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Regulatory role of miRNAs in Wnt signaling pathway linked with cardiovascular diseases



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ABSTRACT

MicroRNAs (miRNAs) are discovered in science about 23 years ago. These are short, a series of non-coding, single-stranded and evolutionary conserved RNA molecules found in eukaryotic cells. It involved post-transcriptional fine-tune protein expression and repressing the target of mRNA in different biological processes. These miRNAs binds with the 3'-UTR region of specific mRNAs to phosphorylate the mRNA degradation and inhibit the translation process in various tissues. Therefore, aberrant expression in miRNAs induces numerous cardiovascular diseases and developmental defects. Subsequently, the miRNAs and Wnt signaling pathway are regulating a cellular process in cardiac development and regeneration, maintain the homeostasis and associated heart diseases. In Wnt signaling pathway majority of the signaling components are expressed and regulated by miRNAs, whereas the inhibition or dysfunction of the Wnt signaling pathway induces cardiovascular diseases. Moreover, inadequate studies about the important role of miRNAs in heart development and diseases through Wnt signaling pathway has been exist still now. For this reason in present review we summarize and update the involvement of miRNAs and the role of Wnt signaling in cardiovascular diseases. We have discussed the mechanism of miRNA functions which regulates the Wnt components in cellular signaling pathway. The fundamental understanding of Wnt signaling regulation and mechanisms of miRNAs is quite essential for study of heart development and related diseases. This approach definitely enlighten the future research to provide a new strategy for formulation of novel therapeutic approaches against cardiovascular diseases.

1. Introduction

Heart disease is a leading cause of human morbidity, mortality, and physical disability worldwide. Present day the heart diseases are rising, and it has been found that about 10% of people globally will be suffering from heart failure of the total population in the year 2030 (Salinas and Lin, 2019). Major organ and multiple gene encoded protein signaling also affected by biological, genetic and vascular risk factors that influence several type heart diseases. Heart failure is caused by numbers of related heart diseases like myocardial ischemia, valve diseases, heart rhythm disorders, pericardial abnormalities and cardiac dysfunction (Ingall, 2004).

Wnt and Fzd (Frizzled) is significant protein molecules of signal transduction pathway where Wnt act as ligand for the Fzd proteins

family. This signal transduction pathway mainly control tissue development, cells migrate and polarity processes (Qiang and Walsh, 2005). It also noted that a total 19 families of Wnt genes are identified in mammalian genomes, which have glycosylated protein containing 350–400 amino acids and consist with 22–24 cysteine residues (Janda and Garcia, 2015; Clevers, 2006). In molecular signaling pathway Wnt has two binding sites and consist of low-density receptor-related protein (LPR5/LPR6) (Bhanot and Brink, 1996; Joiner and Ke, 2013). The complex receptor of Wnt activates the β -catenin protein signaling, considering as a secondary messenger of canonical signaling pathway. It is phosphorylated by the ubiquitin pathway, consist with the destruction protein complex of axin, adenomatous polyposis coli (APC), casein kinase 1 (CK1) and glycogen synthase kinase β (GSK- β) to showing its imminent activity (Yost and Torres, 1996). Therefore, when the

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lipoprotein receptor-like protein is activated, it formed intracellular adaptor disheveled protein (Dvl) to the plasma membrane. That dissociates and accumulates the β -catenin protein complex. The β -catenin protein migrates to the nucleus as secondary messenger and interacts with the transcription factors of TCF and LEF, and become activated the gene expression (Fagotto and Glück, 1998; MacDonald and Tamai, 2009). Several secondary signaling pathways are activated by Wnt protein, such as planar cell polarity (PCP) and Ca^{2+} pathway, to activate the protein kinase C (PKC) protein by β -catenin mediated molecular signaling (Veeman and Axelrod, 2003). Planer cell polarity pathway activates the Rock and Jnk-kinase pathway by G-protein Rho and Rac receptor and controls the cell orientation to adjacent cells (Carvajal-Gonzalez and Roman, 2016). But in Wnt/ Ca^{2+} pathway activated phospholipase C (PLC) via heterotrimeric G proteins. That results in Ca^{2+} dependent enzyme rising in the cell that leads to activation of heart physiology like protein kinase C (PKC), calcium dependent kinase-II and calcineurin proteins (Kühl and Sheldahl, 2000).

The Wnt signaling pathway performed a major role in the gene expression pattern of cardiovascular diseases. A new point of intervention of the Wnt pathway may lead to low molecular compounds targeted by novel drugs. The pathway inhibitors outlined the cancer treatment and the effects of cardiac diseases of human being. We are providing an overview of the Wnt signaling pathway regulating mechanism with the role of β -catenin in gene expression and the effect of miRNAs against the cardiovascular diseases. We also summarize the key roles and figure out the involvement of miRNAs in Wnt signaling in the cardiovascular diseases. Thus, the signaling modulates an active condition in heart diseases by pharmacological events. Probably this is the first report may provide a novel direction for miRNAs mediated molecular signaling pathway for the treatment of heart diseases.

