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Review article

Circular RNAs as biomarkers and therapeutic targets in environmental chemical exposure-related diseases

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ABSTRACT

Chemical contamination in the environment is known to cause abnormal circular RNA (circRNA) expression through multiple exposure routes; yet, the underlying molecular mechanisms remain unclear. Non-coding RNAs (ncRNAs), especially circRNAs, play important roles in epigenetic regulation and disease pathogenesis; however, few studies have examined the function of circRNAs in chemical contamination-induced diseases. CircRNAs are covalently closed continuous loops that do not possess 5′ and 3′ ends, increasing their structural stability and limiting degradation by exoribonucleases. In addition, environmental chemical exposure-related diseases are often accompanied by aberrant expression of specific circRNAs and those circRNAs are often detected in tissues and body fluids. Based on these characteristics, circRNAs may serve as candidate biomarkers for the diagnosis of diseases related to environmental chemical exposure. Here, we review the generation and function of circRNAs, and the possible molecular mechanisms underlying the regulation of environmental chemical exposure-related disorders by circRNAs. This is the first comprehensive review of the relationship between environmental chemical exposure and circRNAs in chemical exposure-induced diseases.

1. Introduction

Although genetic material contributes to disease risk, environmental chemical exposure is also known to affect human health (Brinchmann et al., 2019; Li et al., 2018b; Siddeek et al., 2018). This risk is related to the biotoxicity of the environmental chemical itself and is closely related to its accumulation and exposure time. However, to assess disease occurrence, bioaccessibility and bioavailability of environmental chemical contaminants are required (Wei et al., 2018). Environmental chemicals induce diseases in humans by disrupting processes involved in epigenetic modification, such as DNA methylation, histone modification, and chromatin remodeling, and exerting effects on non-coding RNAs (Marsit, 2015; Tammen et al., 2013). Exposure to certain toxic environmental chemicals through different routes, such as particles, organic pollutants, inorganic pollutants, and metals (Li et al., 2018b; Wei et al., 2018), can result in abnormal expression of multiple ncRNAs, including microRNAs (Tarale et al., 2018), lncRNAs (Nan et al., 2017), and circRNAs (Xue et al., 2017), which is closely related to the risk of human disease. Compared with microRNAs and lncRNAs, circRNA presents as covalently closed circular loops and is not easily degraded by exoribonucleases (Jeck and Sharpless, 2014; Zhang et al., 2013). Further, circRNA expression may provide an available tool for detecting silicosis, cancer, neurological disease, etc., which are induced by exposure to environmental chemicals (Fang et al., 2018; Nan et al., 2017; Xiao et al., 2018). This makes circRNAs very advantageous as disease biomarkers.

CircRNAs were originally identified in 1976 by Sanger et al. (1976), who discovered that some plant viroids are single-stranded covalently closed RNA molecules. Over time, with the development of high-throughput sequencing technology, circRNAs have been identified in various organisms, including archaea (Danan et al., 2012; Kjems and Garrett, 1988), plants (Sablok et al., 2016), zebrafish (Shen et al., 2017), mice (Capel et al., 1993), and humans (Burd et al., 2010), and are no longer considered aberrant splicing byproducts. CircRNAs are abundant, diverse, and conserved molecules that often exhibit high stability and tissue/developmental stage-specific expression (Hansen et al., 2013). They have been shown to be involved in the regulation of gene expression by binding microRNAs (miRNAs) and RNA-binding proteins (RBPs) (Hansen et al., 2013; Memczak et al., 2013; Salzman et al., 2012). Further, circRNAs mediate transcription and splicing events (Zhang et al., 2013) and protein translation under internal ribosome entry site (IRES) or m6A sequences (Legnini et al., 2017;

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Pamudurti et al., 2017; Yang et al., 2017b). Growing evidence has shown that circRNAs play a critical role in the regulation of environmental chemical exposure-related diseases, regulating among others inflammation, apoptosis, proliferation and metastasis at the molecular level (Yang et al., 2018; Nan et al., 2017; Xiao et al., 2018; Xue et al., 2018). These findings suggest that circRNAs may have potential applications as novel therapeutic targets in diseases induced by environmental chemical exposure.

However, the diversity and complexity of environmental chemicals have created challenges for precise evaluation of circRNA expression. In this review, we discuss the general properties of circRNAs, including their biogenesis and functions, and highlight their roles in environmental chemical exposure-related diseases. Moreover, we evaluate the effects of environmental chemical exposure levels, including time and dose, on circRNA expression. Furthermore, we speculate the regulatory mechanisms underlying the roles of circRNAs during environmental chemical exposure, aiming to establish a mechanistic map for diseases resulting from impaired circRNA regulation. Thereby, we provide novel insights into circRNAs and their roles in modulating cellular processes and disease pathogenesis under environmental chemical exposure and identify new therapeutic strategies for the treatment of such diseases.

