Chapter

Circular RNAs and Its Biological Functions in Health and Disease

Atiye Seda Yar Saglam, Ebru Alp and Hacer Ilke Onen

Abstract

Circular RNAs (circRNAs) belong to the family of long noncoding RNAs (lncRNA) that, unlike linear RNAs, are characterized by a covalently closed circular RNA structure lacking 5′ cap and 3′ poly-adenylated tails. circRNAs have a role in epigenetic regulation of downstream targets. circRNAs play a crucial role in regulating gene and protein expressions by acting as a microRNA (miRNA) sponge and RNA binding protein (RBP) sponge and interact with proteins to affect cell behavior. circRNA expression profiles differ between physiological and pathological states. Moreover, the expression patterns of circRNAs exhibit differences in a tissue-specific manner. Although investigations on circRNAs have been exploding nowadays, yet only a limited number of circRNAs are identified. Furthermore, further researches are needed to shed light on their functions and targets. Therefore, circRNAs are becoming vital as potential biomarkers that may be used for the diagnosis and treatment of diseases. In this chapter, we review the current advancement of cirRNAs with regard to their biogenesis, biological functions, gene regulatory mechanisms, and implications in human diseases and summarize the recent studies on circRNAs as potential diagnostic and prognostic biomarkers based on existing knowledge.

Keywords: circular RNAs, cardiovascular diseases, neurological disorders, immune regulation, cancer

1. Introduction

The ENCyclopedia Of DNA Elements (ENCODE) project reported that noncoding RNAs (ncRNAs) unexpectedly consist of more than 70% of the human genome [1]. After the data released by ENCODE project consortium, numerous studies have focused on the identification and function of these transcripts [2]. ncRNAs can be a group based on their different characteristic features [3]. Long noncoding RNAs (lncRNAs) are subclass of ncRNAs that have been recently proved to have a role in physiological and pathological processes [4]. lncRNAs are >200 nucleotides long, divergent class of RNA transcripts that coordinate expression of protein-coding genes. Yet, they have a lack of ability to encode proteins [5]. Circular RNAs (circRNAs) are a special subtype of lncRNAs [6]. circRNAs are characterized by a single-stranded covalently closed loop structure with neither a 5′ cap nor a 3′ poly (A) tail [7]. Due to their circular structure, circRNAs are more stable than the linear mRNA counterpart and not susceptible to RNA exonuclease cleavage [6, 7]. The presence of circRNA was first demonstrated in the cytoplasm of eukaryotic cells in

1979 [8]. It was thought that circRNAs were a by-product formed during splicing mechanism in the first year [9]. Numerous circRNAs have been predicted with the technical developments in high-throughput RNA sequencing (RNA-seq) and methodological innovations in bioinformatics. The presence and function of the predicted circRNAs in different tissues and cell lines are widely studied nowadays. After the determination of their role in the control of gene expression, circRNAs have gained great attention by researchers in this field. In this chapter, we will focus on circRNAs and their biological functions in health and disease.

2. Biogenesis of circRNAs

According to the gene structure they contain, circRNAs can be divided into three groups: exonic circRNA (ecircRNA), circRNAs from introns (ciRNAs), and exon-intron circRNA (elciRNA) [10]. To date, many studies have shown that circRNAs mainly emerged during pre-mRNA splicing process of protein coding genes. Unlike canonical mRNA splicing mechanism, down-stream donor splice site is covalently joined with an upstream acceptor splice sites during circRNA formation. This splicing mechanism is called "back-splicing" [7]. The back-splicing mechanism is depicted in **Figure 1**. circRNAs can also be formed through the hybridization of complementary inverted sequences (such as human Alu repeats) in introns [10]. If Alu sequences are located in different introns of the same gene, this leads to

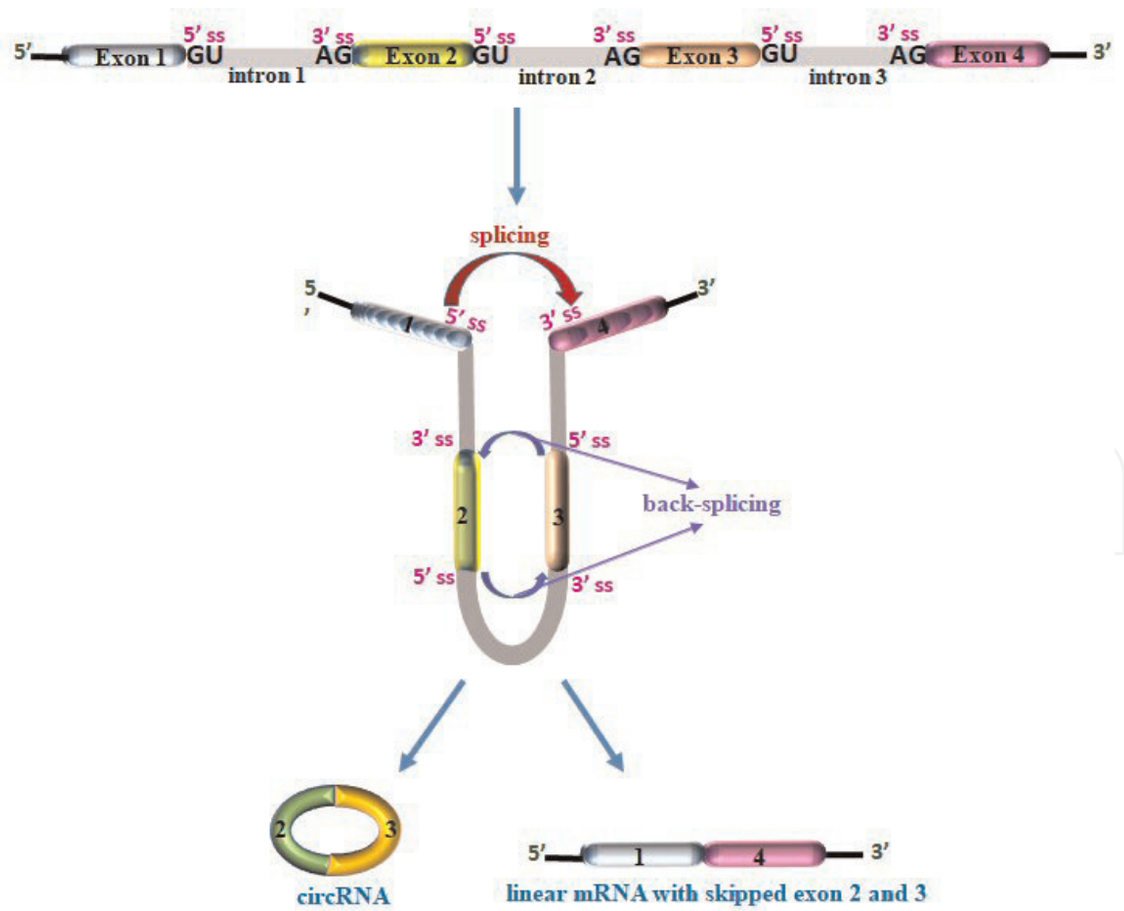

Figure 1.
Schematic illustration of the circRNA formation by back splicing mechanism. Unlike canonical mRNA splicing mechanism, the 3′ splice donor site of exon 1 binds to the 5′ splice acceptor site of exon 4 during circRNA formation. The back-splicing results in a circRNA including exon 2 and 3 and linear mRNA with skipped exon 2 and 3. ss, splice site.

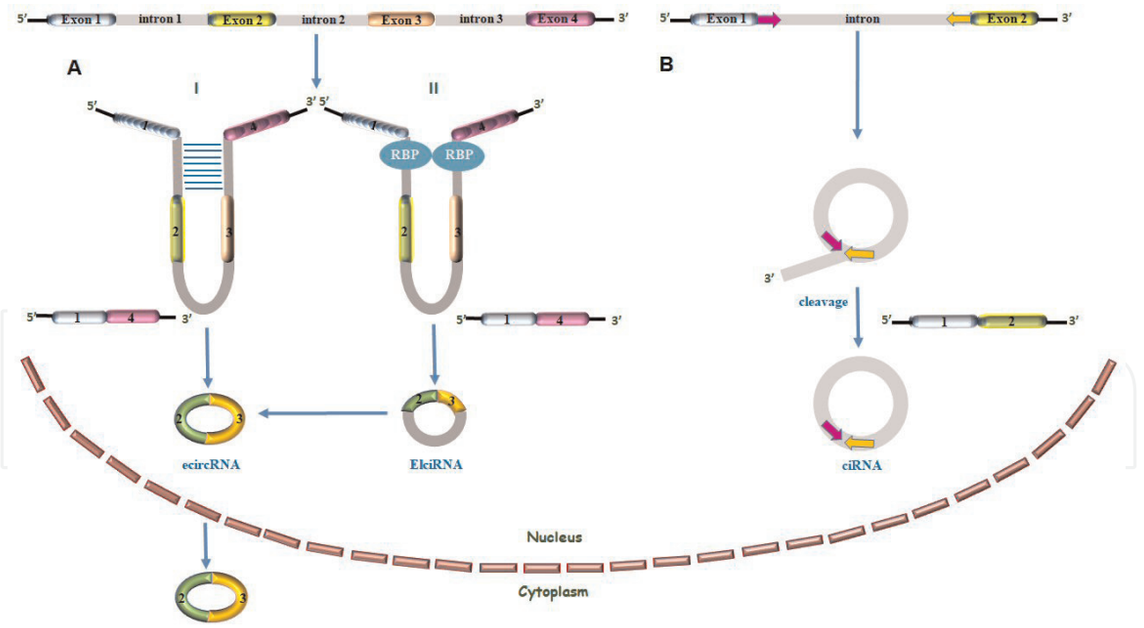

Figure 2.
Possible model for the formation of structurally different circRNA. (AI) Intron-driven circularization: circRNAs may form by hybridization of the introns with inverted repeats or Alu sequence. (AII) RBP-driven circularization: RBPs bind to specific sequence in introns that bring the exons close together and trigger the circularization. At the end of these two ways, elciRNAs or ecircRNAs are generated. Only ecircRNAs can be transported to cytoplasm. (B) Formation of ciRNA. The ciRNAs are generated from intron lariat by splicing reaction. Purple arrow represents 7-nt GU-rich element. Yellow arrow represents 11-nt C-rich element near to the branchpoint site.

generate circRNAs, which contains multiple exons [7]. Exon circularization is facilitated by cis-acting inverted repeat sequences as well as by trans-acting RNA-binding proteins (RBPs), which interact with unique sequences in introns [11, 12]. ecircRNA or elciRNA formation is promoted by either cis-acting elements or trans-acting factors as in **Figure 2A**. ecircRNAs can also be formed from elciRNAs by removal of intronic sequences [13]. Apart from the other circRNAs, ecircRNAs are transported into cytoplasm [14]. In human cells, the existence of ciRNAs is demonstrated by Zhang et al. [15]. ciRNAs are generated through a lariat-derived mechanism relying on mainly a consensus motif containing a 7-nt GU-rich element adjacent to the 5′ splice site and an 11-nt C-rich element adjacent to the branchpoint site. After cleavage of 3′ end, stable ciRNA is produced [15]. The predicted biogenesis of ciRNA is shown **Figure 2B**.

3. Gene regulation and biologic functions of circRNAs

The expression patterns of circRNAs are specific to the cell type or phase of development [16]. Although the all-biological functions of circRNAs are not entirely defined, some are well studied in the literature. Biological functions of circRNAs include micro RNA (miRNA) sponge, regulation of gene expression and properties of mRNA binding, scaffolding, and cellular translocation.

3.1 circRNAs can act as miRNA sponges

As a major component of gene regulators, competing/competetive endogenous RNA (ceRNA) contains a micro RNA response element (MRE-competitively binds miRNA) and can affect the regulatory functions of miRNAs [17]. Growing evidence has indicated that circRNAs can act as ceRNA or miRNA sponge molecules. Because

of containing plenty of MRE, circRNAs can competitively bind to miRNAs (generally several copies of miRNA) and adsorb them like a sponge [18]. As a result, miRNAs can no longer act on their target mRNA [19]. Therefore, circRNAs can regulate the gene expression and also give rise to decreasing of the functional miRNA [17, 18]. Compared to other ceRNAs, circRNA binds more effectively to miRNAs. Therefore, they are also called "super sponge" [20]. The most characteristic miRNA sponge "antisense to the cerebellar degeneration related protein 1 transcript" (CDR1as)/ciRS-7 includes approximately 70 conserved binding sites for miRNA-7 (miR-7) and forms a complex with Argonaute (AGO) proteins [21]. CDR1as-miR-7 complex co-localizes in the cytoplasm and supresses degradation of miR-7-target mRNAs [17]. Interestingly, circRNA has been reported that it is also displayed to be abundant in exosomes in serum [16]. Therefore, Li et al. suggested that sorting of circRNAs to exosomes was regulated by altering levels of associated miRNA in producer cells [16, 22]. In addition, researchers have found that CDR1as including exosomes inhibit miR-7-induced growth in recipient cells [22]. Testes-specific circRNA/circSry [the circular transcript of sex determining region Y (Sry) gene] can also serve as a sponge for miRNA-138 [23]. It contains 16 MREs of miRNA-138 and regulates the expression of miR-138-target genes, functioning similar to CDR1as [17]. Additionaly, many other circRNAs have been identified as miRNA sponges such as hsa_circ_001569, heart-related circRNA (HRCR), itchy E3 ubiquitin protein ligase circRNA (circITCH), forkhead box O3 circRNA (circ-foxo3), homeodomain interacting protein kinase 3 circRNA (circHIPK3), mitochondrial tRNA translation optimization 1 circRNA (circMTO1), zinc finger protein 609 circRNA (cirZNF609), and baculoviral IAP repeat containing 6 circRNA (circBIRC6) [24]. Among them, cirITCH regulates the expression of ITCH by acting as a sponge for miR-214, miR-17, and miR-7 [22].