Recently, modern medical biotechnology demonstrated that the miRNAs have essential regulatory function and emerged as promising diagnostic and therapeutic tools against the high risk cardiac diseases (Ouyang and Wei, 2021). MicroRNAs are single-stranded, small size (19–25 nucleotides), evolutionary conserved RNA molecules with non-coding sequences (Mencía Castaño and Raftery, 2020). Generally, these are the epigenetic regulators that modulate the gene expression and primarily associate with posttranslational modifications (Ardekani and Naeini, 2010). In post transcriptional modification event's the miRNAs target messenger RNAs (mRNAs) to inhibit the translation and loaded into the RNA-induced silencing complex (RISC) (Vaghf and Khansarinejad, 2021). The RISC has endonuclease slicer that required for shaping of mRNAs and other structural core protein, e.g Argonaut protein (Ago2) (Hammond and Boettcher, 2001). The Ago2 protein associate with miRNAs complex that able to bind with ssRNAs and dsRNAs (Martinez and Patkaniowska, 2002).

Recent study revealed that the miRNAs regulates Wnt signaling pathways, and both are interlinking each other to implicated different biological processes in animal body. MicroRNAs are participating at every step of Wnt signaling pathway to performed a key role in Wnt protein regulation and expression (Ueno and Hirata, 2013). During cardiac vascular diseases miRNAs execute the positive or negative regulation of Wnt protein in Wnt signaling pathway (Su, Zhang et al., 2012; Inui, Martello et al., 2010). MicroRNAs are might be potential vital element in cardiac diseases as these are play an important role for signal transduction and cellular development of an organism (Bartels and Tsongalis, 2009). Therefore, the basic knowledge about the miRNAs mediated role of cellular mechanisms are used in therapeutic tools and diagnostic approaches for biological activities, and diseases at cellular level (Wang and Kwong, 2013; Espinoza-Lewis and Wang, 2012; CDC, 2001). Recently, scientific communities are still investigating about the therapeutic tools of miRNAs against heart diseases (Balatti and Acunzo, 2016). Moreover, in this review we briefly reviewed the biogenesis and function of miRNAs, mechanism of action in Wnt signaling pathway, and finally highlighted the functional aspects of miRNAs that are regulates to targeting the Wnt signaling pathway linked with the cardiovascular diseases.

2. Biosynthesis pathway of miRNAs

In miRNA biogenesis pathway multiple protein components regulates the mature miRNA structure and its functions (Cheloufi and Dos Santos, 2010). Similar to proteins, the genes coding for miRNAs are exist in DNA of the nucleus. Each gene is transcribed by RNA polymerase II and produces either a regulatory or messenger RNA. The miRNA profiling, gene regulation, and understanding their biogenesis mechanism as well as the expression patterns is very much significant in defining miRNAs biological roles (Yang and Lai, 2011; Ledda and Otaggio, 2020). Molecular pathway of this whole process is accurate, organized, and stepwise composite procedure which initiated from the inter-nuclear region and persistent to the cytoplasmic part of the cell until its final production completed.

Firstly, the long primary miRNA (pri-miRNA) was sliced by drosha protein along with its co-factor the Di George syndrome chromosomal region 8 (DGCR8). These protein remove the tail portion and developed a hairpin or stem-loop likes precursor miRNA structure (Bhattacharya and Sharma, 2020). Afterwards one of the nucleocytoplasmic transporter proteins, exportin-5 of karyopherin family and Ran-GTP cofactor recognized the pre-microRNA and brings it to the cytoplasm region of the cell (Melo and Melo, 2014). Here, the RNase-III endonuclease together with Dicer complex and its cofactor element, trans-activator RNA binding protein (TRBP)/PKR-activating protein (PACT) remove the loop, resulting as formation of an asymmetrical double stranded mature microRNA (Maurin and Cazalla, 2012). This synthesized the miRNA is of 20–25 nucleotides long. Subsequently, the matured miRNA loaded on Ago2 protein and interacts with dicer molecule to bind the short chain of miRNA. Now the miRNA is unwound, and one strand is completely released. The remaining strand, called as guide strand link with Ago2 and some additional proteins to form the RISC (RNA induced silencing complex). The RISC can now leading to its target and inactivates one or multiple genes of mRNA sequence. The 3'UTR of mRNA (messenger RNA) of a targeted gene is complementary to the sequence of the miRNA, which enables the base pairing of match nucleotides pair (Fig. 1). Once it bound, there are three ways of RISC to inactivate the function of messenger RNA. Within the complex proteins can cut the mRNA chain and further degraded by deadenylation in the cell. Considering the inhibition of translation mechanism; the RISC complex inhibits the ribosomal subunits from binding to the specific mRNA strand. Therefore, in both cases mRNA will unable to translate any protein, and the gene will be silenced (Krol and Loedige, 2010). Besides that, miRNAs also participate in various biological functions and detected all types of human biological fluids. Therefore, it confirmed that miRNAs play an important role as biomarker in human diseases and developmental process (Bhattacharya and Sharma, 2020).