2. Generation and functions of circRNAs

2.1. Generation of circRNAs

Recent studies have shown that circRNA is derived from pre-mRNA, which requires the transcription of RNA polymerase II (PolII) for maturation (Chen, 2016). CircRNA has a typical “back-splicing” structure, which is generated by spliceosome-mediated joining of an upstream 3′ splice site and a downstream 5′ splice site (Zhou et al., 2018a). CircRNAs are mainly divided into three categories: exonic circular RNAs (ecircRNAs), circular intronic RNAs (ciRNAs), and exon–intron circRNA (EIciRNAs) (Han et al., 2018). EcircRNAs are mainly present in the cytoplasm, while ciRNAs and EIciRNAs are primarily present in the nucleus (Jeck and Sharpless, 2014).

The process of circRNA generation is regulated by a number of factors, including cis-regulatory elements, trans-acting factors, and the spliceosome (Fig. 1) (Chen, 2016). Introns flanking the circularized exons generally contain reverse complementary sequences, which, through competitive complementary pairing, form RNA duplexes that may affect the efficiency of circRNA generation. These processes lead to the generation of multiple circRNAs by a gene locus (Fig. 1A) (Zhang et al., 2014). Trans-acting factors mainly include RNA-binding proteins (RBPs) such as muscleblind (MBL) (Ashwal-Fluss et al., 2014), quaking (Conn et al., 2015), and adenosine deaminase acting on RNA 1 (Ivanov et al., 2015). MBL and quaking promote circRNA formation by binding to specific sites on the pre-mRNA flanking introns. In contrast, adenosine deaminase acting on RNA 1 acts as a double-stranded RNA-binding protein that inhibits circRNA formation by interfering with RNA pairing on pre-mRNA flanking introns. The spliceosome, which is mainly composed of proteins and small nuclear ribonucleoproteins (snRNPs), is a large and complex dynamic molecular machine that catalyzes exon cyclization and plays an important role in circRNA formation (Fig. 1B) (Jeck and Sharpless, 2014). However, its specific catalytic mechanism is not clear. Moreover, circRNAs can be produced through a lariat-driven circularization pathway, which involves exon skipping and intron cyclization (Jeck and Sharpless, 2014; Zhang et al., 2013). An exon-containing lariat is created by exon skipping. Subsequently, the lariat removes the intronic sequence and produces ecircRNAs or EIciRNAs (Fig. 1C) (Jeck and Sharpless, 2014). CiRNAs are also generated via lariat-derived mechanisms, which are dependent on a consensus motif containing a 7-nt GU-rich element near the 5′ splice site and an 11-nt C-rich element close to the branchpoint site, with the resulting splice site unable to debranch (Fig. 1D) (Zhang et al., 2013). Further, Noto et al. (2017) found that tricRNA (tRNA intronic circRNA) formation was caused by the ligation of exon halves and intron termini through tRNA splicing endonuclease (TSEN) complex-specific cleavage of the bulge-helix-bulge (BHB) motif on pre-tRNA (Fig. 1E). Taken together, these findings indicate that circRNA generation is a complex process.

2.2. Functions of circRNAs

CircRNAs may be produced in any region of the genome (Memczak et al., 2013; Qu et al., 2016). This feature creates diversity in the length and sequence of circRNAs, which ultimately leads to the diversity of circRNA functions.

