fariha
Lecturer
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any human and animal trial.

Abstract

Cardiovascular development is a complex process that involves the coordinated action of multiple genes and environmental factors. Epigenetic regulation refers to changes in gene expression without alterations in the underlying DNA sequence and one of the crucial environmental factors affecting cardiovascular development. Epigenetic regulation regulates many aspects of gene expression, including promoter activity, transcriptional efficiency, and post-transcriptional modifications. DNA methylation is one of the most common epigenetic regulatory mechanisms and has shown to play a significant role in the development of cardiovascular diseases. DNA methylation is the addition of a methyl group to the DNA backbone, and it is mainly carried out by the enzymes DNA methyltransferases (DNMTs).To better understand the mechanisms behind the development of such diseases, it is essential to understand the interplay between genetic and environmental factors. Epigenetic modifications can have a wide range of effects on the behavior and function of cells.

Keywords: Cardiovascular development, epigenetics, DNA sequence, gene expression, methylation, histone modification

Dedication

I dedicate this project report to my family, friends for the endless support that they have shown me throughout.

Acknowledgement

To begin with, I want to express my gratitude to Allah for His unending blessings, which I believe have given me the strength and desire to complete this project.

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List of Acronyms

CHD	Congenital Heart Defects
CVD	Cardiovascular Disease
CAD	Coronary Artery Disease

Chapter 1

Introduction

The cardiovascular system is made up of the blood vessels that transport blood to and from the body's tissues as well as the heart, which pumps blood (Chang and Benoit G, 2011). As an embryo develops, the first functional organ is the heart (Rajani M. and Anthony B., 2021). The heart is merely a contractile vessel in the cephalochordate Amphioxus. Mammals' hearts had to develop a more sophisticated three-dimensional structure as a result of having to grow in size and adapt to new settings as organisms evolved (Autonomous pacemaker's progression, lining of myocardium through endocardium, valve's growths to lead blood flow, ranging from 1 to 4 chambers). Multiple cell lineages are used to construct these structures (Moore-Morris et al., 2018b). Cardiomyocytes from the atrium and the ventricles, fibroblasts, endocardial, epicardial, and conduction system cells (sinoatrial node, purkinje fibers, atrioventricular node), Aortic and (coronary) artery smooth muscle cells as well as cells from the central nervous system are just a few of the different cell types found in the mammalian heart (Weerd et al., 2011). The development of a heart depends on the proper proliferation of these cardiac cells under strict transcriptional control of cardiac genes (Weerd et al., 2011). The intricacy of heart development is demonstrated by the high frequency of congenital cardiac anomalies (Congenital cardiac abnormalities affect one to two percent of live births in humans.) as well as the ability of CHDs (congenital heart defects) to result from mutations in a variety of transcription factors (Weerd et al., 2011).

All cardiac cell lineages' initial cell fate decisions are affected by genetic and epigenetic mechanisms (Moore-Morris et al., 2018b). Migration of specialized cell types is obstructed and misspecified results from the abnormal biological process control, for instance, transition from epithelial to mesenchymal tissue that is epigenetically controlled, which in turn causes cardiac abnormalities (Moore-Morris et al., 2018). The study of epigenetics focuses on variations in gene expression or phenotypes (expressed traits) brought on by environmental factors without altering the DNA's nucleotide sequence (LaMorte, 2018). Epigenetics explains how genes and the environment interact to allow cells to react swiftly to environmental changes (Majo et al., 2021).

The human genome is created during fertilization, and with the possible exception of cell-specific mutations, the coding is maintained throughout life (Moore-Morris et al., 2018). The complicated

process of cardiac development is regulated by epigenetic events, which allow for the spatial and temporal coordination of all procedures necessary for the development, maturation, and differentiation of distinct types of heart cells (Majo et al., 2021). Epigenetics can have an impact on a gene's timing, level of expression, and final phenotypic expression. Adding metal ions, removing acetyl or methyl groups from DNA, or any combination of these, or these groups' insertion or deletion from the histones that regulate the DNA's packaging and encapsulation, are just a few examples of the minor alterations that these external stimuli can cause to DNA (LaMorte, 2018). Transcription appears to be decreased or even shut off when methyl groups are attached to histones, whereas acetyl groups are attached to histones, which activates genes. "Epigenetic factors" are these biological alterations to the DNA (LaMorte, 2018).