Apart from common phenomenon, in some cases, the binding of circRNAs to miRNAs may not always lead to inhibition of miRNAs. Linearization and AGO2-mediated cleavage of CDR1as can occur when CDR1as interacts with miR-671. Thus, bound miR-7 is released from CDR1as [25]. On the other hand, in spite of the role of circRNA in gene regulation as a classical sponge effect, some recent studies have revealed that the number of circRNAs with miRNA sponge property is limited. Besides inhibition effect, it has been regarded that the interaction between circRNAs and miRNA is also related to sorting, storage and localization of miRNA [18].

3.2 circRNAs regulate gene expression and interact with protein

In addition to their miRNA sponge function, circRNAs can also act as sponges for other components as RBPs. There are many proteins known as RBP such as AGO protein, RNA quaking, muscleblind (MBL) protein, RNA polymerase II (Pol II), eukaryotic initiation factor 4A-III [26]. RBPs bind specific sequences to their target genes and control all stages of mRNA lifecycle including splicing, nuclear export, stability and subcellular localisation [27]. A number of circRNAs contain a large amount of binding sites for a single or multiple RNA-binding proteins. For example, circRNA protein sponge derived from the *MBL* locus includes binding sites of mbl protein. Thus, mbl is prevented from binding to other targets. In a parallel study, circular RNA of polyadenylate-binding nuclear protein 1 (circPABPN1) derived from PABPN1 gene binds to HuR (enhance PABPN1 translation) and prohibits its binding to PABPN1 mRNA [28].

circRNAs also inhibits parental gene transcription in target genes via invading RNA binding sites. Strongly binding of circRNA, derived from sepallata3 (SEP3) gene, to its cognate DNA locus blocks the binding of its linear isoform to the

cognate DNA. The formation of R-loop (RNA:DNA hybrid) gives rise to termination of SEP3 gene transcription [13]. Moreover, circRNAs can be paired with DNA to generate DNA-RNA triple helixes. Therefore, this pairing may affect DNA replication [29].

Some ciRNAs (e.g., ci-ankrd52, ci-sirt7) and eIciRNAs (e.g., circEIF3J, circPAIP2) regulate the transcription of their parental genes. eIciRNAs can regulate parental gene transcription in a cis-acting manner [18, 23, 24]. Recent studies have been indicated that nuclear elciRNAs (localized to the promoter of their parental genes) interact with U1 small nuclear ribonucleoproteins (snRNPs) and RNA pol II and promote the transcription initiation of their parental genes [28, 30]. For example, eukaryotic translation initiation factor 3J circRNA (circEIF3J) and poly(A)-binding protein-interacting protein 2 circRNA (circPAIP2) have been suggested to have cis-regulatory effects on parental genes and promote transcription of EIF3J and PAIP2. This cis-regulatory effect occurs by binding of its circRNAs to Pol II, U1 snRNP, and their parental gene promoters [18, 25]. When transcription is initiated, the production of eIciRNA can be increased so that this phenomenon generates a positive feedback loop. [23]. Moreover, they have a function as positive regulators through their interactions with the elongating Pol II complex [24, 25, 31]. In addition, exonic circular antisense noncoding RNA in the INK4 (a family of cyclin-dependent kinase inhibitors) locus (circANRIL/cANRIL) reduces ANRIL that inhibits transcription of INK4/ARF gene by binding to the Polycomb Gene (PcG) complex. Thus, cANRIL regulates the transcription of INK4/ARF [32].

3.3 Cellular translocation properties

Some circRNAs may affect nuclear translocation of other proteins to nucleus and regulation of gene transcription. For example, CircAmotl1 may increase nuclear translocation of signal transducer and activator of transcription 3 (STAT3) to regulate the expression of mitosis-related genes [24].

Another capability of circRNAs is to ensure that cellular proteins remain in their natural cellular position. It has been reported that circAmotl1 can enhance stability of c-myc by maintaining its nuclear retention and increase its binding affinity to several promoters. Therefore, it upregulates c-myc targets such as hypoxia inducible factor-1 alpha (HIF-1α), cell division cycle 25A (Cdc25a), ETS Like-1 (ELK-1) [24]. In another example, cytoplasmic circ-foxo3 interacts with differentiation-1 (ID-1), HIF-1α, focal adhesion kinase (FAK), the transcription factor E2 (E2F1) and prevents their translocation from cytoplasm to other location [13].

3.4 Scaffolding properties

circRNAs also serve as scaffolding in the assembly of protein complexes [13]. It has been reported that circ-foxo3 acts as an adaptor to bridge between cyclin-dependent kinase 2 (CDK2) and CDK inhibitor p21 (cyclin-dependent kinase inhibitor 1A). This interaction (circ-foxo3/CDK2/p21) inhibits cell-cycle progression within G1 to S-phase transition [18, 24]. However, downregulation of circ-foxo3 leads to the release of CDK2 from p21 and CDK2 phosphorylates cyclin E and cyclin A for cell cycle progression. On the other hand, the circ-foxo3 connects the murine double minute 2 (MDM2) to tumor protein p53 (p53), and induces the degradation of p53 by ubiquitination. However, circ-foxo3 weakly interacts with foxo3 and suppresses foxo3 from MDM2-mediated polyubiquitination and proteasome degradation [30].

3.5 mRNA binding properties

Most circRNAs are capable of interaction with mRNAs. It has been reported that they can be able to regulate the stability of mRNAs as well. In addition to its miRNA sponge function, CDR1as is also proposed to form a duplex structure with CDR1 mRNA and stabilizes it. Similarly, stabilization of mature intercellular adhesion molecule 1 mRNAs in macrophages was found to be facilitated by RasGEF domain family member 1B circRNA (circRasGEF1B) [18].

3.6 The effect of circRNA as a translator

Recent studies have shown that some circRNAs can be entered to translational process in spite of considering noncoding RNA [33, 34]. A limited number of studies have indicated the potential protein coding properties of circRNAs until now but the translational efficiency might be low [33]. circRNA containing internal ribosomal entry site (IRES) and open reading frame can be translated into protein or polypeptide. In eukaryotes, IRES is an alternative way of initiating translation, independent of 5′ cap structure and 3′ poly (A) tail recognition [19]. It has been demonstrated that the 40S subunit of the eukaryotic ribosome can interact with circRNA-containing IRES and then begin translation in *in vivo* and *in vitro* experiments. It has been shown that zinc finger protein 609 circRNA (circZNF609) can be translated into a novel ZNF609 protein isoform and potential function during myogenesis. Another study indicated that novel proteins have been translated from F-box and WD repeat domain containing 7 circRNA (circFBXW7) and SNF2 histone linker PHD ring helicase circRNA (circSHPRH) in glioblastoma cell lines. A new isoform protein encoded by circFBXW7 with open reading frame was found to inhibit glioma cell growth [18, 34].

A recent study reported that N6-methyladenosine (m6A), a most common base modification of RNA, can promote the protein translation of circRNA in human cells, even if one m6A motif can initiate circRNA translation [18, 19, 29]. m6A-driven circRNA translation is prevalent, and several endogenous circRNAs have the potential for translation and regulatory role in a cell against enviromental factors [29].

3.7 The effect of circRNAs on splicing

Recent studies have shown that there is a competition between backsplicing and linear splicing. Thus, the biogenesis of circRNAs leads to loss of protein-coding mRNA levels and inhibits parental gene expression [13]. On the other hand, the level of circRNA is negatively correlated to the splicing efficiency of certain genes due to the competition between linear splicing and circRNA biogenesis [30].

4. circRNAs in cardiovascular diseases

Cardiovascular disease (CVD) is one of the most important health problems. It causes most of the deaths worldwide [35]. According to recent studies, a number of circRNAs may play a significant role during development of CVD or pathological conditions such as cardiac hypertrophy, coronary artery disease, atherosclerotic vascular disease, cardiomyopathy, cardiac fibrosis, heart failure (HF), ischemia, and myocardial infarction (MI) [36–38]. However, in development of heart disease, the regulatory mechanisms and functional importance of several circRNAs are not clear [38]. circRNAs are also concentrated in body fluids such as seminal fluid,

circRNA	Possible target	CVD	Biological function or description	Ref
circANRIL (ex 5–7)	PES-1	AS and CAD	Impairs pre-rRNA maturation and ribosome biogenesis and increases nucleolar stress and apoptosis	[32, 47]
circANRIL (ex 4–6)		ASVD	Neighboring gene regulation such as INK4a	[32]
Hsa_circ_0003575	miR-199-3p, mir-9-5p, mir-377-3p, and miR-141-3p	AS	Regulates endothelial cell proliferation and angiogenesis acting as a miRNA sponge	[48]
Hsa_circ_0010729	mir-186	AS and CHD	Regulates vascular endothelial cell proliferation and apoptosis via targeting miR-186 and HIF-1α axis	[49]
circACTA2	miR-548f-5p	AS and CHD	Maintains contractile phenotype of VSMC Mediates NRG-1-ICD regulation of α-SMA expression in HASMCs	[50]
circWDR77	mir-124	AS	Regulates VSMC proliferation and migration via targeting miR-124 and FGF2 Inhibits the expression of SM22a and STIM1 by acting as a miRNA sponge	[51]
circ-SATB2	mir-939	AS	Inhibits the expression of SM22a and STIM1 by acting as a miRNA sponge Regulates cell phenotypic differentiation, proliferation, apoptosis, and migration in VSMC	[52]
circR-284	miR-221	AS and carotid plaque rupture	Reduces the proliferation of VSMCs by circR-284/mir-221/$p27^{Kipi}$ axis Upregulated circR-284:miR-221 ratio in the early stage of carotid plaque rupture	[53, 54]
hsa_circ_0124644		CAD	Potential biomarker of coronary artery disease	[55]
hsa_-circ_0001879		CAD	Significant upregulated expression levels in CAD patients	[56]
hsa_circ_0004104			Dysregulation of atherosclerosis-related genes by overexpression of hsa_circ_0004104	[56]
CDR1as	miR-7a	MI	Upregulates the expression of PARP and SP1 acting as a miRNA sponge and promotes apoptosis	[57]
MICRA		Acute MI, HF, and LVD	Potential biomarker of left ventricular dysfunction in the patients with acute MI	[58, 59]
MFACR	miR-652-3p	MI	Upregulates apoptosis and mitochondrial fission	[60]

circRNA	Possible target	CVD	Biological function or description	Ref
HRCR	mir-223	HF and cardiac hypertrophy	Increases the expression of ARC by acting as a miRNA sponge. Suppresses cardiac hypertrophy	[61]
circ-081881	mir-548	Acute MI	Positively regulates PPARγ acting as a miRNA sponge	[62]
circRNA-010567	miR-141	MI	May mediate fibrosis-associated protein resection	[63]
circNCX1	miR-133a-3p	Ischemic myocardial injury	Promotes cardiomyocyte apoptosis by acting as a miRNA sponge and increased in response to ROS	[64]
circAmotl1	AKT and PDK	Cardiac repair and cardiomyopathy	Facilitates the nuclear translocation of AKT and PDK1 Improves survival and decreases apoptosis	[45]
circTTN		DCM	Dysregulated in disease model	[65, 66]
circRyr2		Cardiomyopathy		[65]
circZNF609	miR-615-5p and miR-150-5p	Hypertension and CAD	Inhibits cell proliferation, migration, and tube formation and promotes cell apoptosis Acts as a miRNA sponge and leads to upregulation of MEF2A expression	[67]
Hsa-circ-0005870	hsa-miR-619-5p, hsa-miR-5095, hsa-miR-1273 g-3p, and hsa-miR-5096	Hypertension	Downregulated in hypertension patients	[68]
rno_circRNA_016002		Hypertension	Upregulated in hypertensive rat strains compared to normotensive rats	[69]
hsa_circ_0014243	hsa-miR-10a-5p	EH	Crucial role in the genesis and development of EH and presents a certain diagnostic capability for EH	[70]
hsa_circ_0037911	miR-637	EH	Upregulated in hypertension patients	[65, 71]
hsa_circ_0126991		EH	May serve as a stable biomarker for early diagnosis of EH	[72]
circ-foxo3	ID-1, E2F1, FAK, and HIF-1α	Cardiac senescence	Interacts with ID-1, E2F1, FAK, and HIF-1α and induces cellular senescence in aging hearts	[46]

CVD, cardiovascular disease; AS, atherosclerosis; ASVD, atherosclerotic vascular disease; CHD, coronary heart disease; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; LVD, left ventricular dysfunction; EH, essential hypertension; DCM, dilated cardiomyopathy; VSMC, vascular smooth muscle cell; ROS, reactive oxygen species; ANRIL, antisense noncoding RNA in the INK4 locus; PES1, pescadillo homologue 1; ACTA2, actin alpha 2; WDR77, WD repeat domain 77; STIM1, stromal interaction molecule 1; SATB2, special AT-rich sequence-binding protein 2; CDR1, cerebellar degeneration-related protein 1; MICRA, myocardial infarction associated circRNA; MFCAR, mitochondrial fission and apoptosis-related circRNA; HRCR, heart-related circRNA; ARC, apoptosis repressor with CARD domain; NCX1, sodium/calcium exchanger 1; AMOTL1, angiomotin like 1; AKT, protein kinase B; PDK, phosphoinositide-dependent protein kinase; TTN, titin; RYR2, ryanodine receptor 2; Foxo3, forkhead box O3; ID1, inhibitor of DNA binding 1; E2F1, E2F transcription Factor 1; FAK, focal adhesion kinase; HIF-1α, hypoxia inducible factor-1; FGF2, fibroblast growth factor2; PARP, poly ADP-ribose polymerase; and MEF2A, myocyte enhancer factor 2A.

Table 1.
Summary of identified circRNA in the cardiovascular disease.

saliva, and blood. Thus, their potential usage as clinical biomarkers may be possible in the future [39].