2.2.1. MicroRNA sponge (adsorption of miRNA)

The function of circRNA as a miRNA sponge is its most common

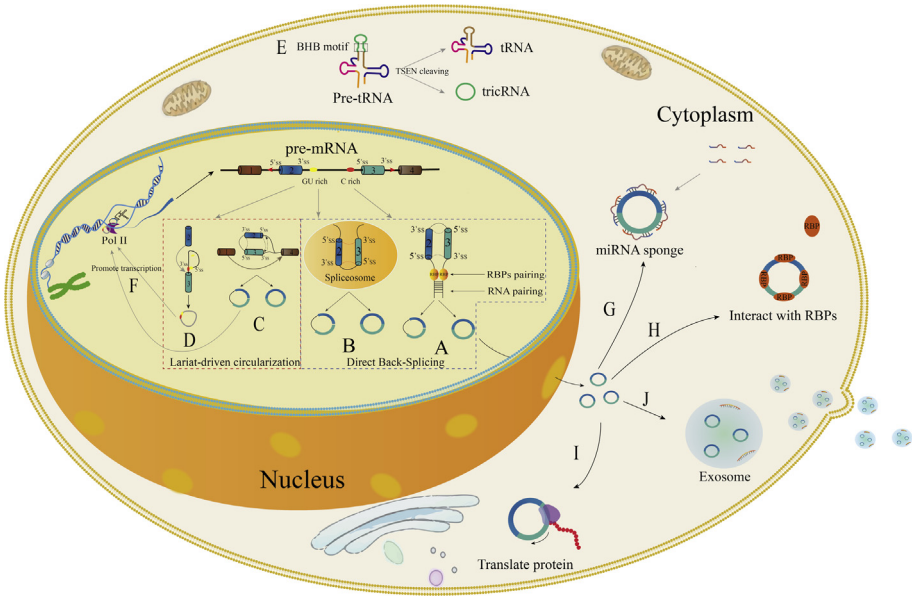

Fig. 1. Generation and functions of circRNAs. (A) Cis-regulatory elements and trans-acting factors that control splicing. Cis-regulatory elements regulate circRNA formation through direct base-pairing of the introns flanking inverted repeats or complementary sequences. Trans-acting factors regulate circRNA generation by flanking intronic reverse complementary sequences (e.g., Alu elements). Among them, MBL and QIK promote circRNA formation, and ADAR1 inhibits circRNA formation. (B) Spliceosomes utilize snRNPs to form circRNAs through a downstream 5′ donor site of an exon joined to an upstream 3′ acceptor site. (C, D) Lariat-driven circularization pathway that controls splicing. Lariat-driven circularization includes exon skipping and intron cyclization. Exon skipping results in the formation of a lariat containing exons 5 and 6, which removes introns through internal splicing to form circRNAs. Intron cyclization forms ciRNA that avoid degradation, which is dependent on GU-rich sequences close to the 5′ splice site (red ellipse) and C-rich sequences near the branch point (yellow ellipse). (E) Pre-tRNA forms a tricRNA to cleave the BHB motif via the TSEN complex. (F) EIciRNA and ciRNA regulate transcription of their parental genes by binding to Pol II. (G) circRNAs act as miRNA sponges to inhibit miRNA activity. (H) CircRNAs bind RBPs and affect gene expression. (I) Some circRNAs can be translated into proteins. (J) CircRNAs or exosomal circRNAs can be used as molecular markers for disease diagnosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

regulatory mechanism (Fig. 1G). Two circRNAs, CDR1as and circSry, were first demonstrated to act as miRNA sponges (Hansen et al., 2013; Memczak et al., 2013; Salzman et al., 2012). CDR1as (also known as ciRS-7) is widely found in the mammalian brain, comprising at least 60 conserved miR-7 target sites that strongly inhibit miR-7 activity through targeted binding to miR-7. In zebrafish, expression of human CDR1as has been shown to impair midbrain development, similar to knockdown of miR-7 expression, suggesting that CDR1as is a miR-7 antagonist (Hansen et al., 2013). CircSry is a testis-specific circRNA containing 16 miR-138 binding sites that specifically bind to miR-138 (Memczak et al., 2013). In addition to CDR1as and circSry, human hepatocellular carcinoma tissue-specific circRNA (circMTO1), acting as a sponge of oncogenic miR-9, promotes p21 expression, thus suppressing human hepatocellular carcinoma progression (Han et al., 2017). Furthermore, other circRNAs, such as circBIRC6 and circHIPK2, bind to miR-34a, miR-145, and miR 124-2HG to regulate human embryonic stem cells pluripotency, differentiation, and astrocyte activation, respectively (Huang et al., 2017; Yu et al., 2017). However, many circRNAs that do not contain miRNA binding sites still have biological functions, indicating that circRNAs possess other regulatory functions.

2.2.2. Regulation of transcription and splicing

Although most circRNAs are present in the cytoplasm, ciRNAs and EIciRNAs are mainly found in the nucleus and have been shown to be involved in transcriptional regulation and splicing (Fig. 1F) (Li et al., 2015b; Zhang et al., 2013). Ci-ankrd52 is derived from the second intron of the *ANKRD52* gene and binds to the Pol II transcriptional complex in the *ANKRD52* mRNA promoter region, thereby affecting the rate or efficiency of transcription. Knockdown of ci-ankrd52 has been shown to lead to reduced expression of *ANKRD52* (Zhang et al., 2013). Similarly, knockdown of ci-sirt7 and ci-mcm5 has been shown to affect transcription of the parental genes *SIRT7* and *MCM5,* respectively (Zhang et al., 2013). However, transcriptional regulation by EIciRNA differs from that by ciRNA. EIciRNA and U1snRNP contain regulatory regions approximately 300 bp upstream of the parental transcription initiation site, indicating that EIciRNA, U1snRNP, and Pol II interact with each other at the promoter regions of the parental genes. As such, EIciRNA (circEIF3J and circPAIP2) and U1snRNP interact via specific RNA-RNA interactions to form EIciRNA–U1snRNP complexes, which interact with the Pol II transcription complex to enhance *EIF3J* and *PAIP2* transcription (Li et al., 2015b). In addition, U2snRNP may play a role in the regulation of EIciRNA (Li et al., 2015b).

CircRNA, derived from exon 6 of the *Arabidopsis SEP3* gene, is mainly located in the nucleus and is produced by exon skipping of pre-mRNA, which can bind strongly to its cognate DNA locus, forming an RNA:DNA hybrid or R-loop that weakens binding between linear RNA and DNA. Formation of the R-loop directly leads to cessation of transcription, resulting in increased splicing efficiency of *SEP3* mRNA (Conn et al., 2017). Together with the above studies, these findings demonstrate that circRNAs present in the nucleus regulate gene expression and splicing.