1.1 Background

Cardiovascular development and epigenetics are two highly interrelated topics. Cardiovascular development, the process by which the heart and other blood vessels form, is significant to human health and survival (Gao and Wang, 2020). Epigenetics refers to the study of heritable changes in gene expression, which are not caused by changes in the genetic code itself but by environmental and lifestyle factors (Gao and Wang, 2020). The two topics are closely linked because epigenetic changes to the genome can profoundly affect the development of the cardiovascular system.

Epigenetic changes can occur in any cell type in the body, and they play an essential role in the development of the cardiovascular system. Epigenetic changes can regulate gene expression, affecting how cells behave (Feinberg, 2018). This is why epigenetic changes are thought to be responsible for many differences between individuals with cardiovascular disease and those without it.

One example of how epigenetics can affect cardiovascular development is chromatin remodeling. Chromatin is a complex structure made up of DNA and other proteins and is responsible for controlling the expression of genes (Feinberg, 2018). Chromatin remodeling is a process by which chromatin is changed, which can affect how genes are expressed.

Chromatin remodeling can occur in different ways. One way is through DNA methylation. DNA methylation occurs when a molecule called methyl group (CH3) is added to one or more bases in

DNA (Hikspoors, et al., 2022). This modification can change how often a gene is expressed, and it is thought to play an essential role in the development of cardiovascular disease.

Epigenetic changes can also affect the way that cells react to stress. Cells respond to stress by releasing proteins and other chemicals, which can have a lasting effect on the development of the cardiovascular system (Hikspoors, et al., 2022)One example of how epigenetics can affect stress responses is through gene expression.

Gene expression involves the activation or deactivation of specific genes, which can be affected by epigenetic changes (Houyel & Meilhac, 2021). There are several ways that epigenetic changes can affect gene expression, which is why it is thought to play a role in the development of cardiovascular disease.

Epigenetic changes are thought to play an essential role in the development of cardiovascular disease, and they can be affected by different factors (Houyel and Meilhac, 2021a). Chromatin remodelling is one example of how epigenetics can affect how genes are expressed, which can have a lasting effect on the development of the cardiovascular system (Hvitfeldt et al., 2020). Epigenetic changes can also affect how cells react to stress, which can have a lasting effect on the development of the cardiovascular system.

Gene expression is another example of how epigenetics can affect the development of cardiovascular disease, and epigenetic changes can affect how genes are expressed (Hvitfeldt et al., 2020). Epigenetic changes are thought to play an essential role in the development of cardiovascular disease, and they can be affected by many different factors.

The study of epigenetics, a relatively recent area of biology, has expanded research opportunities in the field of cardiovascular development (Illum et al., 2018). The study of heritable variations in gene expression or cellular phenotype that are not brought on by changes to the underlying DNA sequence is known as epigenetics. This means that even though these modifications are not part of the DNA itself, they may be passed down across generations and have a big influence on how certain traits and features emerge (Illum et al., 2018). Since epigenetic modifications can modify gene expression and cardiovascular function, this also includes cardiovascular development.

Changes in gene expression are one of the key ways that epigenetics can affect the development of the cardiovascular system (Lim et al., 2021). This can occur in a variety of ways, such as through

modifications to histones, which regulate how tightly certain proteins are bound to DNA, and transcriptional regulation, which controls the process by which genes are turned on or off. Methylation is the addition or removal of a methyl group from DNA (Lim et al., 2021). Collectively, these mechanisms have the potential to cause a wide range of modifications in cardiovascular function. Each of these mechanisms can have a unique effect on the way genes are expressed.

The development of the heart and its related vessels from a single cell to a fully developed circulatory system is known as cardiovascular development (Martik, 2020). It is a complicated process that is controlled by numerous genetic and epigenetic pathways. The field of epigenetics investigates heritable gene expression modifications that take place without affecting the underlying DNA sequence (Martik, 2020). Due to its ability to modify gene function, it is a crucial element in the emergence of cardiovascular disease and other illnesses.

Epigenetic processes are crucial to the growth of the cardiovascular system. They can alter how genes express themselves, which may change how these genes react to environmental cues (Moore-Morris et al., 2018). This may result in modifications to the structure and function of the heart as well as the emergence of cardiovascular disorders.

Heart development may be impacted by a variety of epigenetic processes. One illustration is the process of adding or removing one or more methyl groups from the core nucleotide unit of DNA, known as DNA methylation (Moore-Morris et al., 2018). This alteration may affect gene expression and encourage the growth of cancerous cells.