3. Wnt signaling pathway and miRNAs regulation

Wnt (Wingless and int-1) signaling pathways are evolutionarily conserved and are classified as canonical β -catenin-independent, non-canonical β -catenin-dependent, Wnt cell polarity and calcium pathways (Villarroel and del Valle-Pérez, 2020). It consists of 19 secreted glycoproteins, Wnt ligands, Fzd (Frizzled) receptors, associate co-receptor and scaffolding proteins (Astudillo, 2020). These proteins are employed in a diverse plethora of cellular activity. While these proteins are not functioning in cellular system, this signaling pathway is correlated with various diseases (Wang, de Marco et al., 2019; Cici, Corrado et al., 2019; Huang and Wei, 2018). From transcriptional regulation in the cytoplasm to post-translation modification of Wnt protein is tightly regulated at every level cellular expression (Ma and Hottiger, 2016). It also noted that the Wnt signaling mechanism is absent to result in phosphorylation of cytoplasmic β -catenin degraded by destruction complex with Axin, β -catenin, adenomatous polyposis coli (APC), Ser/Thr kinases GSK-3 β and casein kinase I α (CKI α) protein subunit (MacDonald and Tamai, 2009; Tolwinski and Wieschaus, 2004). Simultaneously the destruction

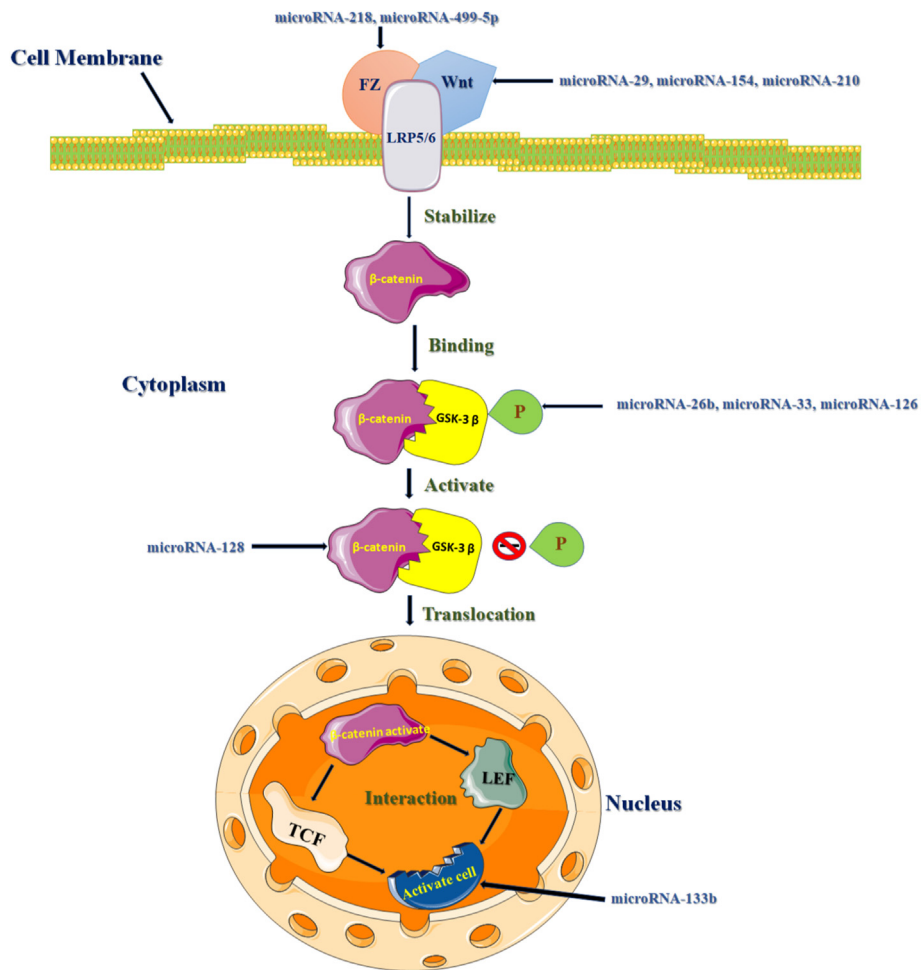


Fig. 1. Graphical model of miRNA biogenesis, expression and their biological function in cell.