Some heart specific RNA-splicing regulators are also important players for heart development. One of the RNA-splicing regulators is RBM20 that is required for splicing of cardiac-related genes such as titin [38]. Its mutation leads to exon retention in the region of I-band and results in larger titin isoforms [30]. According to RNA-seq researches in tissues from dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy, 80 different circRNAs are derived from the titin gene (TTN) [30, 40].

circANRIL is generated as an antisense transcript from the INK4A/ARF gene locus by alternative splicing [36]. SNPs localized within chromosome 9p21 are likely to affect the INK4/ARF locus. These SNPs can regulate ANRIL splicing and may lead to circANRIL production [39]. Interestingly, there is an association between 9p21 SNPs and the susceptibility to atherosclerosis [41]. circANRIL is also implicated in the pathogenesis of atherosclerosis [42]. In another study, Burd et al. suggested that 9p21 SNPs affect the coordination of ANRIL expression and splicing via interaction of different PcG complexes. Furthermore, PcG complexes are targeted to the INK4/ARF locus and that leads to inhibition of INK4/ARF transcription. Moreover, they also indicated that their study is the first to provide evidence for relationship between circRNA and atherosclerotic vascular disease (ASVD) [32].

circANRIL also disrupts exonuclease-mediated pre-rRNA processing and ribosome biogenesis by binding to pescadillo homologue 1 (PES1). This leads to nuclear stress and p53 activation in cells [38, 39]. Therefore, it supresses cell proliferation and inhibits apoptosis in vascular smooth muscle cells and macrophages. Consequenly, circANRIL acts as a protective factor against atherosclerosis [41, 43]. On the other hand, it has been indicated that a novel circular RNA product of ANRIL, cANRIL (exon4-6) also regulates the expression of INK4/ARF [32].

In addition, circRNA serves as a protein scaffold such as circAmotl1 in cardiac dysfunction [35, 43]. circAmotl1 facilitates phosphorylation of protein kinase B (AKT) and nuclear translocation of pAKT by forming ternary complexes with AKT and phosphoinositide-dependent protein kinase (PDK) [43–45]. Zeng et al. have suggested that pAKT translocation may be responsible for protection of heart cells from cardiomyopathy caused by doxorubicin [45].

circ-foxo3 is another circRNA described to may have a role in the cardiovascular diseases. Stress-related proteins (HIF-1α and FAK) and senescence-related proteins [inhibitor of DNA-binding protein (ID1) and E2F1] are arrested in cytoplasm by circ-foxo3. Therefore, circ-foxo3 prevents translocation of these proteins into the nucleus. As a consequence, this mechanism promotes cardiac senecence through ectopic expression of circ-foxo3 [41, 46]. Besides these functions, circRNAs are reported to also show their effects as miRNA sponge in cardiovascular diseases. circRNAs and their function in cardiovascular diseases are indicated in **Table 1**.

Although there is limited number of studies until today, CVD-related studies for circRNA are in progress. Therefore, it is still required the identification of circRNA as candidate biomarkers for CVDs. Moreover, biologic functions of circRNA in vascular endothelial cell and heart tissue should be validated in further studies.

5. circRNAs in neurological disorders

Recent studies have shown that circRNAs are plentifully expressed in normal neuronal cells [73–75]. They may be found abundantly in neuronal cells for several reasons: (i) brain contains more host genes of circRNA such as neuronal genes,

which play roles in neurogenesis, neuronal development, and neuronal differentiation [11, 74], (ii) the expression levels of circRNAs are higher in brain than other tissues [75, 76], (iii) due to the slow division rates of neurons, circRNAs may accumulate more in the brain than other tissues [77], (iv) neuronal genes contain long introns (>10 kb) with inverted repeat sequences, thereby simplifying formation of circRNAs [10], and (v) circRNAs due to the absence of 5′ and 3′ ends result in greater stability than linear RNAs, leading to a relatively longer half-life [78]. The half-life of circRNAs is approximately 20 h, compared with corresponding linear isoforms (no more than 8 h) [79].

The latest studies have shown that circRNAs could attenuate cell senescence and cell survival and may be involved in the regulation of aging and age-related neurological diseases [80–82]. Thus, circRNAs are expected to be new potential biomarkers and target for aging and age-related neurological diseases (**Table 2**). These studies have suggested that circRNAs may play an important role in pathological mammalian brain function, which is implicated in disorders in central nervous system (CNS) including Alzheimer's disease (AD), Parkinson's disease (PD), neuropsychiatric disorders, prion disease, and inflammatory neuropathy.

CDR1as, a circRNA, is highly plentiful and specifically expressed in the mammalian brain [85]. Some studies have indicated that ciRS-7 contains multiple anti-miR-7 sequences. This suggests that ciRS-7 may function as a sponge to sequester the normal functions of miR-7 [57, 95–97]. ciRS-7 can regulate the stability of

CircRNA	Target	Neurological disease	Possible mechanisms	Ref
ciRS-7	miR-7	AD	ciRS-7 is reduced in AD, and miR-7 can downregulate AD relevant targets, such as ubiquitin conjugating enzyme UBE2A, which play an essential role in the clearance of amyloid peptides	[83, 84]
circSry	miR-138	AD	mir-138 participate in learning and memory ability and is increased in AD, and it promotes tau phosphorylation by targeting the RARA/GCK-3β pathway	[85–87]
ciRS-7	miR-7	PD	miR-7 may downregulate α-synuclein expression, promotes the degradation of α-synuclein mRNA levels, and protects cells against oxidative stress	[88]
ciRS-7	miR-7 miR-671	Neuropsychiatric disorders	miRNA deregulation and affects brain function	[78, 89, 90]
ciRS-7	miR-7	Prion disease	Prion protein PrPc can upregulate expression of ciRS-7	[91, 92]
hsa-circRNA 2149	—	Inflammatory neuropathy	Hsa-circRNA 2149 has been detected in CD19+ leukocytes	[53]
circSry	miR-138 circRNA100783	Inflammatory neuropathy	miR-138 can balance the ratio of Th1 and Th2 via suppressing the function of RTF3 CircRNA100783 may be involved in chronic CD28-associated CD8 (+) T cell aging	[93, 94]

AD, Alzheimer's disease; PD, Parkinson disease; UBE2A, ubiquitin conjugating enzyme E2 A; RARA/GCK-3β, retinoic acid receptor alpha/glycogen synthase kinase-3β; and RTF3, runt-related transcription factor 3.

Table 2.
Functional mechanism of cirRNAs in neurological disease.

mRNA targets in the brain by binding to miR-7 [78, 85]. Besides, ciRS-7 can interact with multiple protein subunits, thus acting as "scaffolding" for RBPs [7, 98]. Thereby, it facilitates the interaction by potentially increasing the stability of the circRNA transcripts. Due to its multiple functions in brain, researchers have suggested that ciRS-7 can be a potential biomarker for neurodegenerative disorders including AD and PD [83].

5.1 circRNA in Alzheimer's disease

Alzheimer's disease is a chronic neurological disease. Lukiw et al. showed that the expression level of ciRS-7 is decreased in hippocampal CA1 region in sporadic AD [83]. Functional deficiency of ciRS-7 can lead to upregulation of miR-7 in AD brain and may cause the downregulation of several AD-relevant mRNA targets, including the ubiquitin conjugating enzyme E2A (UBE2A) [83, 84, 99, 100]. This autophagic protein, UBE2A, is a central effector in the ubiquitination cycle. UBE2A is crucial for clearing amyloid peptides via phagocytosis and contributes to amyloidogenesis [99]. In contrast to the previous studies, Shi et al. have shown that ciRS-7 promotes the degradation of amyloid precursor protein (APP) and beta-secretase 1 (BACE1) in an nuclear factor kappa beta (NF-κB)-dependent manner [101]. Hence, future studies are needed to reveal ciRS-7 function/functions and its exact role in AD pathology.

CircSry can serve as a miRNA sponge in neural cells. CircSry inhibits miR-138 [53, 85], which is a potential molecular regulator of human memory function [102]. CircSry has multiple binding sites for miR-138 and promotes tau phosphorylation by targeting the "retinoic acid receptor alpha/glycogen synthase kinase-3β" (RARA/GCK-3β) pathway [86]. Some studies have indicated that miR-138 influences learning and memory abilities by regulating acyl protein thioesterase 1 [87, 102]. Therefore, association of circSry and miR-138 in AD should be further investigated.

5.2 circRNA in Parkinson's disease

Parkinson disease, progressive age-related neurodegenerative disorder, is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta [103, 104]. To date, five genes have been determined to cause PD, such as α-synuclein (SNCA), parkin, dj-1, PTEN-induced kinase 1 (pink1), and leucine-rich repeat kinase 2 (lrrk2) [105]. SNCA is the key player in the pathogenesis of PD based on neuropathologic, genetic, and cellular evidence [106]. The overexpression and aggregation of SNCA, a target gene of miR-7, is considered as a distinctive marker in PD [107, 108]. miR-7 has been proposed to play a role in PD by reducing expression of SNCA [88]. ciRS-7 plays a protective role by inhibiting miR-7 that directly regulates the expression of SNCA [109]. miR-7 alleviates SNCA expression dose-dependently and induces the degradation of SNCA mRNA levels [88]. These results suggest that ciRS-7 serves as a miR-7 sponge *in vitro*. Furthermore, the silencing of ciRS-7 increases miR-7 activity and decreases the expression of miR-7 target genes [110]. In addition, circSNCA, another circRNA, can sponge miR-7, thereby regulating expression of SNCA, resulting in decreased autophagy and increased apoptosis in cells [111]. These findings are in concordance with the results of a study, which showed that autophagy can prevent PD [112], and that of the other study, which demonstrated that apoptosis is related to PD [113].

5.3 circRNA and inflammatory neuropathy

circRNAs may participate in inflammatory reactions that induce neuropathy. Some circRNAs may affect immune responses due to the fact that they contain virus

miRNA binding sites. For instance, hsa-circRNA 2149 contains 13 unique, head to tail spanning reads. Researchers discovered hsa-circRNA 2149 in CD19+ leukocytes, but not CD341 leukocytes or neutrophils. On the other hand, circRNA100783 may be involved in chronic CD28-related CD8(+) T cell aging and for this reason could be a novel biomarker for this conditions [93]. Furthermore, circSry, another circRNA, can repress miR-138 activity, which could balance T helper 1 (Th1) and T helper 2 (Th2) expressions through suppressing the function of runt-related transcription factor 3 (RUNX3) [94].

5.4 circRNA and prion diseases

Most prion diseases are infectious via transmissible particles composed of prion protein in scrapie (PrPSc), an isomer of noninfectious cellular prion protein (PrPc). Studies have discovered that ciRS-7 expression is induced by PrPc overexpression [91, 92]. ciRS-7 may suppress miR-7 activity and therefore ciRS-7 may be involved in the prion disease pathogenesis.

5.5 circRNA and neuropsychiatric disorders

Apart from in brain tumors, ciRS-7 may also play a role in neuropsychiatric disorders. Increased miR-7 levels have been determined in neuropsychiatric disorders, serving as a proof for ciRS-7-mediated deregulation of dendritic spine density via a miR-7-SHANK3 (SH3 and multiple ankyrin repeat domains 3) axis [89, 90]. In recent study, Piwecka et al. showed that ciRS-7 knockout mice display behavioural phenotypes related to neuropsychiatric disorders. Deleting of ciRS-7 locus in mice leads to synaptic transmission function disorder and unusual neuropsychiatric-like behavior. [78]. Other than miR-7, ciRS-7 also has a binding site to miR-671, which is deregulated in all brain regions in ciRS-7 deficient mice; however, the direction of changes was opposite. It is designated that the binding site on ciRS-7 is completely complementary to miR-671, and the interaction of these two molecules could lead to AGO-mediated ciRS-7 slicing and miR-671 deterioration. On the contrary, the binding sites on ciRS-7 are partial complementaries to miR-7. For this reason, it is likely that circRNAs can serve as a platform to store and transport certain miRNAs [78, 89, 90].

Currently, circRNA studies in the CNS are in progress. To date, there is a limited number of circRNA identified in neurological disorders. Moreover, previous studies mainly focus on ciRS-7 function. Therefore, it is still needed to identify candidate circRNAs as a potential biomarker in neurological disease. In addition, their functional properties in neuronal cells should be also validated in further studies.

6. The role of circRNAs in immune regulation

Although many circRNAs are under survey, their roles in autoimmune diseases remain incomprehensible, and there are insufficient data to determine their exact role of circRNAs in such diseases [24, 114].