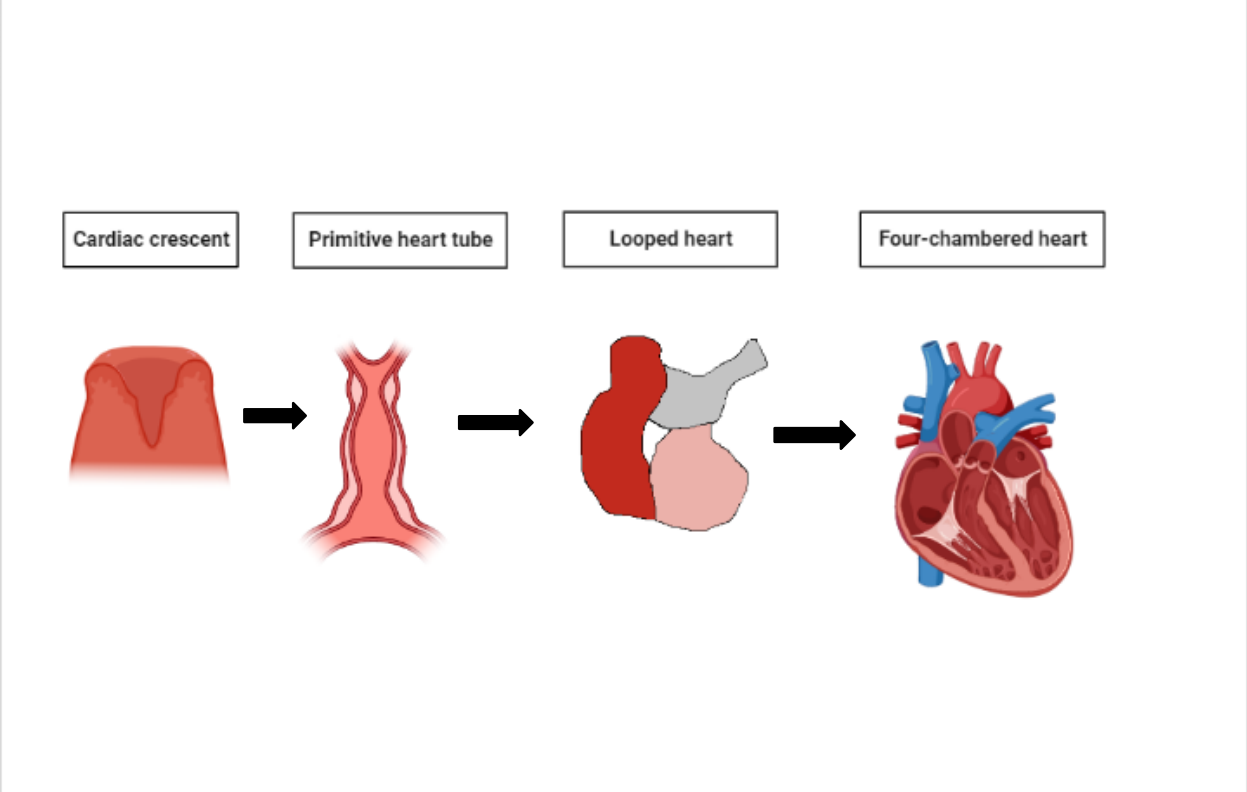

Figure 1: Development of heart (Martinez et al., 2015); The development of the heart is a complicated process that includes coordinated cell migration, proliferation, differentiation, and programmed cell death in addition to structural remodeling such as septation and looping.

1.2 Objective of the study

- To explore the role of epigenetics in cardiovascular development
- To identify the molecular and cellular mechanisms that regulate the epigenetic pathways influencing cardiovascular development
- To examine the potential therapeutic implications of targeting epigenetic pathways for treating cardiovascular diseases
- To understand the epigenetic changes that occur in the development of CVDs, so that researchers can develop new treatments and interventions that target the underlying causes of the disease
- To add value to the scientific community by helping to understand the causes and mechanism of CVDs better

1.3 Rationale of the study

This review article will focus on understanding how epigenetic processes control gene expression, how these processes interact with environmental influences, and how this affects the development of the cardiovascular system. By understanding the underlying basis of these processes, it may be possible to improve the health of those with cardiovascular disease. This research has the potential to provide new insights into the prevention and treatment of cardiovascular diseases. Epigenetic mechanisms are chemical modifications that occur on DNA and other chromosomes without altering their sequence. These modifications can affect the expression of genes, resulting in changes in cellular behavior and phenotype. Many different epigenetic processes have been implicated in the development of cardiovascular disease. One necessary process is DNA methylation. DNA methylation is a type of epigenetic modification that involves the addition or removal of a methyl group from a DNA molecule. Another necessary epigenetic process is histone modification. Histone modifications can affect how genes are expressed by altering how they are packaged within the nucleus.