2.2.3. Interaction with RBPs

CircRNAs interact with different proteins to form specific circRNPs (Fig. 1H), which affect the modes of action of binding proteins. CircMbl is produced from its own second exon of pre-mRNA, and MBL can affect its biogenesis. When excessive amounts of MBL are present, a negative feedback loop is created, in which MBL mRNA levels are reduced via the promotion of circMbl generation. In addition, the generated circMbl contains many MBL protein-binding sites, which can reduce MBL levels by acting as an MBL protein sponge (Ashwal-Fluss et al., 2014). This mode of action of circRNA was also observed in the significantly expressed circPABPN1 in human cervical carcinoma HeLa cells. As an RBP, HuR positively regulates *PABPN1* mRNA expression. CircPABPN1, derived from *PABPN1* pre-mRNA, contains an HuR binding site, which can compete with HuR for binding to *PABPN1* mRNA and thus negatively regulate its expression (Abdelmohsen et al., 2017). Another example is circ-Foxo3, which interacts with p21 and CDK2 to form a circ-Foxo3-p21-CDK2 ternary complex that blocks cell cycle progression (Du et al., 2016b). In addition, circ-Foxo3 can bind to senescence-related proteins ID1 and E2F1 and stress-related proteins HIF1a and FAK, thus promoting cardiac senescence (Du et al., 2016a). The results observed of combining single or multiple RBPs suggest that circRNAs may be widely used as RBP sponges.

2.2.4. Translation into proteins

Most annotated circRNAs are found in the cytoplasm, suggesting that they may be translated into proteins (Fig. 1I). In general, linear mRNA translation proteins depend on the 5′ cap structure; however, circRNA lacks a 5′ cap and 3′ poly (A) tail, indicating that its translation into a protein involves a specific molecular mechanism. It was initially believed that circRNAs required IRES to translate proteins. For example, it was found that circMbl, circZNF609, and circ-FBXW7 containing IRES promoted the direct binding of initiation factors or the ribosome, allowing them to cap independent translation (Legnini et al., 2017; Pamudurti et al., 2017; Yang et al., 2017b). Another study found that circRNAs without IRESs could also be translated into proteins. Yang et al. (2017a) found that circRNA could be m6A-modified by the METTL3/METTL14 complex and m6A de-modified by FTO. Further, circRNAs containing the m6A modification site were shown to recruit the eTH4G2 protein and other translation initiation factors through YTHDF3 recruitment, thereby initiating the protein translation process (Yang et al., 2017a).

2.2.5. Packaging into exosomes or as a biomarker for disease

The unique structure of circRNA allows it to be stably present in the cell or extracellular space without being degraded by nucleases. CircRNAs are found in both blood and saliva (Bahn et al., 2015; Memczak et al., 2015), indicating their potential ability to act as biomarkers. In addition, circRNAs function by packaging into exosomes and through transport into recipient cells (Dou et al., 2016) (Fig. 1J). The abundance of exosomal circRNA is often higher than that of parent cells (Li et al., 2015a). These findings indicate that exosomal circRNAs have important biological functions and are promising biomarkers for disease diagnosis.

3. Role of circRNAs in environmental chemical exposure-related diseases

Exposure to environmental chemicals occurs via numerous exposure routes (Li et al., 2018b; Wambaugh et al., 2014), including ingestion, skin contact, and inhalation, and is reported to increase the risk of developing human disease (Li et al., 2018b; Weschler and Nazaroff, 2008) (Fig. 2). Accumulating evidence has shown that dysregulation of the circRNA regulatory network plays an important role in environmental chemical exposure-related diseases. Here, we discuss the state of knowledge regarding the effects of exposure to various environmental chemicals on circRNA expression and the associated disease risk.

3.1. Silica exposure

Long-term inhalation of air containing free silica dust is the main cause of silicosis. Silica exposure is reported to directly affect circRNA expression, with abnormal circRNA expression affecting silicosis progression. Inhalation of silica leads to activation of alveolar macrophages and triggers an inflammatory response, which also activates circZC3H4 and increases its expression in alveolar macrophages. Further, the highly expressed circZC3H4 upregulates ZC3H4 protein expression by acting as a miR-212 sponge. This increase in ZC3H4 protein levels causes macrophages to undergo proliferation and migration, which promotes the development of silicosis (Yang et al., 2018). Another circRNA, named circHECTD1, has been shown to play multiple roles in