The connection between miRNAs and immunity has been well-studied, which has led to the hypothesis that circRNAs may contribute to immune regulation by interacting with miRNAs. In particular, due to their abilities to serve as miRNA and protein sponges, they can regulate gene expression and encode proteins. Therefore, circRNAs can participate in the development and progression of different immune responses and immune diseases [23, 24, 114]. On the basis of the current studies, the majority of circRNAs defined in autoimmune diseases are ecircRNAs, and a few are

Disease	CircRNA	Regulation	miRNA sponge targets	Potential functions	Ref
SLE	Hsa_circ_102584	↑	miR-766-3p miR-762 miR-412-3p let-7i-3p miR-431-3P	It may be improved as novel noninvasive biomarkers for SLE	[117]
	Hsa_circ_400011	↑	miR-296-3p miR-146b-3p miR-181d-3p miR-504-3p		
	Hsa_circ_101471	↑	miR-328-5p miR-136-5p miR-665 miR-486-3p miR-601		
	Hsa_circ_100226	↓	miR-30b-3p miR-138-5p miR-145-3p miR-24-3p miR-620 miR-875-3p		
	CDR1as/ciRS-7	↓	—	It functions as the miR-7 sponge to increase expression of PTEN and restricts hyper-responsiveness of B cells	[100, 118]
RA	Hsa_circ_104871	↑	—	It serves as potential biomarkers for diagnosis and performs severity or pathological course of RA	[119]
	Hsa_circ_003524	↑	—		
	Hsa_circ_101873	↑	—		
	Hsa_circ_103047	↑	—		
	Hsa_circ_0057980	↓	miR-181d	It functions as the miR-181d sponge to suppress the development of RA	[86, 120]
	Hsa_circ_0088088	↓	miR-16	It functions as the miR-16 sponge to suppress the development of RA	[121–123]
	Hsa_circ_0001045	↑	miR-30a	It functions as the miR-30a sponge to promote the biogenesis of RA	
MS	Hsa_circ_0005402	↓	—	It can be improved as MS biomarkers	[124]
	Hsa_circ_0035560	↓	—	It arranges negatively the biogenesis of MS	
	GSDMB ecircRNA	↑	miR-1275	It functions as the miR-1275 and miR-149 sponges to induce MS	[124, 125]
			miR-149	Both circRNAs are derived from the ANXA2	
PBC	Hsa_circ_402458	↑	miR-522-3p	It may be appropriate for PBC diagnosis	[121, 126]
			miR-943	It functions as the miR-522 and miR-943 sponges to counter chronic	[127]

Disease	CircRNA	Regulation	miRNA sponge targets	Potential functions	Ref
				inflammation and aberrant TGF-β signalling of PBC	
SCID	Circ-CDC42BPA	↑	—	It disrupts transduction of B cell signalling to induce formation of SCID	[128, 129]
	Circ-TNFRSF11A	↑	—	It attends in the SCID-mediated alteration of different signalling pathways	[128, 130]
WAS	Circ-ROBO1	↑	—	It activates the pathogenesis of WAS	[128, 131]
	Circ-CDC42BPA	↑	—	It disrupts transduction of B cell signalling to induce formation of WAS	[128]

MS, multiple sclerosis; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency disease; SLE, systemic lupus erythematosus; and WAS, Wiskott-Aldrich syndrome.

Table 3.
circRNAs are associated with immune diseases.

ciRNAs and eIciRNAs [23, 24, 114–116]. The circRNAs identified to date, their functions, and roles in immunological diseases are shown in **Table 3**.

It will be important in future studies to determine biological functions of circRNAs in immune cells. circRNAs may serve as both potential biomarkers and immune regulators [23, 24, 114–116]. Hence, it may be helpful to improve our understanding of the molecular biological basis of autoimmune diseases.

7. circRNAs in cancer

Cancer is one of the most common causes of death in worldwide. As stated in world cancer report (2014), 10 million people of the world develop all types of cancer each year. Moreover, over 6 million patients around the world die from this disease annually [132]. Unfortunately, the number of patients diagnosed with cancer is increasing and is estimated to increase in future in worldwide [133, 134]. Even if, a functional improvement in the treatment approach is established, and new therapeutic strategies are still needed for therapy of cancer. Therefore, the identification of the altered pathways and gene transcripts has been the subject of researches recently. miRNAs have a role in gene regulation and affect various molecular biological processes such as cell growth, development, differentiation, proliferation, and cell death [135]. As circRNAs interact with miRNAs and then influence the mRNA expression levels of target genes, the identification of circRNA-miRNA-mRNA network has become the objective of cancer researches.

There are numerous investigations on circRNAs and their functions in cancer as compared with other diseases. To date, most of the studies have focused on miRNA sponge function of circRNAs. miRNAs have been classified depending on the effect of miRNAs on downstream target/targets [136]. miRNAs can act as oncogenes or tumor suppressors during carcinogenesis [137]. Likewise, circRNAs are also named according to their behaviour during tumorigenesis. While some circRNAs contribute to tumor progression and metastasis, the others suppress oncogenesis.

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
hsa_circ_0001946	↓	hsa-miR-7-5p, hsa-miR-671-5p, hsa-miR-1270, hsa-miR-3156-5p	↑	NER signaling pathway	Activated	Compared to pairs of adjacent nontumor tissues, expression of hsa_circ_0001946 is downregulated in 43 NSCLC tissues There was a decrease in hsa_circ_0001946 expression on the cisplatin-resistant A549/CDDP cells compared with the parental A549 cells	[138]
	↑	miR-135a-5p	↓	SIRT1	↑	Compared to pairs of adjacent nontumor tissues, expression of circ_0001946 is upregulated in 72 lung adenocarcinoma tissues The circ_0001946 expression is upregulated in the four lung adenocarcinoma cell lines compared with the nonmalignant human lung epithelial cell line The increase in circ_0001946 expression in tumor samples is an independent prognostic factor for the patients with lung adenocarcinoma as well as advanced TNM stages	[139]
circAGFG1	↑	miR-203	↓	ZNF281	↑	Compared to pairs of adjacent nontumor tissues, expression of circAGFG1 is upregulated in 20 NSCLC tissues circAGFG1 enhances ZNF281-mediated migration and proliferation of NSCLC	[140]
hsa_circRNA_102984 (circPTPRA)	↓	miR-96-5p	↑	RASSF8/ e-cadherin	↑	Compared to pairs of adjacent nontumor tissues, expression of hsa_circRNA_102984 (circPTPRA) is downregulated in 34 NSCLC tissues circPTPRA acts as a miR-96-5p sponge, and it leads to upregulation of RASSF8 levels in both *in vitro* and H23 xenograft model	[141]
circ_0020123	↑	miR-488e3p	↓	ADAM9	↑	Compared to pairs of adjacent nontumor tissues, expression of circ_0020123 is upregulated in 55 NSCLC tissues	[142]

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
						The circ_0020123 expression is upregulated in the four NSCLC cell lines compared with the nonmalignant human bronchial epithelial cells The increase in circ_0020123 expression in tumor samples has been correlated with short overall survival rate in NSCLC patients	
	↑	miR-144	↓	ZEB1 EZH2	↑	Compared to pairs of adjacent nontumor tissues, expression of hsa_circ_0020123 is upregulated in 80 NSCLC tissues Upregulation of hsa_circ_0020123 expression in tumor samples has been correlated with short overall survival in NSCLC patients The hsa_circ_0020123 expression is upregulated in the six lung cancer cell lines	[143]
circVANGL1	↑	miR-195	↓	Bcl2	↑	Compared to pairs of adjacent nontumor tissues, expression of circVANGL1 is upregulated in 95 NSCLC tissues The circVANGL1 expression is upregulated in the five NSCLC cell lines compared with the nonmalignant human bronchial epithelial cells Upregulation of circVANGL1 expression leads to higher stage, bigger tumor size, and shorter overall survival in NSCLC patients	[144]
hsa_circRNA_102231 (hsa_circ_0046263) (named as circP4HB)	↑	miR-133a-5p	↓	Vimentin	↑	Compared to pairs of adjacent nontumor tissues, expression of circP4HB is upregulated in 80 NSCLC tissues Upregulation of circP4HB expression leads to higher metastatic capacity and shorter survival in NSCLC patients	[145]

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
circ_0026134	↑	miR-1256 miR-1287	↓ ↓	TCTN1 and GAGE1	↑	Compared to pairs of adjacent nontumor tissues, expression of Circ_0026134 is upregulated in 30 NSCLC tissues The Circ_0026134 expression is upregulated in the four NSCLC cell lines compared with the nonmalignant human bronchial epithelial cells	[146]
Circ-FOXM1 (hsa_circ_0025033)	↑	miR-1304-5p	↓	PPDPF and MACC1	↑	Compared to pairs of adjacent nontumor tissues, expression of Circ-FOXM1 is upregulated in 80 NSCLC tissues The Circ-FOXM1 expression is upregulated in the four NSCLC cell lines compared with the nonmalignant human bronchial epithelial cells The increase in circ-FOXM1 expression in tumor samples was correlated with short overall survival rate in NSCLC patients	[147]
circ_0003645	↑	miR-1179	↓	TMEM14A	↑	Compared to pairs of adjacent nontumor tissues, expression of circ_0003645 is upregulated in 59 NSCLC tissues The circ_0003645 expression is upregulated in the four NSCLC cell lines compared with the nonmalignant human bronchial epithelial cells The increase in circ_0003645 expression in tumor samples is an independent prognostic factor for the patients with NSCLC as well as advanced TNM stages	[148]
hsa_circ_0002360	↑	hsa-mir-3620-5p	↓	PHF19	↑	Compared to pairs of adjacent nontumor tissues, expression of hsa_circ_0002360 is upregulated in 18 lung adenocarcinoma tissues	[149]
circRNA 100146	↑	miR-361-3p miR-615-5p	↓	SF3B3	↑	Compared to pairs of adjacent nontumor tissues, expression of circRNA 100146 is upregulated in 40 NSCLC tissues	[150]

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
circFGFR3	↑	miR-22-3p	↓	Gal-1 Akt and Erk 1/2 signaling pathway	↑ Activated	Compared to pairs of adjacent nontumor tissues, expression of circFGFR3 is upregulated in 63 NSCLC tissues The increase in circFGFR3 expression in tumor samples is correlated with the poor prognosis of NSCLC patients	[151]
hsa_circ_0006427	↓	miR-6783-3p	↑	DKK1 Wnt/b-catenin signaling pathway	↑ Inactivated	Compared to pairs of adjacent nontumor tissues, expression of circ_0006427 is downregulated in 94 lung adenocarcinoma The circ_0006427 expression is downregulated in the four lung adenocarcinoma cell lines compared with the nonmalignant human lung epithelial cell line The decrease in circFGFR3 expression in tumor samples is correlated with the poor prognosis of lung adenocarcinoma patients	[152]
hsa_circ_0008305 circPTK2	↓	miR-429 miR-200b-3p	↑	TIF1γ	↓	circPTK2 has an important role in regulating TGF-β-induced EMT and tumor metastasis	[153]
hsa_circ_100395	↓	miR-1228	↑	TCF21		Compared to pairs of adjacent nontumor tissues, expression of hsa_circ_100395 is downregulated in 69 NSCLC The hsa_circ_100395 expression is downregulated in the six lung cancer cell lines compared with the the nonmalignant human bronchial epithelial cells Downregulation of hsa_circ_100395 expression in tumor samples is correlated with TNM stage and lymphoid node metastases	[154]
circ-BANP	↑	miR-503	↓	LARP1	↑	Compared to pairs of adjacent nontumor tissues, expression of circ-BANP is upregulated in 59 NSCLC The circ-BANP expression is upregulated in the four lung cancer cell lines compared with the nonmalignant human bronchial epithelial cells	[155]

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
						Upregulation of circ-BANP expression in tumor samples predicted lower Survival rate	
hsa_circRNA_103595 circMAN2B2	↑	miR-1275	↓	FOXK1	↑	Compared to pairs of adjacent nontumor tissues, expression of circMAN2B2 is upregulated in 41 NSCLC The circMAN2B2 expression is upregulated in the four lung cancer cell lines compared with the nonmalignant human lung epithelial cells	[156]
circ_0016760	↑	miR-1287	↓	GAGE1	↑	Compared to pairs of adjacent nontumor tissues, expression of circ_0016760 is upregulated in 83 NSCLC The circ_0016760 expression is upregulated in the four lung cancer cell lines compared with the nonmalignant human bronchial epithelial cells Upregulation of circ_0016760 expression in tumor samples predicted short overall survival in NSCLC patients	[157]

NER, nucleotide excision repair; NSCLC, nonsmall cell lung cancer; CDDP, cisplatin; SIRT1, sirtuin 1; AGFG1, ArfGAP with FG repeats 1; ZNF281, zinc finger protein 281; PTPRA, protein tyrosine phosphatase receptor type A; RASSF8, ras association domain family member 8; ADAM9, ADAM metallopeptidase domain 9; ZEB1, zinc finger E-box binding homeobox 1; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; VANGL1, VANGL planar cell polarity protein 1; BCL2, B-cell CLL/lymphoma 2; P4H1, prolyl 4-hydroxylase subunit beta; TCTN1, tectonic family member 1; GAGE1, G antigen 1; FOXM1, forkhead box M1; PPDPF, pancreatic progenitor cell differentiation and proliferation factor; MACC1, metastasis-associated in colon cancer 1; TMEM14A, transmembrane protein 14A; PHF19, PHD finger protein 19; SF3B3, splicing factor 3b subunit 3; FGFR3, fibroblast growth factor receptor 3; DKK, Dickkopf WNT signaling pathway inhibitor 1; PTK2, protein tyrosine kinase 2; TIF1γ, transcription intermediary factor 1-gamma; TGF-β, tumor growth factor beta; EMT, epithelial-mesenchymal transition; TCF21, transcription factor 21; BANP, BANP BTG3 associated nuclear protein; LARP1, La ribonucleoprotein domain family member 1; MAN2B2, mannosidase alpha class 2B member 2; FOXK1, forkhead box K1; and GAGE, G antigen 1.

Table 4.
The expression profile of circRNA-miRNA-mRNA network in lung cancer tissues.