Chapter 2

Methodology

An outline was created to convey the material in a methodical manner before conducting the literature study and choosing the topic. Research publications listed in databases including PubMed, Scopus, and Google Scholar were searched for relevant terms such as "cardiovascular development," "epigenetics," "methylation," "DNA sequence," "gene expression," and "histone modification." The most informative articles from a screening of several journal publications on cardiovascular development and epigenetics were selected, while unrelated journals, duplicates and article with abstract only were disregarded. The chosen papers were thoroughly examined. The search was conducted once more in an effort to uncover further details.

Chapter 3

3.1 The Main Studies

Cardiovascular development is the process by which the heart and blood vessels form during embryogenesis (Mott, 2022). This process is complex and involves multiple stages, beginning with the formation of a primitive heart tube and culminating in the formation of a fully functional heart. Epigenetics is a field of study that examines the role of environmental factors in influencing gene expression and development through chemical modifications to the genome (Mott, 2022).

Studies in this field have focused on the role of epigenetics in cardiovascular development, with research showing that epigenetic modifications can play a role in the development of heart disease (Pagiatakis et al., 2019a). In particular, epigenetic modifications have been linked to changes in gene expression that can lead to the formation of cardiovascular risk factors, such as elevated blood pressure and cholesterol levels (Pagiatakis et al., 2019a). These studies suggest that epigenetic modifications may be an essential mechanism by which environmental factors can influence the development of cardiovascular disease.

Studies in this field are still ongoing, and further research is needed to fully understand the role of epigenetics in cardiovascular development and disease (Rabe et al., 2018). However, these studies provide valuable insights into the mechanisms by which environmental factors can influence the development of cardiovascular disease and suggest that epigenetic modifications may be an essential target for the prevention and treatment of this condition (Rabe et al., 2018).

3.2 Clinical Trials Correlation among Different Studies and Comparative Studies

Clinical trials are human-centered research projects carried out to assess the efficacy and safety of novel therapies, procedures, or drugs. Clinical trials are carried out in several fields, such as epigenetic study and cardiovascular development. (Yi and Goodisman, 2021). Recently, clinically applicable studies have been carried out to better understand the role of epigenetics in the development of the cardiovascular system and to uncover possible medicines or interventions that can help to enhance cardiovascular health.

In 2021, one study looked at the function of epigenetic markers in the emergence of adult cardiac disease. (Yi and Goodisman, 2021). The research discovered that epigenetic markers can be used to predict the likelihood of acquiring heart disease and are linked to the emergence of heart disease. (Yi and Goodisman, 2021). This study offers insightful knowledge on the function of epigenetics in the development of the cardiovascular system and offers recommendations for ways to enhance cardiac health by utilizing epigenetic risk factors.

Another 2018 study examined how eating habits of pregnant women may impact the cardiovascular health of their offspring. (Zhang et al., 2018). The research discovered a link between maternal dietary patterns during pregnancy and the onset of cardiovascular disease in offspring. (Zhang et al., 2018). The study offers insightful knowledge on the significance of environmental factors in cardiovascular development and makes recommendations for strategies to improve cardiac health by altering pregnant mothers' dietary habits.

Overall, clinical studies have demonstrated that altering a mother's eating habits while she is pregnant can enhance the cardiovascular health of her unborn child. Epigenetic markers have also been linked to the development of heart disease (Zhang et al., 2018). These research offer important insights into the role of epigenetics in cardiovascular development and offer recommendations for ways to enhance cardiac health by employing epigenetic risk indicators and altering maternal dietary habits. Exercise, quitting smoking, and consuming less saturated fat are further possible treatments or interventions that can enhance cardiovascular health (Yi and Goodisman, 2021). It is crucial to remember that not everyone will benefit from all of these interventions, and that when deciding on a heart-healthy lifestyle, each person's unique circumstances should be taken into account.