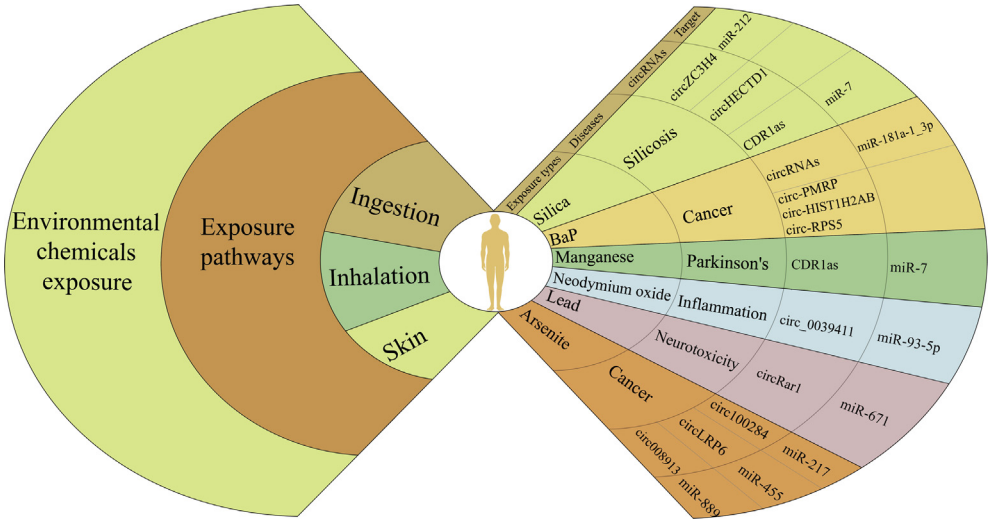

Fig. 2. Overview of the role of circRNAs in environmental chemical exposure-related diseases.

silicosis. Silica exposure promotes mouse microvascular lung (MML1) cells endothelial–mesenchymal transition (EndMT), thus triggering MML1 cells proliferation and migration. The EndMT process initiates circHECTD1 activity, which is derived from alternative splicing of *hectd1* pre-mRNA. CircHECTD1 activation increases its expression level, which results in reduced HECTD1 expression, eventually decreasing the levels of endothelial markers that contribute to irreversible fibrosis in patients with silicosis (Fang et al., 2018). However, silica exposure reduces circHECTD1 expression, which is suppressed by inflammation, and increases HECTD1 protein levels in RAW264.7 cells. ZC3H12A protein degradation via the ubiquitination pathway is attributed to HECTD1 protein induction, which promotes macrophage apoptosis and ultimately results in overproduction of profibrogenic cytokines (Zhou et al., 2018b). This process is closely related to the development of silicosis. Taken together, the above results indicate that circHECTD1 exhibits differential expression patterns in different cell types in the lungs and may represent a biomarker for early diagnosis of silicosis.

3.2. Effect of persistent organic pollutants on circRNA expression

Persistent organic pollutants are a heterogeneous group of harmful chemicals that are not easily degraded in the environment, and may persist for long periods in the human body (Rantakokko et al., 2015; Zong et al., 2016). Although organic pollutants increase the risk of diseases, the molecular mechanisms that lead to alterations in circRNA expression during these processes remain unclear. However, recent research has provided some insights into this subject.

3.2.1. Benzo(a)pyrene (BaP) exposure

BaP is a polycyclic aromatic hydrocarbon that is ubiquitous in the environment. It is mainly formed through incomplete combustion of organic materials (such as fossil fuels) or by smoking, and is highly carcinogenic (Caiment et al., 2015; Lizarraga et al., 2012). BaP exposure produces stress, including DNA damage, reactive oxygen species (ROS) production, and transcription factor aryl hydrocarbon receptor (AhR) activation (Caiment et al., 2015; Cheng et al., 1989; Portal-Nunez et al., 2012), and these factors may be important elements to activate or inhibit circRNA expression. In a report by Caiment et al. (2015), a transcriptomic analysis in HepG2 cells exposed to BaP was conducted, recording results at six different time points of exposure. By data integration, they proposed that BaP exposure rapidly induced miR-181a-1_3p expression in HepG2 cells (within 6 h), which subsequently interacted with a DNA damage response enzyme (MGMT), reducing its expression within 12 h. However, circRNA was demonstrated to attenuate the inhibitory effect of miR-181a-1_3p on *MGMT* expression by acting as a miR-181a-1_3p sponge at 24 h (Caiment et al., 2015). However, circRNA acting as a miR-181a-1_3p sponge to regulate *MGMT* expression requires further verification, and the special circRNA must be determined. Another study confirmed that BaP exposure significantly upregulated expression of circ-PMRP, circ-HIST1H2AB, and circ-RPS5 in bronchial epithelial cells, and that disruption of the mRNA-microRNA-circRNA regulatory network played an important role in the metastasis of bronchial epithelial cells (Jiang et al., 2018). Thus, BaP exposure-induced abnormal expression of circRNAs may be involved in cancer development.

3.2.2. Organic pesticide pollution

Organic pesticides, such as glyphosate and atrazine, have been reported to directly affect the expression of circRNAs in animal models, which were closely related to reproductive system toxicity and neurotoxicity (Sai et al., 2018; Shelton et al., 2014; Yu et al., 2018). Glyphosate-based herbicides are the most widely used herbicides worldwide; therefore, large amounts of their residues are found in the environment (Yu et al., 2018). Glyphosate exposure affects circRNA expression in the hippocampi of perinatal mice and significantly alters expression of 663 circRNAs, including upregulation of 330 circRNAs and downregulation of 333 circRNAs (Yu et al., 2018). These findings indicate that glyphosate exposure leads to changes in circRNAs that may play potential roles in neurotoxicity.