complex of GSK-3β and CK1α phosphorylate β-catenin also be degraded by ubiquitination (Clevers and Nusse, 2012). Whereas, the β-catenin play a vital role in Wnt signaling pathways since the lack of β-catenin in the nucleus results to inhibit the TCF-mediated activation of targeted signaling genes. When the TCF protein is present and accumulates the

β-catenin in the cytoplasm, the complex has undergoes in nuclear translocation, activation and finally initiates the transcription of heart related genes (Rao and Kühl 2010). Subsequently, the inhibitory factors protein Dickkopf (DKK) bind to the extracellular Wnt ligands, and secreted the Frizzled-related protein (sFRP) family, LRP6 or LRP5 and Wnt

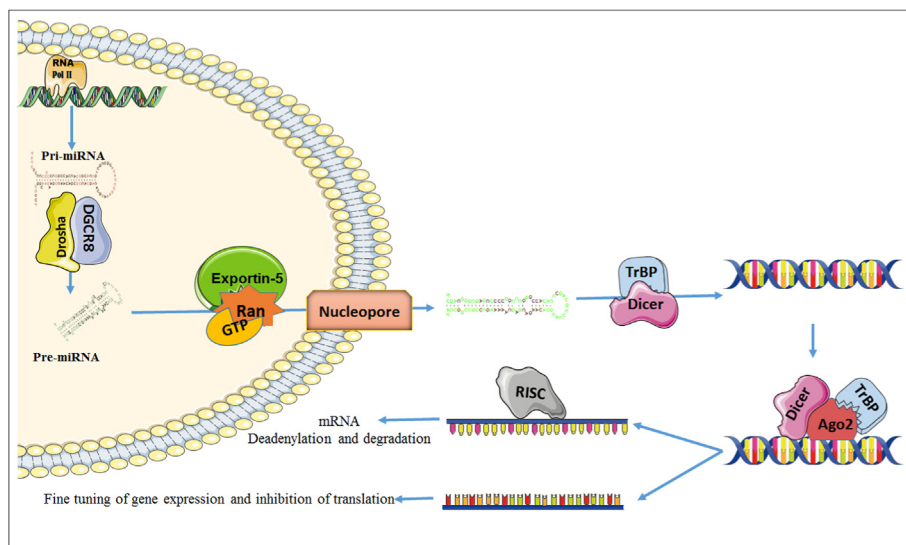


Fig. 2. Concise model shows that intervention in Wnt signaling pathway regulated by miRNAs to activate the cardiac cells.

inhibitory factor 1 (WIF1) that inhibits the active status of β -catenin (Kawano and Kypka, 2003; He and Semenov, 2004; Clevers, 2006). Dickkopf protein have consist four members of secreted glycoproteins, these are bind with low-density lipoprotein receptor related protein (LRP) and initiate the Wnt signal inhibition with high affinities (Bafico and Liu, 2001). Recent studies have seen the numbers of cardiovascular disease are performed a very important factor in sudden heart attacks. These diseases are cardiac hypertrophy, arrhythmias, fibrosis, coronary artery diseases, myocardial infarction and heart failure due to the lack of Wnt signaling protein activation (Calore and Lorenzon, 2019; Raso and Dirckx, 2019). The genetic mutation in Wnt protein families in Wnt signaling pathway causes cardiovascular diseases within the human body. Thus, the Wnt protein performed a crucial role in cardiovascular diseases at recent era of modern peoples (Fig. 2). The regulation mechanism of mRNA directly depends on miRNAs binding to the corresponding 3'-UTR sequence in the target mRNA gene at diverse levels, and controlling the Wnt signal transduction in cardiovascular diseases (Bhat and Jarmolowski, 2016). Several studies found that miRNAs act as a vital element in Wnt signaling pathway, these are miR-1, miR-16, miR-27b, miR-30d, miR-126, and miR-133 (Thum and Catalucci, 2008; Ardekani and Naeni, 2010). The human miRNAs are annotated by their gene ID of human genome organization and its mature sequences (Hayashi and Chuva de Sousa Lopes, 2008). These all miRNAs which regulate the Wnt signaling pathway associated components and have significant impacts on various cardiovascular diseases is listed in Table 1.