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
circ_0006528	↑	miR-7-5p	↓	Raf1 MAPK/ERK signaling pathway	↑ Activated	Compared to adjacent nontumor tissues, expression of circ_0006528 is upregulated in BCa tissues The increase in circ_0006528 expression in tumor samples has been correlated with advanced TNM stage and poor prognosis	[158]
circKIF4a (hsa_circ_0007255)	↑	miR-375	↓	KIF4A	↑	Compared to pairs of adjacent nontumor tissues, expression of circKIF4A is upregulated in 57 TNBC tissues circKIF4A expression increased in the five TNBC cell lines compared with the four NTNBC and nonmalignant breast epithelial cell line The increase in circKIF4A expression in tumor samples has been correlated with worse outcome of TNBC patients	[159]
hsa_circ_0004771	↑	miR-653	↓	ZEB2	↑	Compared to pairs of adjacent nontumor tissues, expression of hsa circ 0004771 is upregulated in BCa tissues hsa circ 0004771 expression increased in the five BCa cell lines compared with nonmalignant breast epithelial cell line The increase in hsa circ 0004771 expression in tumor samples has been correlated poorer survival prognosis	[160]
circTADA2A-E6	↓	miR-203a-3p	↑	SOCS3	↓	Compared to adjacent nontumor tissues, expression of Hsa circTADA2A-E6 is downregulated in TNBC tissues The decline in Hsa circTADA2A-E6 expression in tumor samples was associated with poor patient survival for TNBC	[161]
circAGFG1	↑	miR-195-5p	↓	CCNE1	↑	Compared to adjacent nontumor tissues, expression of circAGFG1 is upregulated in TNBC tissues circAGFG1 expression increased in the six TNBC cell lines compared with nonmalignant breast epithelial cell line The expression levels of circAGFG1 were reversely correlated with overall survival of patients with TNBC	[162]
hsa_circ_000479	↑	miR-4753 miR-6809	↓	BCL11A	↑	Compared to pairs of adjacent nontumor tissues, expression of circEPSTI1 is upregulated in 10 TNBC tissues	[163]

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
						The increase in circEPSTI1 expression in tumor samples was positively correlated with tumor size, lymph node infiltration and TNM stage, and associated with poor prognosis	
hsa_circ_0008039	↑	miR-432-5p	↓	E2F3	↑	Compared to pairs of adjacent nontumor tissues, expression of hsa_circ_0008039 is upregulated in 38 TNBC tissues hsa_circ_0008039 expression increased in the six BCa cell lines compared with nonmalignant breast epithelial cell line	[164]
hsa_circ_0007534	↑	miR-593	↓	MUC19	↑	Compared to pairs of adjacent nontumor tissues, expression of hsa_circ_0007534 is upregulated in 40 BCa tissues hsa_circ_0007534 expression increased in the five BCa cell lines compared with nonmalignant breast epithelial cell line	[165]
circRNA-000911	↓	miR-449a	↑	Notch1 NF-κB pathway	↓ Activated	Compared to pairs of adjacent nontumor tissues, expression of circRNA-000911 is downregulated in 35 BCa tissues hsa_circRNA_000911 expression decreased in the six BCa cell lines compared with nonmalignant breast epithelial cell line	[166]
hsa_circ_0001846 circ-UBAP2	↑	miRNA-661	↓	MTA1	↑	Compared to pairs of adjacent nontumor tissues, expression of circ-UBAP2 is upregulated in 78 TNBC tissues circ-UBAP2 expression increased in TNBC cell lines compared with nonTNBC cell lines The increase in circ-UBAP2 expression in tumor samples has been correlated with reduced OS in TNBC patients	[167]
circRNA_0005505 circIRAK3	↑	miR-3607	↓	FOXC1	↑	Compared to pairs of adjacent nontumor tissues, expression of CircIRAK3 is upregulated in 35 BCa tissues CircIRAK3 expression increased in TNBC cell lines compared with normal mammary epithelial or ER-positive cell lines The increase in CircIRAK3 expression in tumor samples has been correlated worse recurrence-free survival in breast cancer patients	[168]
circ_0005230	↑	miR-618	↓	CBX8	↑	Compared to pairs of adjacent nontumor tissues, expression of circ_0005230 is upregulated in 76 BCa tissues	[169]

CircRNA	circRNA expression status	Target miRNA	miRNA expression status	Target mRNA/ signaling pathway	mRNA expression status	Main findings of the studies	Ref
						circ_0005230 expression increased in six BCa cell lines compared with nonmalignant mammary epithelial cell lines The increase in circ_0005230 expression in tumor samples has been correlated worse overall survival in breast cancer patients	
hsa_circ_0007294 circANKS1B	↑	miR-148a-3p miR-152-3p	↓	USF1 TGF-β1/Smad signalling	↑ Activated	Compared to pairs of adjacent nontumor tissues, expression of CircANKS1B is upregulated in 23 TNBC tissues CircANKS1B expression increased in TNBC cell lines compared with NTNBC cell lines The increase in CircANKS1B expression in tumor samples has been correlated worse overall survival in breast cancer patients	[170]
hsa_-circ_005239 circGFRA1	↑	miR-34a	↓	GFRA1	↑	Compared to pairs of adjacent nontumor tissues, expression of circGFRA1 is upregulated in 51 TNBC tissues The increase in circGFRA1 expression in tumor samples has been correlated short overall survival in TNBC patient circGFRA1 expression increased in TNBC cell lines compared with NTNBC cell lines	[171]

KIF4A, kinesin family member 4A; ZEB2, zinc finger E-box binding homeobox 2; CCNE1, cyclin E1; FOXC1, forkhead box C1; TNBC, triple negative breast cancer; NTNBC, nontriple negative breast cancer; Bca, Breast cancer; TADA2A, transcriptional adaptor 2A; SOCS3, suppressor of cytokine signaling 3; AGFG1, ArfGAP with FG repeats 1; EPSTI1, epithelial stromal interaction 1; BCL11A, B-cell CLL/lymphoma11A; E2F3, E2F transcription factor 3; MUC19, mucin 19; NOTCH1, notch receptor 1; NF-κB, nuclear factor Kappa beta; UBAP2, ubiquitin associated protein 2; MTA1, metastasis associated 1; IRAK3, interleukin 1 receptor associated kinase 3; CBX8, chromobox 8; ANKS1B, ankyrin repeat and sterile alpha motif domain containing 1B; USF1, upstream transcription factor 1; GFRA1, GDNF family receptor alpha 1; and TGF-β1, transforming growth factor beta 1.

Table 5.
The expression profile of circRNA-miRNA-mRNA network in breast cancer tissues.

Studies on altered expression of circRNAs in (lung and breast cancer) tumor samples are summarized in **Tables 4** and **5**. Moreover, in these selected studies, the circRNA-miRNA-mRNA interaction network is well defined.

By taking all studies together, circRNAs may be candidate surrogate molecular markers for cancer in different aspects, such as angiogenesis, metastasis, and drug resistance. Although to date some circRNA-miRNA-mRNA axis is predicted in cancer-associated pathways, the function and importance of dysregulated circRNAs still need to be supported in larger numbers of samples and patients, in various cancers.

8. Research databases of circRNA

With the increasing interest in circRNAs, comprehensive circRNA databases are required for prediction of circRNAs and their targets [172]. To evaluate and simplify the properties and interaction of various circRNAs with other RNAs from different aspects, numerous databases have been published (circlncRNAnet, starBase v2. 0, circBase, circRNABase, circ2Traits, nc2Cancer, DeepBase v2. 0, CircInteractome, TSCD, CIRCpedia, circRNADb, CircNet, CircR2Disease, circBank, and so on) [173]. Examples of circRNA databases and their usage in researches are shown.

- starBase v2. 0 determines miRNA-circRNA interactome and includes miRNA, mRNA, and lncRNA information [174].
- circ2Traits can be provided information about miRNA-circRNA interaction and its association with particular diseases [109].
- CircInteractome can be used in coupling the circRNA with related RNA-binding proteins [175].
- TSCD is helpful to describe tissue-specific circRNAs in mouse and human genomes [176].
- CIRCpedia includes reverse and variable splicing sites of circRNAs from individuals and mouse samples [177].
- circBank can be a resource to facilitate the research of function and regulation of circRNAs [178].

9. Conclusion

In summary, circRNAs, a new class of noncoding RNAs, are widely investigated by researchers due to their role in post transcriptional gene regulation. Recent studies have indicated their effects on the development of diverse diseases by acting as a miRNA sponge, RBP sponge, and transcriptional modulator or direct encoding proteins. Although the miRNA sponge function of circRNAs is currently investigated in the diseases, other mechanisms of circRNAs are still under investigation, and further studies are needed. After the interpretation of their function in disease pathogenesis, they may have a potential to become a drug target. Using circRNAs as biomarkers or therapeutic targets needs to be further investigated due to their complex roles. Based on these characteristics, circRNAs are likely to guide the development of new diagnostic and therapeutic strategies as well as prevention of diseases.

Conflict of interest

The authors declare no conflict of interest.

Author details

Atiye Seda Yar Saglam[1], Ebru Alp[2] and Hacer Ilke Onen[1*]

1 Department of Medical Biology, Faculty of Medicine, Gazi University, Ankara, Turkey

2 Department of Medical Biology, Faculty of Medicine, Giresun University, Giresun, Turkey

*Address all correspondence to: ilkeonen@yahoo.com; hionen@gazi.edu.tr

References

[1] ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012;**489**:57-74. DOI: 10.1038/nature11247

[2] Clark MB, Choudhary A, Smith MA, Taft RJ, Mattick JS. The dark matter rises: The expanding world of regulatory RNAs. Essays in Biochemistry. 2013;**54**: 1-16. DOI: 10.1042/bse0540001

[3] St. Laurent G, Wahlestedt C, Kapranov P. The landscape of long noncoding RNA classification. Trends in Genetics. 2015;**31**:239-251. DOI: 10.1016/j.tig.2015.03.007

[4] Batista PJ, Chang HY. Long noncoding RNAs: Cellular address codes in development and disease. Cell. 2013; **152**:1298-1307. DOI: 10.1016/j.cell.2013.02.012

[5] Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Research. 2012;**22**:1775-1789. DOI: 10.1101/gr.132159.111

[6] Lasda E, Parker R. Circular RNAs: Diversity of form and function. RNA. 2014;**20**:1829-1842. DOI: 10.1261/rna.047126.114

[7] Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. Nature Biotechnology. 2014;**32**:453-461. DOI: 10.1038/nbt.2890

[8] Hsu MT, Coca-Prados M. Electron microscopic evidence for the circular form of RNA in the cytoplasm of eukaryotic cells. Nature. 1979;**280**: 339-340. DOI: 10.1038/280339a0

[9] Cocquerelle C, Mascrez B, Hétuin D, Bailleul B. Mis-splicing yields circular RNA molecules. The FASEB Journal. 1993;**7**:155-160. DOI: 10.1096/fasebj.7.1.7678559

[10] Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;**19**:141-157. DOI: 10.1261/rna.035667.112

[11] Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, et al. circRNA biogenesis competes with pre-mRNA splicing. Molecular Cell. 2014;**56**:55-66. DOI: 10.1016/j.molcel.2014.08.019

[12] Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, et al. The RNA binding protein quaking regulates formation of circRNAs. Cell. 2015;**160**:1125-1134. DOI: 10.1016/j.cell.2015.02.014

[13] Wang M, Yu F, Wu W, Zhang Y, Chang W, Ponnusamy M, et al. A novel type of non-coding RNA and their potential implications inantiviral immunity. International Journal of Biological Sciences. 2017;**13**:1497-1506. DOI: 10.7150/ijbs.22531

[14] Yu B, Shan G. Functions of long noncoding RNAs in the nucleus. Nucleus. 2016;**7**:155-166. DOI: 10.1080/19491034.2016.1179408

[15] Zhang Y, Zhang XO, Chen T, Xiang JF, Yin QF, Xing YH, et al. Circular intronic long noncoding RNAs. Molecular Cell. 2013;**51**:792-806. DOI: 10.1016/j.molcel.2013.08.017

[16] Li Y, Zheng Q, Bao C, Li S, Guo W, Zhao J, et al. Circular RNA is enriched and stable in exosomes: A promising biomarker for cancer diagnosis. Cell Research. 2015;**25**:981-984. DOI: 10.1038/cr.2015.82

[17] He J, Xie Q, Xu H, Li J, Li Y. Circular RNAs and cancer. Cancer Letters. 2017;**396**:138-144. DOI: 10.1016/j.canlet.2017.03.027

[18] Zhang Z, Yang T, Xiao J, Circular RNA. Promising biomarkers for human diseases. eBioMedicine. 2018;**34**: 267-274. DOI: 10.1016/j.ebiom.2018.07.036

[19] Yu CX, Sun S. An emerging role for circular RNAs in osteoarthritis. Yonsei Medical Journal. 2018;**59**:349-355. DOI: 10.3349/ymj.2018.59.3.349

[20] Zhang M, Xin Y. Circular RNAs: A new frontier for cancer diagnosis and therapy. Journal of Hematology & Oncology. 2018;**11**:21. DOI: 10.1186/s13045-018-0569-5

[21] Kosik KS. Molecular biology: Circles reshape the RNA world. Nature. 2013; **495**:322-324. DOI: 10.1038/nature11956

[22] Liu L, Wang J, Khanabdali R, Kalionis B, Tai X, Xia S. Circular RNAs: Isolation, characterization and their potential role in diseases. RNA Biology. 2017;**14**:1715-1721. DOI: 10.1080/15476286.2017.1367886

[23] Yang L, Fu J, Zhou Y. Circular RNAs and their emerging roles in immune regulation. Frontiers in Immunology. 2018;**9**:2977. DOI: 10.3389/fimmu.2018.02977

[24] Xu Z, Li P, Fan L, Wu M. The potential role of circRNA in tumor immunity regulation and immunotherapy. Frontiers in Immunology. 2018;**22**:9. DOI: 10.3389/fimmu.2018.00009

[25] Wang M, Yu F, Li P. Circular RNAs: Characteristics, function and clinical significance in hepatocellular carcinoma. Cancers (Basel). 2018;**10**:pii: E258. DOI: 10.3390/cancers10080258

[26] Liu KS, Pan F, Mao XD, Liu C, Chen YJ. Biological functions of circular RNAs and their roles in occurrence of reproduction and gynecological diseases. American Journal of Translational Research. 2019;**11**: 1-15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357300/

[27] Haque S, Harries LW. Circular RNAs (circRNAs) in health and disease. Genes (Basel). 2017;**8**:pii: E353. DOI: 10.3390/genes8120353

[28] Kristensen LS, Hansen TB, Venø MT, Kjems J. Circular RNAs in cancer: Opportunities and challenges in the field. Oncogene. 2018;**37**:555-565. DOI: 10.1038/onc.2017.361