Atrazine is an endocrine disruptor, and exposure to this organic substance is harmful to the growth of organisms (Sai et al., 2016, 2018). Sai et al. (2018) found that long-term exposure to an atrazine-containing environment caused growth abnormalities in male *Xenopus laevis* and changed the expression profiles of gonad-related circRNAs, including 44 upregulated circRNAs and 361 downregulated circRNAs. This indicated that changes in circRNA expression in response to atrazine exposure were closely related to the growth and development of *Xenopus laevis* testes.

However, the current studies have only confirmed that organic pesticides affect circRNA expression in model animals. Due to the lack of research in human cells, more evidence is needed to determine whether organic pesticide exposure affects the expression profiles of human circRNAs and induces the development of related diseases.

3.3. Effect of metal exposure on circRNAs

Metals, a major category of distributed pollutants in the environment, are associated with many diseases (Zeng et al., 2018). Metal

Table 1
Effects of environmental chemical exposure levels on circRNAs (in vivo).

Environmental chemical pollutants	Exposure concentration	Exposure time	Animal model	Specific circRNAs	Expression level	Biological pathway	Related diseases	Reference
$PM_{2.5}$	5 mg/kg in 50 μL saline	8 weeks (once a week	BALB/c mice (9 weeks	142 circRNAs	–	–	Lung inflammation	Zhong et al. (2019)
Silica	0.2 g/kg in 50 mg/mL saline	28 d	Tie2-GFP mice (aged 6–8 weeks, 17–20 g)	circHECTD1	Up-regulated	circHECTD1/HECTD1 pathway	Silicosis	Fang et al. (2018)
	5 mg/mL	28 d	C57BL/6N mice (male, 6–8 wk)	circZC3H4	Up-regulated	circZC3H4/ZC3H4 pathway	Silicosis	Yang et al. (2018)
	50 mg/kg in 0.05 mL sterile saline	1 d, 7 d, 14 d, 28 d	Male C57BL/6 mice (5–6weeks of age, 18–20 g)	CDR1as	Up-regulated	CDR1as/miR-7/TGFBR2 axis	Pulmonary fibrosis	Yao et al. (2018)
Atrazine	100 μg/L	180 d	male *Xenopus laevis*	405 circRNAs	–	–	Testicular degeneration	Sai et al. (2018)
Glyphosate	50 mg/kg/day	21 d	ICR mice (aged 9–11 weeks)	663 circRNAs	–	–	Neurotoxicity (brain hippocampus)	Yu et al. (2018)

Note: BALB/c mice, concatenation of Bagg and Albino mice; Tie2-GFP mice, STOCK TEK-GFP 287 Sato/JNju mice; ICR mice, institute of cancer research mice.

exposure has been reported to affect circRNA expression profiles to different degrees and trigger related diseases (Hua et al., 2019; Xue et al., 2017).

3.3.1. Manganese exposure

Manganese is an important trace element with strictly controlled levels in the human body; however, exposure to elevated concentrations has been shown to be closely related to the risk of idiopathic Parkinson's disease (Tarale et al., 2018). Chronic manganese exposure has been suggested to cause *SNCA* overexpression in SH-SY5Y cells by diminishing miR-7 levels. Elevated expression of *SNCA* can cause toxicity to dopaminergic neuronal cells, resulting in Parkinson's disease (Tarale et al., 2018). CDR1as is present in the mammalian brain in high amounts and can interfere with miR-7 to promote the pathogenesis of Parkinson's disease (Hansen et al., 2013; Junn et al., 2009). Further research is needed to determine whether manganese exposure leads to decreased miR-7 levels, ultimately leading to CDR1as-regulated development of Parkinson's disease.

3.3.2. Lead exposure

Lead is a neurotoxic metal that has been reported to directly affect circRNA expression (Nan et al., 2017; Tong et al., 2000). Lead-induced neurotoxicity increases lncRpa and circRar1 expression in the hippocampus and cerebral cortex of mice, which results in increased mRNA and protein levels of apoptosis-related factors caspase8 and p38 via miR-671 targeting, ultimately leading to neuronal apoptosis (Nan et al., 2017).

3.3.3. Arsenite exposure

In addition to manganese and lead, arsenic has been reported to directly affect circRNA expression and induce disease. Long-term exposure to inorganic arsenic can lead to cardiovascular disease as well as lung and skin cancers (Hughes et al., 2011; Lu et al., 2014; Xue et al., 2017). According to current reports, circRNA regulates cancer development caused by arsenic exposure in three ways.

CircRNA regulates the cell cycle and metastasis of human keratinocyte (HaCaT) cells and human liver (L-02) cells induced by arsenic exposure. Arsenic exposure activates circ100284, which is derived from back-splicing of pre-glutamate-cysteine ligase (GCLM) mRNA, and acts as a miR-217 sponge to regulate EZH2 protein expression. Cyclin D1 and CDK4 are upregulated by EZH2 in combination with the *CCND1* promoter, which directly leads to uncontrolled proliferation and transformation of HaCaT cells (Xue et al., 2017). Furthermore, arsenic exposure elevates circRNA_100284 levels, which is sorted into exosomes and secreted by L-02 cells. When circ100284 enters adjacent cells through exosomes, it regulates the metastasis of L-02 cells via the same mechanism (Dai et al., 2018); therefore, circ100284 may also regulate the metastasis of cells under arsenic exposure.