3.1. GSK-3 β protein

The GSK-3 β (glycogen synthase kinase-3 β) protein is associated with cardiovascular diseases and also involved in the Wnt signaling pathway. This protein based enzyme is a multifunctional proline rich serine-threonine kinase residue coded by the human GSK-3 β gene and a key regulator of insulin-dependent glycogen synthesis (Stambolic and Woodgett, 1994; Doble and Woodgett, 2003; Luo, 2009). The GSK-3 β protein is inactivating mediator and a phosphorylating agent of enzyme glycogen synthase within the eIF2B enzymes component. It also observed that GSK-3 β protein is directly involved in heart growth, metabolism and developmental stages of embryonic conditions. Basically, the GSK-3 β protein undergoes phosphorylation at position of Ser9/21 amino acid as

an inhibitory domain that inactivates in the heart failure patients (Haq and Choukroun, 2001; Doble and Woodgett, 2003; Woodgett, 2001). When the GSK-3 β protein is phosphorylated the overexpression of protein prevents heart development and cardiac diseases (Michael and Haq, 2004). But in active cases, the GSK-3 β protein primarily induces heart failure. Accumulation of β -catenin in the nucleus built a protein complex with TCF/LEF during the inactivation of GSK-3 β protein functions (Simon and Grandage, 2005). Besides that, the cellular regulations also carried out by different proteins such as β -catenin, c-myc, cyclin D1, cyclin E, and p21CIP1 these are phosphorylated by GSK-3 β . Researcher also noted that the GSK-3 β protein act as a vital role in the destruction of ubiquitin-dependent Wnt signaling pathway (Stakheev, 2020).

Earlier study also found that miR-26b is bound with the GSK-3 β encoded gene. This miRNA consist with 77 nts long nucleotides and encoded from chromosome Ch2q35 in human (Gao and Ye, 2021). It affects β -catenin activities and translocation to the nucleus with down-regulated function subsequently the up regulation of the protein C-myc and cyclin D1 expression (El Sabeh and Saha, 2021; Xie and Li, 2021). Conversely, the miRNA-33a is retained on chromosome Ch22q13.2 position of MIR33A gene and exist as 69 nts sequence in human. It has a vital role in Wnt signaling pathway regulation in cardiac diseases. Several studies have found that the expression of miRNA-33a is mediated the down regulation of Pim-3 kinase enzyme caused the pancreatic diseases (Liang and Yu, 2015; Romaine and Tomaszewski, 2015). Both the miRNA-33a and miRNA-26b together inhibit the functions of β -catenin and GSK-3 β protein which is lead the cardiovascular diseases. Recently, some findings demonstrated that the GSK-3 β protein phosphorylates by the action of miRNA-126. This miRNA has situated at human chromosome ch9q34.3 and 85 nts long sequence of the miRNA-126 gene. The miRNA-126 is involved in reduced phosphorylation activity of GSK-3 β which might be disturbed throughout the heart tissue (Guo and Ji, 2022). It also regulates the IGF-I, PI3K, insulin, and AKT signaling pathway in human body (Huang and Fang, 2013; Sonntag and Woo, 2012; Lechman and Gentner, 2012). Furthermore, the potential phosphorylation activity of miRNA-33a and miRNA-26b initiates cardiac diseases via targeting the GSK-3 β protein within the Wnt signaling pathway (Zhang and Han, 2021). The significant human miRNAs stem-loop or secondary structure interlinking with the Wnt signaling pathway in cardiovascular diseases are shown in Fig. 3.

Table 1

A Brief outline of miRNAs regulates the Wnt signaling pathway associated components and its impacts on various cardiovascular diseases.

Sl. no	Names of the miRNA	Target gene	Possible role in Wnt signaling pathway	Type of cardiovascular diseases	References
1.	hsa-miR-26b	GSK3- β and Wnt5a	Inhibition of β -catenin activity	Cardiomyocyte	(Wang and Liu, 2017)
2.	hsa-miR-29a	GSK3- β , ICAT/CTNBP1, HBP1, and GLIS2	Regulate the Wnt/ β -catenin signaling activity	Hypertrophic cardiomyopathy, fibrosis	(Rubiś and Totoń-Zurańska, 2017) (Sassi and Avramopoulos, 2017)
3.	hsa-mir-29c	GSK3- β , ICAT/CTNBP1, HBP1, and GLIS2	Regulate the Wnt/ β -catenin signaling activity	Cardiomyocyte hypertrophy, fibrosis	(Roncarati and Viviani Anselmi, 2014) (Sassi and Avramopoulos, 2017)
4.	hsa-mir-33a	GSK3- β , p38	Negatively Regulates Wnt/ β -Catenin signaling pathway	Myocardial fibrosis	(Fang and Feng, 2013) (Chen and Ding, 2018)
5.	hsa-miR-126	GSK3- β , SPRED1, LRP6, WRCH1, FZ4	Suppressing Wnt/ β -catenin signaling	Heart failure	(Kura and Parikh, 2019) (Song and Nigam, 2015)
6.	hsa-mir-128	Axin1	Promotes Wnt1/ β -catenin activation	Cardiac hypertrophy	(Li and Li, 2021)
7.	hsa-miR-133b	TCF7, NFAT5, Itpr2	Wnt signalling mediates for the transcriptional control of Dnmt3b in cardiac cells	Apoptosis of cardiac muscle cells long QT syndrome and dilated cardiomyopathy, coronary artery diseases	(Wang and Rao, 2019) (Katoh and Katoh, 2006) (Rubiś and Totoń-Zurańska, 2017) (Di Mauro and Crasto, 2019) (Bernardo and Nguyen, 2016)
8.	hsa-mir-154	Cdkn2b	-	Hypertrophy	
9.	hsa-miR-210	APC	Regulating Wnt/ β -catenin signaling activity	Atherosclerosis, smooth muscle cell differentiation	(Eken and Jin, 2017)
10.	hsa-miR-218	β -catenin, P-FZD, sFRP2	enhanced Wnt/ β -catenin signaling activity	Induced hypertrophy in cardiomyocytes	(Song and Nigam, 2015) (Liu and Zhao, 2016) (Hu and Sun, 2017)
11.	hsa-miR-499-5p	PDCD4	-	Arrhythmogenic cardiomyopathy/arrhythmias, ischaemic injury	(Calore and Lorenzon, 2019) (Li and Lu, 2016)