[29] Wang Y, Lu T, Wang Q, Liu J, Jiao W. Circular RNAs: Crucial regulators in the human body (Review). Oncology Reports. 2018;**40**:3119-3135. DOI: 10.3892/or.2018.6733

[30] Hsiao KY, Sun HS, Tsai SJ. Circular RNA—New member of noncoding RNA with novel functions. Experimental Biology and Medicine (Maywood, N.J.). 2017;**242**:1136-1141. DOI: 10.1177/1535370217708978

[31] Hou LD, Zhang J. Circular RNAs: An emerging type of RNA in cancer. International Journal of Immunopathology and Pharmacology. 2017;**30**:1-6. DOI: 10.1177/0394632016686985

[32] Burd CE, Jeck WR, Liu Y, Sanoff HK, Wang Z, Sharpless NE. Expression of linear and novel circular forms of an INK4/ARFassociated non-coding RNA correlates with atherosclerosis risk. PLoS Genetics. 2010;**6**:e1001233. DOI: 10.1371/journal.pgen.1001233

[33] Meganck RM, Borchardt EK, Castellanos Rivera RM, Scalabrino ML, Wilusz JE, Marzluff WF, et al. Tissue-dependent expression and translation of circular RNAs with recombinant AAV vectors in vivo. Molecular Therapy:

Nucleic Acids. 2018;**13**:89-98. DOI: 10.1016/j.omtn.2018.08.008

[34] Liang WC, Wong CW, Liang PP, Shi M, Cao Y, Rao ST, et al. Translation of the circular RNA circβ-catenin promotes liver cancer cell growth through activation of the Wnt pathway. Genome Biology. 2019;**20**:84. DOI: 10.1186/s13059-019-1685-4

[35] Wang W, Wang Y, Piao H, Li B, Huang M, Zhu Z, et al. Circular RNAs as potential biomarkers and therapeutics for cardiovascular disease. PeerJ. 2019;**7**: e6831. DOI: 10.7717/peerj.6831

[36] Fan X, Weng X, Zhao Y, Chen W, Gan T, Xu D. Circular RNAs in cardiovascular disease: An overview. BioMed Research International. 2017; **2017**:5135781. DOI: 10.1155/2017/5135781

[37] Lee ECS, Elhassan SAM, Lim GPL, Kok WH, Tan SW, Leong EN, et al. The roles of circular RNAs in human development and diseases. Biomedicine & Pharmacotherapy. 2019; **111**:198-208. DOI: 10.1016/j.biopha.2018.12.052

[38] Li M, Ding W, Sun T, Tariq MA, Xu T, Li P, et al. Biogenesis of circular RNAs and their roles in cardiovascular development and pathology. The FEBS Journal. 2018;**285**:220-232. DOI: 10.1111/febs.14191

[39] Borghini A. Circular RNAs: Emerging players in coronary artery disease. Annals of Atherosclerosis Research. 2018;**1**:1-2. Available from: https://pdfs.semanticscholar.org/5d14/63fbe393f33601a5695ab0840b5738b6b8f3.pdf

[40] Carrara M, Fuschi P, Ivan C, Martelli F. Circular RNAs: Methodological challenges and perspectives in cardiovascular diseases. Journal of Cellular and Molecular Medicine. 2018;**22**:5176-5187. DOI: 10.1111/jcmm.13789

[41] Zhou MY, Yang JM, Xiong XD. The emerging landscape of circular RNA in cardiovascular diseases. Journal of Molecular and Cellular Cardiology. 2018;**122**:134-139. DOI: 10.1016/j.yjmcc.2018.08.012

[42] Zhao G. Significance of non-coding circular RNAs and micro RNAs in the pathogenesis of cardiovascular diseases. Journal of Medical Genetics. 2018;**55**: 713-720. DOI: 10.1136/jmedgenet-2018-105387

[43] Altesha MA, Ni T, Khan A, Liu K, Zheng X. Circular RNA in cardiovascular disease. Journal of Cellular Physiology. 2019;**234**: 5588-5600. DOI: 10.1002/jcp.27384

[44] Gong X, Wu G, Zeng C. Role of circular RNAs in cardiovascular diseases. Experimental Biology and Medicine (Maywood, N.J.). 2019;**244**: 73-82. DOI: 10.1177/1535370218822988

[45] Zeng Y, Du WW, Wu Y, Yang Z, Awan FM, Li X, et al. Circular RNA binds to and activates AKT phosphorylation and nuclear localization reducing apoptosis and enhancing cardiac repair. Theranostics. 2017;**7**:3842-3855. DOI: 10.7150/thno.19764

[46] Du WW, Yang W, Chen Y, Wu ZK, Foster FS, Yang Z, et al. Foxo3 circular RNA promotes cardiac senescence by modulating multiple factors associated with stress and senescence responses. European Heart Journal. 2017;**38**: 1402-1412. DOI: 10.1093/eurheartj/ehw001

[47] Holdt LM, Stahringer A, Sass K, Pichler G, Kulak NA, Wilfert W, et al. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. Nature Communications. 2016;**7**:12429. DOI: 10.1038/ncomms12429

[48] Li CY, Ma L, Circular YB. RNA hsa_circ_0003575 regulates oxLDL induced

vascular endothelial cells proliferation and angiogenesis. Biomedicine & Pharmacotherapy. 2017;**95**:1514-1519. DOI: 10.1016/j.biopha.2017.09.064

[49] Dang RY, Liu FL, Li Y. Circular RNA hsa_circ_0010729 regulates vascular endothelial cell proliferation and apoptosis by targeting the miR-186/HIF-1alpha axis. Biochemical and Biophysical Research Communications. 2017;**490**:104-110. DOI: 10.1016/j.bbrc.2017.05.164

[50] Sun Y, Yang Z, Zheng B, Zhang XH, Zhang ML, Zhao XS, et al. A novel regulatory mechanism of smooth muscle alpha-actin expression by NRG-1/circACTA2/miR-548f-5p axis. Circulation Research. 2017;**121**:628-635. DOI: 10.1161/CIRCRESAHA.117.311441

[51] Chen J, Cui L, Yuan J, Zhang Y, Sang H. Circular RNA WDR77 target FGF-2 to regulate vascular smooth muscle cells proliferation and migration by sponging miR-124. Biochemical and Biophysical Research Communications. 2017;**494**:126-132. DOI: 10.1016/j.bbrc.2017.10.068

[52] Mao YY, Wang JQ, Guo XX, Bi Y, Wang CX. Circ-SATB2 upregulates STIM1 expression and regulates vascular smooth muscle cell proliferation and differentiation through miR-939. Biochemical and Biophysical Research Communications. 2018;**505**:119-125. DOI: 10.1016/j.bbrc.2018.09.069

[53] Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;**495**:333-338. DOI: 10.1038/nature11928

[54] Bazan HA, Hatfield SA, Brug A, Brooks AJ, Lightell DJ Jr, Woods TC. Carotid plaque rupture is accompanied by an increase in the ratio of serum circR-284 to miR-221 levels. Circulation: Cardiovascular Genetics 2017;**10**:pii: e001720. DOI: 10.1161/CIRCGENETICS.117.001720

[55] Zhao Z, Li X, Gao C, Jian D, Hao P, Rao L, et al. Peripheral blood circular RNA hsa_circ_0124644 can be used as a diagnostic biomarker of coronary artery disease. Scientific Reports. 2017;**7**:39918. DOI: 10.1038/srep39918

[56] Wang L, Shen C, Wang Y, Zou T, Zhu H, Lu X, et al. Identification of circular RNA Hsa_circ_0001879 and Hsa_circ_0004104 as novel biomarkers for coronary artery disease. Atherosclerosis. 2019;**286**:88-96. DOI: 10.1016/j.atherosclerosis

[57] Geng HH, Li R, Su YM, Xiao J, Pan M, Cai XX, et al. The circular RNA Cdr1as promotes myocardial infarction by mediating the regulation of miR-7a on its target genes expression. PLoS One. 2016;**11**:e0151753. DOI: 10.1371/journal.pone.0151753

[58] Vausort M, Salgado-Somoza A, Zhang L, Leszek P, Scholz M, Teren A, et al. Myocardial infarction-associated circular RNA predicting left ventricular dysfunction. Journal of the American College of Cardiology. 2016;**68**:1247-1248. DOI: 10.1016/j.jacc.2016.06.040

[59] Salgado-Somoza A, Zhang L, Vausort M, Devaux Y. The circular RNA MICRA for risk stratification after myocardial infarction. International Journal of Cardiology. Heart & Vasculature. 2017;**17**:33-36. DOI: 10.1016/j.ijcha.2017.11.001

[60] Wang K, Gan TY, Li N, Liu CY, Zhou LY, Gao JN, et al. Circular RNA mediates cardiomyocyte death via miRNA-dependent upregulation of MTP18 expression. Cell Death and Differentiation. 2017;**24**:1111-1120. DOI: 10.1038/cdd.2017.61

[61] Wang K, Long B, Liu F, Wang JX, Liu CY, Zhao B, et al. A circular RNA

protects the heart from pathological hypertrophy and heart failure by targeting miR-223. European Heart Journal. 2016;**37**:2602-2611. DOI: 10.1093/eurheartj/ehv713

[62] Deng YY, Zhang W, She J, Zhang L, Chen T, Zhou J, et al. GW27-e1167 circular RNA related to PPAR[gamma] function as ceRNA of microRNA in human acute myocardial infarction. Journal of the American College of Cardiology. 2016;**68**:68-C52. DOI: 10.1016/j.jacc.2016.07.189

[63] Wu HJ, Zhang CY, Zhang S, Chang M, Wang HY. Microarray expression profile of circular RNAs in heart tissue of mice with myocardial infarction-induced heart failure. Cellular Physiology and Biochemistry. 2016;**39**:205-216. DOI: 10.1159/000445617

[64] Li M, Ding W, Tariq MA, Chang W, Zhang X, Xu W, et al. A circular transcript of ncx1 gene mediates ischemic myocardial injury by targeting miR-133a-3p. Theranostics. 2018;**8**:5855-5869. DOI: 10.7150/thno.27285

[65] Khan MA, Reckman YJ, Aufiero S, van den Hoogenhof MM, van der Made I, Beqqali A, et al. RBM20 regulates circular RNA production from the titin gene. Circulation Research. 2016;**119**:996-1003. DOI: 10.1161/CIRCRESAHA.116.309568

[66] Tan WL, Lim BT, Anene-Nzelu CG, Ackers-Johnson M, Dashi A, See K, et al. A landscape of circular RNA expression in the human heart. Cardiovascular Research. 2017;**113**:298-309. DOI: 10.1093/cvr/cvw250

[67] Liu C, Yao MD, Li CP, Shan K, Yang H, Wang JJ, et al. Silencing of circular RNA-ZNF609 ameliorates vascular endothelial dysfunction. Theranostics. 2017;**7**:2863-2877. DOI: 10.7150/thno.19353

[68] Wu N, Jin L, Cai J. Profiling and bioinformatics analyses reveal differential circular RNA expression in hypertensive patients. Clinical and Experimental Hypertension. 2017;**39**:454-459. DOI: 10.1080/10641963.2016.1273944

[69] Cheng X, Joe B. Circular RNAs in rat models of cardiovascular and renal diseases. Physiological Genomics. 2017;**49**:484-490. DOI: 10.1152/physiolgenomics.00064.2017

[70] Zheng S, Gu T, Bao X, Sun J, Zhao J, Zhang T, et al. Circular RNA hsa_circ_0014243 may serve as a diagnostic biomarker for essential hypertension. Experimental and Therapeutic Medicine. 2019;**17**:1728-1736. DOI: 10.3892/etm.2018.7107

[71] Bao X, Zheng S, Mao S, Gu T, Liu S, Sun J, et al. A potential risk factor of essential hypertension in case-control study: Circular RNA hsa_circ_0037911. Biochemical and Biophysical Research Communications. 2018;**498**:789-794. DOI: 10.1016/j.bbrc.2018.03.059

[72] Liu L, Gu T, Bao X, Zheng S, Zhao J, Zhang L. Microarray profiling of circular RNA identifies hsa_circ_0126991 as a potential risk factor for essential hypertension. Cytogenetic and Genome Research. 2019;**157**:203-212. DOI: 10.1159/000500063

[73] Westholm JO, Miura P, Olson S, Shenker S, Joseph B, Sanfilippo P, et al. Genome-wide analysis of drosophila circular RNAs reveals their structural and sequence properties and age-dependent neural accumulation. Cell Reports. 2014;**9**:1966-1980. DOI: 10.1016/j.celrep.2014.10.062

[74] Rybak-Wolf A, Stottmeister C, Glažar P, Jens M, Pino N, Giusti S, et al. Circular RNAs in the mammalian brain are highly abundant, conserved, and dynamically expressed. Molecular Cell.