CircRNA regulates the epithelial-mesenchymal transition (EMT) and transformation of HaCaT cells under arsenic exposure. Further, arsenic exposure induces the EMT of HaCaT cells, which subsequently activates circLRP6, increases its expression levels to act as a miR-455 sponge, and upregulates ZEB1 protein levels. ZEB1 is a transcriptional regulator that participates in tumor progression and invasion by promoting EMT. Further, an increase in its levels results in the induction of EMT in HaCaT cells, thus promoting metastasis (Xue et al., 2018).

CircRNA regulates the induction of cancer stem cell (CSC)-like properties in HaCaT cells under arsenic exposure. Arsenic exposure reduces circ008913 expression in HaCaT cells, which acts as a miR-889 sponge to downregulate DAB2IP protein levels. DAB2IP upregulates ZEB1 and increases the mRNA levels of cell surface markers on skin stem cells (k5 and CD34). Ultimately, this signaling cascade leads to the acquisition of CSC-like properties and neoplastic transformation of HaCaT cells (Xiao et al., 2018).

Taken together, arsenic exposure directly affects the normal expression of a series of circRNAs, which individually or synergistically

Table 2
Effects of environmental chemical exposure levels on circRNAs (in vitro).

Environmental chemical pollutants	Exposure concentration	Exposure time	cell	Specific circRNAs	Expression level	Biological pathway	Related diseases	Reference
Silica	0.5mg/each	7 d	Human alveolar macrophages and RAW264.7 macrophage cells	circHECTD1	Down-regulated	circHECTD1/HECTD1 -Dependent Ubiquitination pathway	Silicosis	Zhou et al. (2018b)
BaP	2 mM	6, 12, 18, 24, 36 and 48 h	HepG2 cells	163 circRNAs	–	–	Liver cancer	Caiment et al. (2015)
Neodymium oxide	80 μg/mL	48 h	16HBE cells	circ_0039411	Up-regulated	circ_0039411/miR-93–5p/ STAT3 pathway	Pulmonary inflammation	Hua et al. (2019)
Lead	0.1 μM	48 h	N2a cells	circRar1	Up-regulated	circRar1/miR-671/caspase8, p38 pathway	Neurotoxicity (brain hippocampus and cerebral cortex)	Nan et al. (2017)
Arsenite	1 μM	48–72 h (continued for about 20 weeks)	HaCaT cells	circ100284	Up-regulated	Circ100284/miR-217/EZH2 pathway	Accelerates the cell cycle	Xue et al. (2017)
	1 uM	48–72 h (continued for about 20 weeks)	HaCaT cells	circLRP6	Up-regulated	circLRP6/miR-455/ZEB1 pathway	Malignant Transformation	Xue et al. (2018)
	1 uM	48–72 h (continued for about 20 weeks)	HaCaT cells	circ008913	Down-regulated	circ008913/miR-889/DAB2IP, ZEB1 pathway	Malignant Transformation	Xiao et al. (2018)

Note: RAW264.7 cells, mouse mononuclear macrophage leukemia cells; HepG2 cells, human hepatocellular carcinoma cells; 16HBE cells, Human bronchial epithelial 16HBE cells; N2a cells, mouse neuroblastoma cells; HaCaT cells, human immortalite keratinocyte cells.

regulate corresponding signaling pathways, leading to cell metastasis. These results suggest that circRNAs may serve as early screening markers for cancer development in response to arsenic exposure.

4. Effects of chemical exposure level on circRNAs

The composition of environmental chemicals is complex. When different chemical pollutants are simultaneously present, their toxicity may be reduced or increased due to their antagonistic or synergistic action (Zhang et al., 2017). The concentration of chemical contaminants in the environment is often used to assess the extent of human exposure to environmental chemicals; however, this approach may overestimate chemical uptake (Pelletier et al., 2017; Wei et al., 2018). Therefore, it is necessary to evaluate the bioaccessibility and bioavailability of chemical pollutants reasonably and effectively. Table 1 and Table 2 from in vivo and in vitro studies list the effects of exposure levels of chemical contaminants that have been demonstrated on circRNAs to date.

5. Regulatory roles Of circRNAs in diseases induced by environmental chemical exposure

To carry out normal physiological functions, cells must maintain homeostasis (Fischer and Leung, 2017). CircRNAs lack 5′ and 3′ ends, which makes them highly stable and resistant to degradation by nucleases (Li et al., 2018d). This feature suggests that circRNAs play an important role in the maintenance of cellular homeostasis under environmental chemical exposure. Notably, we hypothesized that the molecular mechanisms underlying the induction of disorders related to abnormal circRNA expression caused by environmental chemical exposure occur in three different pathways (Fig. 3).