One abundant miRNA (miR-128) expressed high level in various types of cardiovascular diseases. It exists in the chromosomal position of Ch2q21.3 and consist 82 nts long chain of nucleotide bases. This miRNA regulates the upstream direction and inhibits the GSK-3 β protein function, and also accumulates β -catenin for translocate to the nucleus. The β -catenin bind to the TCF/LEF protein that might leads to the gene activation of cardiac cells and promote associate cardiovascular diseases (Foulquier and Daskalopoulos, 2018).

3.2. Protein complex (FZD-WNT-LRP5/6)

In the activation state of the Wnt signaling pathway, the Wnt ligand protein bind with cellular membrane protein (frizzled receptor and LRP5/6 proteins). The frizzled protein is a G-protein coupled receptor that is more essential for Wnt pathway (Malbon, 2004). These trimeric protein complex phosphorylated by the protein kinase and inhibits the activity of β -catenin and block the phosphorylation of GSK-3 β . Consequently the β -catenin is accumulates in the cytoplasm and followed by nuclear translocation in the nucleus. The GSK-3 β protein dissociates with β -catenin and result into the binding with transcription factors TCF/LEF in the nucleus. Whereas, the transcription factors activated the Wnt responsive gene and expressed the linked disorders (Wang and Shu, 2005; Nusse and Clevers, 2017). This trimeric protein complex controls the numbers of biological activities like growth, metabolisms and development of cardiovascular diseases. These cardiovascular diseases are negatively regulated by miRNA-154, miRNA-499 and positively regulated by miRNA-210, miRNA-218 and miRNA-29 (Sun and Liu, 2021; Foulquier and Daskalopoulos, 2018). The miRNA-154 has encoded from the chromosomal position Ch14q32.31 and 84 nts long, whereas microRNA-499 has 122 nts base pair length and coded from the Ch20q11.22 chromosome position in human (Ibrahim and Fritz, 2021; Wang and Zhang, 2021). However, the miRNA-29 family, namely miRNA-29a/c found in chromosome position is Ch7q32.3 and Ch1q32.2, respectively. It also noted that the miRNA-154 and miRNA-499 suppress the Wnt signaling pathway. The miRNA-210 and miRNA-218 are equal 110 nts long and induce the Wnt signaling by blocking the APC, DKK and sFRPs receptor protein. This phenomena offered the Wnt protein plays a vital role in cardiovascular diseases.

3.3. Transcription factors family protein

The TCF/LEF protein family member plays vital role for heart

development during the embryonic stage and different types of heart disease in adult condition. The transcription factors family protein interlinked with the cofactors that regulated by the Wnt protein subunit. The TCF7L1 protein is stage dependent and very enigmatic; it may be specially required for heart formation. Conversely deletion of TCF7L1 protein led to cardiomyocyte formation as the study was carried out on the mouse model (Athanasouli and Balli, 2022). TCF7L12 is the main TCF (T-cell factor) member of β -catenin protein expressed in CMs (cardiomyocytes), particularly during the late stage of cardiogenesis. During heart development and maturation stage the TCF7 and LEF1 protein decreased while TCF7L1 and TCF7L12 remain moderately constant level (Ye and Li, 2019). The TCF7L12 targets and restrict the cardiac function of heart in diseased condition (Iyer and Nagarajan, 2018). However, multiple factors promote the target gene of cardiovascular diseases because the activation of TCF/LEF protein stimulates the heart functions at the cardiovascular disease stage. The miRNA-133b/a functionally lowering the activities of β -catenin and TCF/LEF (Lin and Lin, 2021). The miRNA-133b/a consist with 119 nts and encoded from the Ch6p12.2 in humans. Previously, limited number of studies shown on the involvement of miRNAs in cardiovascular diseases through Wnt signalling pathway. Therefore, it is essential to do more scientific research on miRNAs as considering potential and functional aspects of molecular biology. Additional experimental and laboratory based studies are also required to identify how the Wnt signalling protein family regulates heart diseases coupled with the miRNAs.