2015;**58**:870-885. DOI: 10.1016/j.molcel.2015.03.027

[75] You X, Vlatkovic I, Babic A, Will T, Epstein I, Tushev G, et al. Neural circular RNAs are derived from synaptic genes and regulated by development and plasticity. Nature Neuroscience. 2015;**18**:603-610. DOI: 10.1038/nn.3975

[76] Chen W, Schuman E. Circular RNAs in brain and other tissues: A functional enigma. Trends in Neurosciences. 2016;**39**:597-604. DOI: 10.1016/j.tins.2016.06.006

[77] Zhang Y, Xue W, Li X, Zhang J, Chen S, Zhang JL, et al. The biogenesis of nascent circular RNAs. Cell Reports. 2016;**15**:611-624. DOI: 10.1016/j.celrep.2016.03.058

[78] Piwecka M, Glažar P, Hernandez-Miranda LR, Memczak S, Wolf SA, Rybak-Wolf A, et al. Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. Science. 2017;**357**:pii: eaam8526. DOI: 10.1126/science.aam8526

[79] Enuka Y, Lauriola M, Feldman ME, Sas-Chen A, Ulitsky I, Yarden Y. Circular RNAs are long-lived and display only minimal early alterations in response to a growth factors. Nucleic Acids Research. 2016;**44**:1370-1383. DOI: 10.1093/nar/gkv1367

[80] Maiese K. Disease onset and aging in the world of circular RNAs. Journal of Translational Science. 2016;**2**:327-329. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5026119/

[81] Panda AC, Grammatikakis I, Kim KM, De S, Martindale JL, Munk R, et al. Identification of senescence-associated circular RNAs (SAC-RNAs) reveals senescence suppressor CircPVT1. Nucleic Acids Research. 2017;**45**:4021-4035. DOI: 10.1093/nar/gkw1201

[82] Knupp D, Miura P. CircRNA accumulation: A new hallmark of aging? Mechanisms of Ageing and Development. 2018;**173**:71-79. DOI: 10.1016/j.mad.2018.05.001

[83] Lukiw WJ, Circular RNA. (circRNA) in Alzheimer's disease (AD). Frontiers in Genetics. 2013;**4**:307. DOI: 10.3389/fgene.2013.00307

[84] Bingol B, Sheng M. Deconstruction for reconstruction: The role of proteolysis in neural plasticity and disease. Neuron. 2011;**69**:22-32. DOI: 10.1016/j.neuron.2010.11.006

[85] Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;**495**(7441):384-388. DOI: 10.1038/nature11993

[86] Wang X, Tan L, Lu Y, Peng J, Zhu Y, Zhang Y, et al. MicroRNA-138 promotes tau phosphorylation by targeting retinoic acid receptor alpha. FEBS Letters. 2015;**589**:726-729. DOI: 10.1016/j.febslet.2015.02.001

[87] Tatro ET, Risbrough V, Soontornniyomkij B, Young J, Shumaker-Armstrong S, Jeste DV, et al. Short-term recognition memory correlates with regional CNS expression of microRNA-138 in mice. The American Journal of Geriatric Psychiatry. 2013;**21**:461-473. DOI: 10.1016/j.jagp.2012.09.005

[88] Junn E, Lee KW, Jeong BS, Chan TW, Im JY, Mouradian MM. Repression of alpha-synuclein expression and toxicity by microRNA-7. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**:13052-13057. DOI: 10.1073/pnas.0906277106

[89] Choi SY, Pang K, Kim JY, Ryu JR, Kang H, Liu Z, et al. Post-transcriptional regulation of SHANK3 expression by

microRNAs related to multiple neuropsychiatric disorders. Molecular Brain. 2015;**8**:74. DOI: 10.1186/s13041-015-0165-3

[90] Zhang J, Sun XY, Zhang LY. MicroRNA-7/Shank3 axis involved in schizophrenia pathogenesis. Journal of Clinical Neuroscience. 2015;**22**: 1254-1257. DOI: 10.1016/j.jocn.2015.01.031

[91] Satoh J, Yamamura T. Gene expression profile following stable expression of the cellular prion protein. Cellular and Molecular Neurobiology. 2004;**24**:793-814. DOI: 10.1007/s10571-004-6920-0

[92] Satoh J, Obayashi S, Misawa T, Sumiyoshi K, Oosumi K, Tabunoki H. Protein microarray analysis identifies human cellular prion protein interactors. Neuropathology and Applied Neurobiology. 2009;**35**:16-35. DOI: 10.1111/j.1365-2990.2008.00947.x

[93] Wang YH, Yu XH, Luo SS, Han H. Comprehensive circular RNA profiling reveals that circular RNA100783 is involved in chronic CD28-associated CD8(+)T cell ageing. Immunity & Ageing. 2015;**12**:17. DOI: 10.1186/s12979-015-0042-z

[94] Fu D, Yu W, Li M, Wang H, Liu D, Song X, et al. MicroRNA-138 regulates the balance of Th1/Th2 via targeting RUNX3 in psoriasis. Immunology Letters. 2015;**166**:55-62. DOI: 10.1016/j.imlet.2015.05.014

[95] Xu H, Guo S, Li W, Yu P. The circular RNA Cdr1as, via miR-7 and its targets, regulates insülin transcription and secretion in islet cells. Scientific Reports. 2015;**5**:12453. DOI: 10.1038/srep12453

[96] Stoll L, Sobel J, Rodriguez-Trejo A, Guay C, Lee K, Venø MT, et al. Circular RNAs as novel regulators of β-cell functions in normal and disease conditions. Molecular Metabolism. 2018;**9**:69-83. DOI: 10.1016/j.molmet.2018.01.010

[97] Li P, Yang X, Yuan W, Yang C, Zhang X, Han J, et al. CircRNA-Cdr1as exerts anti-oncogenic functions in bladder cancer by sponging MicroRNA-135a. Cellular Physiology and Biochemistry. 2018;**46**:1606-1616. DOI: 10.1159/000489208

[98] Ledford H. Circular RNAs throw genetics for a loop. Nature. 2013;**494**: 415. DOI: 10.1038/494415a

[99] Lonskaya I, Shekoyan AR, Hebron ML, Desforges N, Algarzae NK, Moussa CE. Diminished parkin solubility and colocalization with intraneuronal amyloid-beta are associated with autophagic defects in Alzheimer's disease. Journal of Alzheimer's Disease. 2013;**33**:231-247. DOI: 10.3233/JAD-2012-121141

[100] Zhao Y, Alexandrov PN, Jaber V, Lukiw WJ. Deficiency in the ubiquitin conjugating enzyme UBE2A in Alzheimer's Disease (AD) is linked to deficits in a natural circular miRNA-7 sponge (circRNA; ciRS-7). Genes (Basel). 2016;**7**:116. DOI: 10.3390/genes7120116

[101] Shi Z, Chen T, Yao Q, Zheng L, Zhang Z, Wang J, et al. The circular RNA ciRS-7 promotes APP and BACE1 degradation in an NF-κB-dependent manner. The FEBS Journal. 2017;**284**:1096-1109. DOI: 10.1111/febs.14045

[102] Schröder J, Ansaloni S, Schilling M, Liu T, Radke J, Jaedicke M, et al. MicroRNA-138 is a potential regulator of memory performance in humans. Frontiers in Human Neuroscience. 2014; **8**:501. DOI: 10.3389/fnhum.2014.00501

[103] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;**386**:896-912. DOI: 10.1016/S0140-6736(14)61393-3

[104] Schapira AH, Jenner P. Etiology and pathogenesis of Parkinson's disease. Movement Disorders. 2011;**26**: 1049-1055. DOI: 10.1002/mds.23732

[105] Thomas B, Beal MF. Parkinson's disease. Human Molecular Genetics. 2007;**16**:R183-R194. DOI: 10.1093/hmg/ddm159

[106] Lim KL, Dawson VL, Dawson TM. The cast of molecular characters in Parkinson's disease: Felons, conspirators, and suspects. Annals of the New York Academy of Sciences. 2003;**991**:80-92. DOI: 10.1111/j.1749-6632.2003.tb07465.x

[107] Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, et al. Aggregation of alphasynuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. The American Journal of Pathology. 1998; **152**:879-884. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1858234/

[108] Rodriguez JA, Ivanova MI, Sawaya MR, Cascio D, Reyes FE, Shi D, et al. Structure of the toxic core of α-synuclein from invisible crystals. Nature. 2015;**525**:486-490. DOI: 10.1038/nature15368

[109] Hancock JM. Circles within circles: Commentary on Ghosal et al. (2013) Circ2Traits: A comprehensive database for circular RNA potentially associated with disease and traits. Frontiers in Genetics. 2015;**5**:459. DOI: 10.3389/fgene.2014.00459

[110] Ghosal S, Das S, Sen R, Basak P, Chakrabarti J. Circ2Traits: A comprehensive database for circular RNA potentially associated with disease and traits. Frontiers in Genetics. 2013;**4**: 283. DOI: 10.3389/fgene.2013.00283

[111] Sang Q, Liu X, Wang L, Qi L, Sun W, Wang W, et al. CircSNCA downregulation by pramipexole treatment mediates cell apoptosis and autophagy in Parkinson's disease by targeting miR-7. Aging (Albany NY). 2018;**10**:1281-1293. DOI: 10.18632/aging.101466

[112] Ghavami S, Shojaei S, Yeganeh B, Ande SR, Jangamreddy JR, Mehrpour M, et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. Progress in Neurobiology. 2014;**112**:24-49. DOI: 10.1016/j.pneurobio.2013.10.004

[113] Kountouras J, Zavos C, Polyzos SA, Deretzi G, Vardaka E, Giartza-Taxidou E, et al. Helicobacter pylori infection and Parkinson's disease: Apoptosis as an underlying common contributor. European Journal of Neurology. 2012; **19**:e56. DOI: 10.1111/j.1468-1331.2012.03695.x

[114] Chen X, Yang T, Wang W, Xi W, Zhang T, Li Q, et al. Circular RNAs in immune responses and immune diseases. Theranostics. 2019;**9**:588-607. DOI: 10.7150/thno.29678

[115] Zhou Z, Sun B, Huang S, Zhao L. Roles of circular RNAs in immune regulation and autoimmune diseases. Cell Death & Disease. 2019;**10**:503. DOI: 10.1038/s41419-019-1744-5

[116] Xia X, Tang X, Wang S. Roles of CircRNAs in autoimmune diseases. Frontiers in Immunology. 2019;**10**:639. DOI: 10.3389/fimmu.2019.00639

[117] Li H, Li K, Lai W, Li X, Wang H, Yang J, et al. Comprehensive circular RNA profiles in plasma reveals that circular RNAs can be used as novel biomarkers for systemic lupus erythematosus. Clinica Chimica Acta. 2018;**480**:17-25. DOI: 10.1016/j.cca.2018.01.026

[118] Wu XN, Ye YX, Niu JW, Li Y, Li X, You X, et al. Defective PTEN regulation

contributes to B cell hyperresponsiveness in systemic lupus erythematosus. Science Translational Medicine. 2014;**6**:246ra99. DOI: 10.1126/scitranslmed.3009131

[119] Ouyang Q, Wu J, Jiang Z, Zhao J, Wang R, Lou A, et al. Microarray expression profile of circular RNAs in peripheral blood mononuclear cells from rheumatoid arthritis patients. Cellular Physiology and Biochemistry. 2017;**42**:651-659. DOI: 10.1159/000477883

[120] Wang W, Zhang Y, Zhu B, Duan T, Xu Q, Wang R, et al. Plasma microRNA expression profiles in Chinese patients with rheumatoid arthritis. Oncotarget. 2015;**6**:42557-42568. DOI: 10.18632/oncotarget.6449

[121] Zheng F, Yu X, Huang J, Dai Y. Circular RNA expression profiles of peripheral blood mononuclear cells in rheumatoid arthritis patients, based on microarray chip technology. Molecular Medicine Reports. 2017;**16**:8029-8036. DOI: 10.3892/mmr.2017.7638

[122] Murata K, Yoshitomi H, Tanida S, Ishikawa M, Nishitani K, Ito H, et al. Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis and osteoarthritis. Arthritis Research & Therapy. 2010;**12**:R86. DOI: 10.1186/ar3013

[123] Xu K, Xu P, Yao JF, Zhang YG, Hou WK, Lu SM. Reduced apoptosis correlates with enhanced autophagy in synovial tissues of rheumatoid arthritis. Inflammation Research. 2013;**62**:229-237. DOI: 10.1007/s00011-012-0572-1

[124] Iparraguirre L, Muñoz-Culla M, Prada-Luengo I, Castillo-Triviño T, Olascoaga J, Otaegui D. Circular RNA profiling reveals that circular RNAs from ANXA2 can be used as new biomarkers for multiple sclerosis. Human Molecular Genetics. 2017;**26**:3564-3572. DOI: 10.1093/hmg/ddx243

[125] Paraboschi EM, Rimoldi V, Soldà G, Tabaglio T, Dall'Osso C, Saba E, et al. Functional variations modulating PRKCA expression and alternative splicing predispose to multiple sclerosis. Human Molecular Genetics. 2014;**23**:6746-6761. DOI: 10.1093/hmg/ddu392

[126] Kang GJ, Lee HJ, Byun HJ, Kim EJ, Kim HJ, Park MK, et al. Novel involvement of miR-522-3p in high-mobility group box 1-induced prostaglandin reductase 1 expression and reduction of phagocytosis. Biochimica et Biophysica Acta—Molecular Cell Research. 2017;**1864**:625-633. DOI: 10.1016/j.bbamcr.2017.01.006

[127] Danza K, De Summa S, Pinto R, Pilato B, Palumbo O, Carella M, et al. miRNA regulation in familial and sporadic breast cancer. Oncotarget. 2017;**8**:50715-50723. DOI: 10.18632/oncotarget.14899

[128] Maass PG, Glažar P, Memczak S, Dittmar G, Hollfinger I, Schreyer L, et al. A map of human circular RNAs in clinically relevant tissues. Journal of Molecular Medicine (Berlin, Germany). 2017;**95**:1179-1189. DOI: 10.1007/s00109-017-1582-9

[129] Brigida I, Sauer AV, Ferrua F, Giannelli S, Scaramuzza S, Pistoia V, et al. B-cell development and functions and therapeutic options in adenosine deaminase-deficient patients. Journal of Allergy and Clinical Immunology. 2014;**133**:799-806.e10. DOI: 10.1016/j.jaci.2013.12.1043

[130] Cassani B, Mirolo M, Cattaneo F, Benninghoff U, Hershfield M, Carlucci F, et al. Altered intracellular and extracellular signaling leads to impaired T-cell functions in ADA-SCID

patients. Blood. 2008;**111**:4209-4219. DOI: 10.1182/blood-2007-05-092429

[131] Sheldon H, Andre M, Legg JA, Heal P, Herbert JM, Sainson R, et al. Active involvement of Robo1 and Robo4 in filopodia formation and endothelial cell motility mediated via WASP and other actin nucleation-promoting factors. The FASEB Journal. 2009;**23**: 513-522. DOI: 10.1096/fj.07-098269