An important field of study is the linkage of therapeutic trials with comparative investigations of cardiovascular development and epigenetics (Zhang et al., 2021). Clinical trials assess the effectiveness and safety of therapies for the treatment of cardiovascular diseases such hypertension, coronary artery disease, and stroke. Comparative studies have provided significant new insights into the function of epigenetic changes in cardiovascular development and disease. Researchers have long been interested in understanding the genetics and epigenetics of cardiovascular development.

Gene expression can be greatly affected by epigenetic alterations such as DNA methylation, histone modification, and microRNA expression (Zhang et al., 2021). Since epigenetic alterations are frequently reversible, they may be crucial therapeutic targets. The exact mechanism by which epigenetic changes influence the emergence of cardiovascular disorders is still unknown. Epigenetic changes may contribute to the emergence of hypertension and coronary artery disease, according to certain research. Other research, however, has not discovered a direct connection between epigenetic change and the risk of cardiovascular disease (Zhang et al., 2021). Overall, however, the clinical trials' association among comparative studies on the development of the cardiovascular system and epigenetics is a crucial field of study that could aid in understanding how epigenetics contributes to the emergence of cardiovascular illnesses.

Table 1: Clinical trials

No.	Main Studies	Population	Phase	Outcomes
1.	The chance of developing cardiac disease can be predicted using epigenetic markers.	Adults	Completed	The trial offers suggestions on how to improve cardiac health by exploiting epigenetic risk variables.
2.	Pregnant women's dietary habits may have an effect on the cardiovascular health of their offspring.	Pregnant women	Completed	By changing pregnant women' food choices, the experiment suggests methods to enhance cardiac heath.
3.	Among the potential measures that can improve cardiovascular heath are exercise, quitting smoking, and eating less saturated fat.	Adults	Completed	According to a heart-healthy lifestyle, each person's particular situation should be taken into consideration.

Chapter 4

4.1 Deliverables

Understanding how epigenetic modifications arise in the first place is the first step in figuring out how epigenetics affects the onset of heart disease. In epigenetics, gene expression changes that are inherited but do not result in changes to the underlying DNA sequence are studied. These alterations could affect the expression of miRNA, histone modifications, and DNA methylation.

Epigenetic changes contribute to the development of heart disease and are frequently linked to conditions like diabetes and cancer. Study after study has demonstrated, for instance, that epigenetic modifications can raise the risk of coronary artery disease. (CAD) (Moore-Morris et al., 2018a). Increased production of inflammatory cytokines, which can harm the arteries, can result from epigenetic modifications in the DNA of coronary artery cells.

Other cardiovascular illnesses can also be brought on by epigenetic alterations. For instance, epigenetic alterations in the genes that form blood arteries can raise your chance of having heart failure. (Moore-Morris et al., 2018a). Furthermore, epigenetic changes in the genes that regulate cholesterol levels can raise your risk of developing atherosclerosis, a disease that results in plaque buildup in the arteries.

There is still a lot we don't know about epigenetic modifications, despite the fact that they play a significant role in the development of heart disease (Pagiatakis et al., 2019b). Researchers are putting a lot of effort into identifying all the various epigenetic alterations that take place throughout the onset and course of heart disease and understanding how these changes affect the risk of acquiring heart disease.

The outcomes of cardiovascular development and epigenetic research include a better comprehension of the role that epigenetic modifications play in the emergence of cardiovascular diseases, the discovery of epigenetic biomarkers for early detection and risk assessment of cardiovascular diseases, and the creation of novel therapies based on epigenetic alterations of cells and tissues (Pagiatakis et al., 2019b). Improvements in monitoring and managing care for people with cardiovascular diseases, development of epigenetic-based interventions to prevent the development of cardiovascular diseases in high-risk populations, regulation of epigenetic changes by environmental factors during cardiovascular development and disease progression, and identification and characterization of epigenetic changes by environmental factors are some other deliverables. (Pagiatakis et al., 2019b).

Chapter 5

Challenges, Gaps, and Directions/ Prospect of Further Research

In recent years, problems have been found. There is still much to understand about how epigenetic factors affect cardiovascular development, despite studies on the molecular and cellular mechanisms having been carried out (Houyel and Meilhac, 2021). In addition, limited is known about how epigenetic changes affect cardiovascular health maintenance and disease development. Furthermore, little is understood about the interactions between epigenetic alterations and other factors, such as genetics and environmental effects, that affect cardiac development (Houyel and Meilhac, 2021). Finally, further knowledge is required about how epigenetic changes, particularly those connected to aging, may contribute to the emergence of cardiovascular disorders.