4. miRNAs mediated cell activation of cardiovascular diseases

The miR-133b/a and miR-1 are dynamic muscle-specific miRNAs which helps in calcium signaling, cell growth and cellular development (Dong and Chen, 2010). In intracellular Ca²⁺ regulation both the miR-133b/a and miR-1 reduced cardiac hypertrophy with the down regulation of mRNA and calcineurin protein (Dong and Chen, 2010; Liu and Bezprozvannaya, 2008). These miRNAs also blocked cardiomyocyte hypertrophy by the effector's gene NFATC4. The GSK-3 β inhibits by Wnt protein complex and activates the β -catenine protein unit. This β -catenine protein also phosphorylate and transfer from cytoplasm to the nucleus and attached with the transcription factors protein (TCF/LEF) to regulates the Wnt signaling pathway. The miRNA-1 also promotes cardiomyocyte hypertrophy in human embryonic stem cell, which is a multipotent progenitor that suppress Wnt signaling pathway (Lu and Lin, 2013). Another pro-hypertrophic miRNA-29 positively regulates the

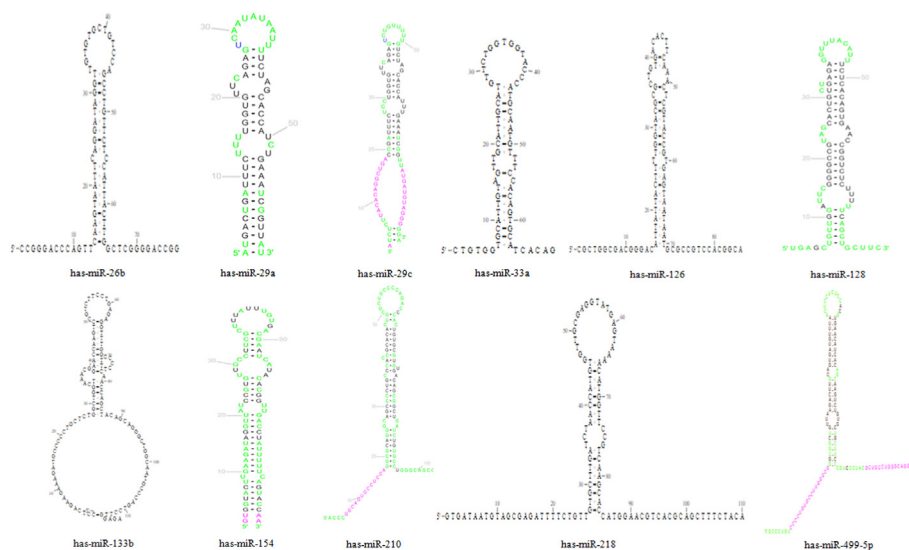


Fig. 3. Collection of human miRNAs stem-loop or secondary structure interlinking with Wnt signaling pathway in cardiovascular diseases, (collected from the <http://rnacentral.org/> and <https://asia.ensembl.org/index.html>).

Table 2

Various human miRNAs and their HGNC ID, chromosome location, gene regulation, pre-microRNAs nucleotide length, the mature sequence and the map accession number interrelated with Wnt signaling pathway in cardiovascular diseases.

Names of the miRNA	HGNC	Chromosome location	Gene regulation	Nucleotide length (nt) of pre-miRNA	Mature sequence of miRNA	miRNA map accession no.
hsa-miR-26b	31612	Ch2q35	DOWN	77 nt	47 - CCUGUUCUCCAUAUACUUGGCU - 67	MI0000084
hsa-miR-29a	31616	Ch7q32.3	UP	64 nt	42 -UAGCACCAUCUGAAAUCGGUUA - 63	MI0000087
hsa-mir-29c	31621	Ch1q32.2	UP	88 nt	54 UAGCACCAUUUGAAAUCGGUUA 75	MI0000735
hsa-mir-33a	31634	Ch22q13.2	DOWN	69 nt	46 CAAUGUUUCCACAGUGCAUCAC 67	MI0000091
hsa-miR-126	31508	Ch9q34.3	DOWN	85 nt	52 - UCGUACCGUGAGUAAUAAUGCG - 73	MI0000471
hsa-mir-128	31510	Ch2q21.3	UP	82 nt	50-UCACAGUGAACCGGUCUCUUU-70	MI0000447
hsa-miR-133b	31759	Ch6p12.2	DOWN	119 nt	66 - UUUGUCCCUUCAACCAGCUA - 87	MI0000822
hsa-mir-154	31541	Ch14q32.31	UP	84 nt	51-AAUCAUACACGGUUGACCUAAU-72	MI0000480
hsa-miR-210	31587	Ch11p15.5	UP	110 nt	66 - CUGUGCGUGUGACAGCGGUGA - 87	MI0000286
hsa-miR-218	31595	Ch4p15.31	UP	110 nt	68-AUGGUUCCGUGAAGACCAUGG-89	MI0000294
hsa-miR-499-5p	32133	Ch20q11.22	DOWN	122 nt	33 - UUAAGACUUGCAGUGAUGUUU - 53	MI0003183