[132] Stewart B, Wild CP. International Agency for Research on Cancer. Lyon, France: WHO: World Health Organization; 2017. World cancer report 2014. Available from: https://www.who.int/cancer/publications/WRC_2014/en/

[133] Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA: A Cancer Journal for Clinicians. 2019;**69**: 363-385. DOI: 10.3322/caac.21565

[134] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015; **136**:E359-E386. DOI: 10.1002/ijc.29210

[135] Osada H, Takahashi T. MicroRNAs in biological processes and carcinogenesis. Carcinogenesis. 2007;**28**: 2-12. DOI: 10.1093/carcin/bgl185

[136] Flynt AS, Lai EC. Biological principles of microRNA-mediated regulation: Shared themes amid diversity. Nature Reviews. Genetics. 2008;**9**:831-842. DOI: 10.1038/nrg2455

[137] Chen CZ. MicroRNAs as oncogenes and tumor suppressors. The New England Journal of Medicine. 2005;**353**: 1768-1771. DOI: 10.1056/NEJMp058190

[138] Huang MS, Liu JY, Xia XB, Liu YZ, Li X, Yin JY, et al. Hsa_circ_0001946 inhibits lung cancer progression and mediates cisplatin sensitivity in non-small cell lung cancer via the nucleotide excision repair signaling pathway. Frontiers in Oncology. 2019;**9**:508. DOI: 10.3389/fonc.2019.00508

[139] Yao Y, Hua Q, Zhou Y, Shen H. CircRNA has_circ_0001946 promotes cell growth in lung adenocarcinoma by regulating miR-135a-5p/SIRT1 axis and activating Wnt/β-catenin signaling pathway. Biomedicine & Pharmacotherapy. 2019;**111**:1367-1375. DOI: 10.1016/j.biopha.2018.12.120

[140] Xue YB, Ding MQ, Xue L, Luo JH. CircAGFG1 sponges miR-203 to promote EMT and metastasis of non-small-cell lung cancer by upregulating ZNF281 expression. Thoracic Cancer. 2019;**10**:1692-1701. DOI: 10.1111/1759-7714.13131

[141] Wei S, Zheng Y, Jiang Y, Li X, Geng J, Shen Y, et al. The circRNA circPTPRA suppresses epithelial-mesenchymal transitioning and metastasis of NSCLC cells by sponging miR-96-5p. eBioMedicine. 2019;**44**: 182-193. DOI: 10.1016/j.ebiom.2019.05.032

[142] Wan J, Hao L, Zheng X, Li Z. Circular RNA circ_0020123 promotes non-small cell lung cancer progression by acting as a ceRNA for miR-488-3p to regulate ADAM9expression. Biochemical and Biophysical Research Communications. 2019;**515**(2):303-309. DOI: 10.1016/j.bbrc.2019.05.158

[143] Qu D, Yan B, Xin R, Ma T. A novel circular RNA hsa_circ_0020123 exerts oncogenic properties through suppression of miR-144 in non-small cell lung cancer. American Journal of Cancer Research. 2018;**8**:1387-1402. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6129481/

[144] Wang L, Ma H, Kong W, Liu B, Zhang X. Up-regulated circular RNA VANGL1 contributes to progression of non-small cell lung cancer through inhibition ofmiR-195 and activation of

Bcl-2. Bioscience Reports. 2019;**39**:pii: BSR20182433. DOI: 10.1042/BSR20182433

[145] Wang T, Wang X, Du Q, Wu N, Liu X, Chen Y, et al. The circRNA circP4HB promotes NSCLC aggressiveness and metastasis by sponging miR-133a-5p. Biochemical and Biophysical Research Communications. 2019;**513**:904-911. DOI: 10.1016/j.bbrc.2019.04.108

[146] Chang H, Qu J, Wang J, Liang X, Sun W. Circular RNA circ_0026134 regulates non-small cell lung cancer cell proliferation and invasion via sponging miR-1256 and miR-1287. Biomedicine & Pharmacotherapy. 2019;**112**:108743. DOI: 10.1016/j.biopha.2019.108743

[147] Liu G, Shi H, Deng L, Zheng H, Kong W, Wen X, et al. Circular RNA circ-FOXM1 facilitates cell progression as ceRNA to target PPDPF and MACC1 by sponging miR-1304-5p in non-small cell lung cancer. Biochemical and Biophysical Research Communications. 2019;**513**:207-212. DOI: 10.1016/j.bbrc.2019.03.213

[148] An J, Shi H, Zhang N, Song S. Elevation of circular RNA circ_0003645 forecasts unfavorable prognosis and facilitates cell progression via miR-1179/TMEM14A pathway in non-small cell lung cancer. Biochemical and Biophysical Research Communications. 2019;**511**:921-925. DOI: 10.1016/j.bbrc.2019.03.011

[149] Yan Y, Zhang R, Zhang X, Zhang A, Zhang Y, Bu X. RNA-Seq profiling of circular RNAs and potential function of hsa_circ_0002360 in human lung adenocarcinom. American Journal of Translational Research. 2019;**11**:160-175. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357307/

[150] Chen L, Nan A, Zhang N, Jia Y, Li X, Ling Y, et al. Circular RNA 100146 functions as an oncogene through direct binding to miR-361-3p and miR-615-5p in non-small cell lung cancer. Molecular Cancer. 2019;**18**:13. DOI: 10.1186/s12943-019-0943-0

[151] Qiu BQ, Zhang PF, Xiong D, Xu JJ, Long X, Zhu SQ, et al. CircRNA fibroblast growth factor receptor 3 promotes tumor progression in non-small cell lung cancer by regulating Galectin-1-AKT/ERK1/2 signaling. Journal of Cellular Physiology. 2019;**234**:11256-11264. DOI: 10.1002/jcp.27783

[152] Yao Y, Hua Q, Zhou Y. CircRNA has_circ_0006427 suppresses the progression of lung adenocarcinoma by regulating miR-6783-3p/DKK1 axis and inactivating Wnt/β-catenin signaling pathway. Biochemical and Biophysical Research Communications. 2019;**508**:37-45. DOI: 10.1016/j.bbrc.2018.11.079

[153] Wang L, Tong X, Zhou Z, Wang S, Lei Z, Zhang T, et al. Circular RNA hsa_circ_0008305 (circPTK2) inhibits TGF-β-induced epithelial-mesenchymal transition and metastasis by controlling TIF1γ in non-small cell lung cancer. Molecular Cancer. 2018;**17**:140. DOI: 10.1186/s12943-018-0889-7

[154] Chen D, Ma W, Ke Z, Xie F. CircRNA hsa_circ_100395 regulates miR-1228/TCF21 pathway to inhibit lung cancer progression. Cell Cycle. 2018;**17**:2080-2090. DOI: 10.1080/15384101.2018.1515553

[155] Han J, Zhao G, Ma X, Dong Q, Zhang H, Wang Y, et al. CircRNA circ-BANP-mediated miR-503/LARP1 signaling contributes to lung cancer progression. Biochemical and Biophysical Research Communications. 2018;**503**:2429-2435. DOI: 10.1016/j.bbrc.2018.06.172

[156] Ma X, Yang X, Bao W, Li S, Liang S, Sun Y, et al. circMAN2B2 facilitates lung cancer cell proliferation and invasion via miR-1275/FOXK1 axis.

Biochemical and Biophysical Research Communications. 2018;**498**:1009-1015. DOI: 10.1016/j.bbrc.2018.03.105

[157] Li Y, Hu J, Li L, Cai S, Zhang H, Zhu X, et al. Upregulated circular RNA circ_0016760 indicates unfavorable prognosis in NSCLC and promotes cell progression through miR-1287/GAGE1 axis. Biochemical and Biophysical Research Communications. 2018;**503**: 2089-2094. DOI: 10.1016/j.bbrc.2018.07.164

[158] Gao D, Zhang X, Liu B, Meng D, Fang K, Guo Z, et al. Screening circular RNA related to chemotherapeutic resistance in breast cancer. Epigenomics. 2017;**9**:1175-1188. DOI: 10.2217/epi-2017-0055

[159] Tang H, Huang X, Wang J, Yang L, Kong Y, Gao G, et al. circKIF4A acts as a prognostic factor and mediator to regulate the progression of triple-negative breast cancer. Molecular Cancer. 2019;**18**:23. DOI: 10.1186/s12943-019-0946-x

[160] Xie R, Tang J, Zhu X, Jiang H. Silencing of hsa_circ_0004771 inhibits proliferation and induces apoptosis in breast cancer through activation of miR-653 by targeting ZEB2 signaling pathway. Bioscience Reports. 2019;**39**. DOI: 10.1042/BSR20181919

[161] Xu JZ, Shao CC, Wang XJ, Zhao X, Chen JQ, Ouyang YX, et al. circTADA2As suppress breast cancer progression and metastasis via targeting miR-203a-3p/SOCS3 axis. Cell Death & Disease. 2019;**10**:175. DOI: 10.1038/s41419-019-1382-y

[162] Yang R, Xing L, Zheng X, Sun Y, Wang X, Chen J. The circRNA circAGFG1 acts as a sponge of miR-195-5p to promote triple-negative breast cancer progression through regulating CCNE1 expression. Molecular Cancer. 2019;**18**:4. DOI: 10.1186/s12943-018-0933-7

[163] Chen B, Wei W, Huang X, Xie X, Kong Y, Dai D, et al. circEPSTI1 as a prognostic marker and mediator of triple-negative breast cancer progression. Theranostics. 2018;**8**: 4003-4015. DOI: 10.7150/thno.24106

[164] Liu Y, Lu C, Zhou Y, Zhang Z, Sun L. Circular RNA hsa_circ_0008039 promotes breast cancer cell proliferation and migration by regulating miR-432-5p/E2F3 axis. Biochemical and Biophysical Research Communications. 2018;**502**:358-363. DOI: 10.1016/j.bbrc.2018.05.166

[165] Song L, Xiao Y. Downregulation of hsa_circ_0007534 suppresses breast cancer cell proliferation and invasion by targeting miR-593/MUC19 signal pathway. Biochemical and Biophysical Research Communications. 2018;**503**: 2603-2610. DOI: 10.1016/j.bbrc.2018.08.007

[166] Wang H, Xiao Y, Wu L, Ma D. Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-000911/miR-449a pathway in breast carcinogenesis. International Journal of Oncology. 2018;**52**:743-754. DOI: 10.3892/ijo.2018.4265

[167] Wang S, Li Q, Wang Y, Li X, Wang R, Kang Y, et al. Upregulation of circ-UBAP2 predicts poor prognosis and promotes triple-negative breast cancer progression through the miR-661/MTA1 pathway. Biochemical and Biophysical Research Communications. 2018;**505**: 996-1002. DOI: 10.1016/j.bbrc.2018.10.026

[168] Wu J, Jiang Z, Chen C, Hu Q, Fu Z, Chen J, et al. CircIRAK3 sponges miR-3607 to facilitate breast cancer metastasis. Cancer Letters. 2018;**430**: 179-192. DOI: 10.1016/j.canlet.2018.05.033

[169] Xu Y, Yao Y, Leng K, Ji D, Qu L, Liu Y, et al. Increased expression of circular RNA circ_0005230 indicates

dismal prognosis in breast cancer and regulates cell proliferation and invasion via miR-618/CBX8 signal pathway. Cellular Physiology and Biochemistry. 2018;**51**:1710-1722. DOI: 10.1159/000495675

[170] Zeng K, He B, Yang BB, Xu T, Chen X, Xu M, et al. The pro-metastasis effect of circANKS1B in breast cancer. Molecular Cancer. 2018;**17**:160. DOI: 10.1186/s12943-018-0914-x

[171] He R, Liu P, Xie X, Zhou Y, Liao Q, Xiong W, et al. circGFRA1 and GFRA1 act as ceRNAs in triple negative breast cancer by regulating miR-34a. Journal of Experimental & Clinical Cancer Research. 2017;**36**:145. DOI: 10.1186/s13046-017-0614-1

[172] Chen X, Han P, Zhou T, Guo X, Song X, Li Y. circRNADb: A comprehensive database for human circular RNAs with protein-coding annotations. Scientific Reports. 2016;**6**:34985. DOI: 10.1038/srep34985

[173] Xu S, Zhou L, Ponnusamy M, Zhang L, Dong Y, Zhang Y, et al. A comprehensive review of circRNA: From purification and identification to disease marker potential. PeerJ. 2018;**6**:e5503. DOI: 10.7717/peerj.5503

[174] Li JH, Liu S, Zhou H, Qu LH, Yang JH. starBase v2.0: Decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. Nucleic Acids Research. 2014;**42**:D92-D97. DOI: 10.1093/nar/gkt1248

[175] Dudekula DB, Panda AC, Grammatikakis I, De S, Abdelmohsen K, Gorospe M. CircInteractome: A web tool for exploring circular RNAs and their interacting proteins and microRNAs. RNA Biology. 2016;**13**:34-42. DOI: 10.1080/15476286.2015.1128065

[176] Xia S, Feng J, Lei L, Hu J, Xia L, Wang J, et al. Comprehensive characterization of tissue-specific circular RNAs in the human and Mouse genomes. Briefings in Bioinformatics. 2016;**18**:984-992. DOI: 10.1093/bib/bbw081

[177] Zhang XO, Dong R, Zhang Y, Zhang JL, Luo Z, Zhang J, et al. Diverse alternative back-splicing and alternative splicing landscape of circular RNAs. Genome Research. 2016;**26**:1277-1287. DOI: 10.1101/gr.202895.115

[178] Liu M, Wang Q, Shen J, Yang BB, Ding X. Circbank: A comprehensive database for circRNA with standard nomenclature. RNA Biology. 2019;**16**:899-905. DOI: 10.1080/15476286.2019.1600395