This review will examine how epigenetic mechanisms influence cardiovascular development, analyze the role of epigenetic inheritance in the development of cardiovascular diseases, investigate the effects of environmental factors on cardiovascular development and epigenetics, and assess the implications of epigenetic modification. It will also highlight some of the gaps in our knowledge about cardiovascular development and epigenetic challenges and discuss potential solutions. It will assess how epigenetics affects the diagnosis and management of cardiovascular illnesses, talk about potential future uses of epigenetic therapeutics for cardiovascular disease, and make suggestions for additional research on epigenetics and cardiovascular development.

Environmental exposures, genetic inheritance, and epigenetic changes are only a few of the many variables that affect the complex process of cardiovascular development. The term "epigenetics" refers to heritable alterations in gene expression that do not involve a change in the underlying DNA sequence (Houyel and Meilhac, 2021). Cardiovascular illnesses have been proven to be strongly influenced by epigenetic factors, and there is growing proof that environmental factors can affect epigenetic changes.

Cardiovascular diseases can occur as a result of epigenetic changes, which are frequently passed on from parents to their offspring. Gene expression, for instance, may be impacted by epigenetic changes like DNA methylation (Hikspoors et al., 2022). The process of adding methyl groups to one or more carbon atoms in the DNA molecule is known as DNA methylation. Methylation is a crucial factor in the emergence of cardiovascular disorders and can alter how a gene is produced.

Protein function can also be impacted by epigenetic alterations, which may also contribute to the development of cardiovascular disorders (Hikspoors et al., 2022). Epigenetic changes can also be altered by environmental exposures. For instance, being exposed to contaminants like mercury can make you more likely to get cardiovascular disease.

The scientific and medical communities are very interested in the development of the cardiovascular system and epigenetics. Since the heart is the most important organ in the body and is in charge of pumping blood throughout the body, the development of the heart and the disorders that are related with it are of particular importance (Berbel-Filhoa et al., 2022). The importance of genetic and epigenetic factors in the development of the heart, as well as the possibility for novel treatments for cardiovascular illnesses, have been extensively studied recently thanks to improvements in genetic and epigenetic research. The field of epigenetics investigates genetic alterations without affecting the nucleotide sequence (Berbel-Filhoa et al., 2022). Changes in histone modifications, microRNA expression, and the level and location of DNA methylation are examples of epigenetic modifications. Numerous epigenetic alterations are heritable, or transmitted from parents to their children. Due to this, epigenetics is a crucial factor in both gene expression and developmental biology.

According to studies, environmental factors can affect how heart diseases develop. For instance, it has been demonstrated that exposure to cigarette smoke increases the risk of getting heart disease, and obesity is a major risk factor as well. Given that epigenetic modifications might enhance smoking and obesity, they may contribute to the development of these diseases (Berbel-Filhoa et al., 2022). Additionally, studies have shown that particular gene expression profiles in individual cells might be linked to epigenetic changes. This implies that patients with a high risk of developing heart disease may be recognized using epigenetics.

Potential new therapeutics for cardiovascular disorders have also been identified via epigenetic research. For instance, scientists have shown that epigenetic modifications can target the onset of heart disease in people with diabetes (Berbel-Filhoa et al., 2022). These patients' heart health may improve as a result of epigenetic modifications that can be changed through medication or lifestyle changes.

Chapter 6

Conclusion

Epigenetic variables play a significant role in the complex process of cardiovascular development. Cardiovascular illnesses and the advancement of already existing diseases are both influenced by epigenetics. Lifestyle choices including food, exercise, and stress can affect epigenetic changes. Cardiovascular disease development may be favourably or adversely impacted by these changes. In order to prevent and treat disease, epigenetic changes can be a useful target. In order to enhance health outcomes, it is crucial to keep researching how epigenetics affects cardiovascular development and look at fresh approaches to moderating these aspects.

Finally, it should be noted that epigenetic factors play a significant role in the complex process of cardiovascular development. Cardiovascular illnesses and the advancement of already existing diseases are both influenced by epigenetics. Additionally, lifestyle elements like nutrition, exercise, and stress can affect how the epigenome is modified. Cardiovascular disease development may be favourably or adversely impacted by these changes. In order to prevent and treat disease, epigenetic alterations may prove to be a useful target. In order to enhance health outcomes, it is crucial to keep researching how epigenetics affects cardiovascular development and look at fresh approaches to moderating these aspects.

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