cardiac fibrosis. It prevents TAC (Transverse aortic constriction)-induced cardiomyocyte hypertrophy and inhibits the genetic deficiency. But during the overexpression of miR-29 it directly promotes phenylephrine-induced cardiomyocyte hypertrophy (Sassi and Avramopoulos, 2017; Roncarati and Viviani Anselmi, 2014). Such phenomenon was induced by the Wnt signaling inhibitory factors such as GSK3 β , ICAT/CTNBP1, HBP1 and GLIS2 proteins (Wehbe and Nasser, 2019). Additionally, the human miRNAs and their HGNC ID, chromosome location, gene regulation, pre-miRNAs nucleotide length, the mature sequence and the map accession number interrelated with the Wnt signaling pathway in cardiovascular diseases are also listed in Table 2.

5. Future perspectives

The miRNA-based research and its future applications for clinical purposes are increasing in faster ways. Within a short period (last decade) from the first reporting of miRNAs in human body has been considered an effective novel tool for diagnosis and therapeutics purposes linked with cardiovascular diseases. Nevertheless, there also still much more significant things that remain to understand. In the outlook of the current research viewpoint, more advanced studies are required to illuminate this precise approach. In fact the miRNAs are competent to suppress the protein translation and initiate the process of mRNA degradation pathways. Likewise, the particular sources, positions and roles of miRNA in light of the cell to cell molecular communication are need to be understood in a well-defined state.

Furthermore, the miRNAs also served as important prognostic and diagnostic biomarkers in the perception of diverse clinical approaches. The superior clinical trials or research analysis are prerequisites factor to establishing whether the current miRNAs candidates offered added advantages over and above those of other prevailing known biomarkers of cardiovascular diseases. Currently, more technological progress are essential to facilitated the quick, consistent and reproducible results targeted to the absolute quantification of cardiovascular diseases linked with miRNAs to facilitated the transition into an effective clinical practices.

Lastly, while there continue a number of vital challenges to overwhelmed, researchers should be aware about the impending arrival of miRNA-based therapeutics within the specified domain of clinical medicine for cardiovascular diseases.

6. Conclusions

Nowadays, human miRNAs can possibly be used as the new promising elements for novel personalized therapies. Numerous scientific reports previously highlighted about the usefulness of miRNA based treatments

(*in vivo*) model. Even through, more significant studies are urgently required to translate these miRNA regulated gene interaction results into the bench to clinical applications. Additionally, the foremost effort also needs to address to test the multiple safety parameters of the miRNAs delivery systems, dosage, and mode of administration, time span of the treatments, the occurrence and also the prevention of side effects specific for the cardiovascular diseases.

Thus, it has been scientifically confirmed that the miRNAs performed a crucial role in numerous types of cardiovascular pathologies. The preliminary studies of Wnt signaling pathway and miRNAs already shown high promises for the scientific uses of miRNA as novel biomarkers and even therapeutic targets in the near future.

CRediT authorship contribution statement

Jiban Kumar Behera: Writing – original draft, Validation, Investigation. **Manojit Bhattacharya:** Conceptualization, Formal analysis, Writing – review & editing. **Pabitra Mishra:** Visualization, Data curation, Formal analysis. **Akansha Mishra:** Visualization, Validation. **Adya Anindita Dash:** Visualization, Validation. **Niladri Bhusan Kar:** Visualization, Validation. **Bhaskar Behera:** Validation, Formal analysis. **Bidhan Chandra Patra:** Supervision, Validation, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviation

miRNA	MicroRNA
UTR	Untranslated region
Fzd	Frizzled
APC	Adenomatous polyposis coli
CK1	Casein kinase 1
GSK-3 β	Glycogen synthase kinase 3 β

Dvl1	Disheveled protein
PKC	Protein kinase C
TCF	T-cell factor
LEF	Lymphoid enhancer factor
PCP	Planar cell polarity
PLC	Phospholipase C
RISC	RNA-induced silencing complex
Ago	Argonaut
DGCR8	Di George syndrome chromosomal region 8
TRBP	Trans-activator RNA binding protein
PACT	PKR-activating protein
sFRP	Frizzled-related protein

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