The first mechanism involves the abnormal expression of circRNA. Environmental chemical exposure induces cells to produce inflammation, ROS, etc. These factors promote the activation of related transcription factors (Fischer and Leung, 2017), such as NF-κB or AP-1, which cause mRNA and non-coding RNAs (microRNAs, circRNAs) to be transcribed consecutively. CircRNA regulates cellular homeostasis through positive and negative pathways. CircRNA levels can maintain cell homeostasis; however, when circRNA is abnormally expressed (upregulated or downregulated), it disrupts homeostasis and exacerbates cell stress, leading to extensive inflammation, autophagy, apoptosis, and disease induction (Li et al., 2018a, 2018c; Nan et al., 2017; Shi et al., 2019).

Additionally, long-term exposure to environmental chemicals promotes disease pathogenesis via DNA methylation changes. Methylation changes often occur in the gene promoter region linked with CpG islands (Shi et al., 2019; Sun et al., 2018), which leads to changes in the gene transcription levels that affect disease development. In addition, studies have indicated that CircIBTK induces DNA methylation in systemic lupus erythematosus (Wang et al., 2018). However, it is not clear whether circRNAs can regulate DNA methylation, and the specific mechanism triggered by environmental chemical exposure is unclear.

The third mechanism is by altering exosome components. The specific contents of exosomes are strongly influenced by their parental cells, and may comprise a wide variety of proteins, lipids, and non-coding RNAs (circRNAs, microRNAs). Exosomes may transport contents to adjacent cells or distant cells (Kalani et al., 2014). Diseased cells affect the levels of microRNAs or circRNAs in adjacent normal cells by secreting exosomes (Dai et al., 2018), thereby accelerating disease progression.

The pathogenesis of disease is an extremely complex process. In many cases, the change in status from healthy to diseased is a quantitative to qualitative process. When the level of environmental chemical exposure reaches a certain intensity or for a certain period of time, it causes damage to cells, disrupting cell function, metabolism, and morphological structure. Early disease detection may be achieved by

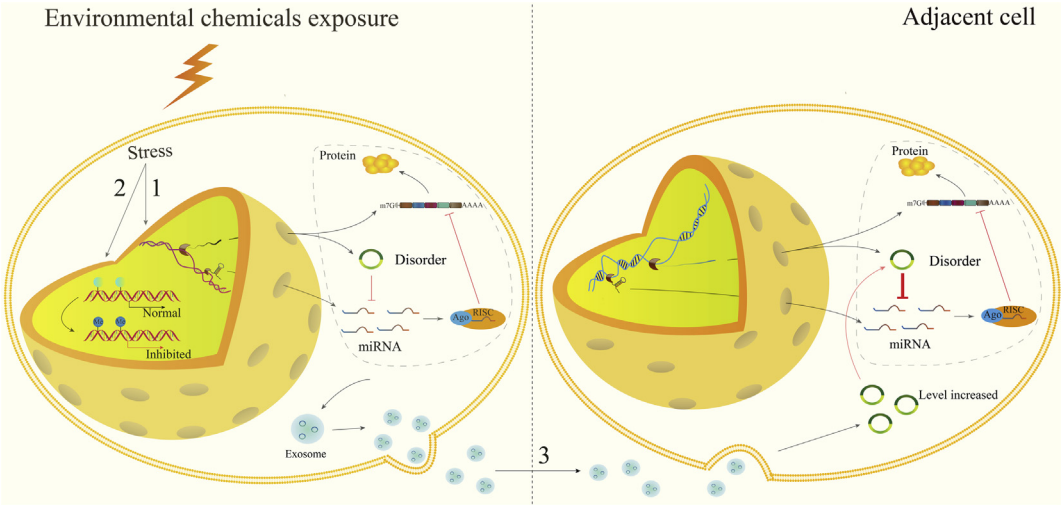

Fig. 3. Regulation of circRNAs in pathway mechanisms of environmental exposure-induced diseases. Environmental chemical exposure induces disease by three possible molecular mechanisms. (1) Chemical exposure may induce the transcription of transcription factors, such as AP-1 and NF-κB, leading to the transcription of related ncRNAs. Long-term disruption of circRNA expression leads to dysregulation of related regulatory networks, which, in turn, induces inflammation, autophagy, and apoptosis, eventually leading to disease. (2) Chemical exposure can lead to changes in DNA methylation, and circRNAs may regulate DNA methylation. (3) The diseased cells secrete exosomes containing microRNAs and circRNAs into adjacent cells. Therefore, the contents of these exosomes disrupt the homeostasis of adjacent cells, thereby accelerating disease progression.

determining circRNA and exosomal circRNA expression levels, which act as markers of health status. In addition, an interaction between microRNAs and circRNAs is often observed in pathological processes, such that the level of microRNAs has been shown to affect circRNAs. Therefore, disease progression may be suppressed via the delivery of potent miRNA sponges to alter the levels of endogenous circRNAs.

6. Conclusions and prospects

Early diagnosis of environmental chemical exposure-induced diseases is critical for prevention and treatment. CircRNAs are widely present in body fluids, which holds promise that circRNAs might be used as biomarkers. Numerous circRNAs have been identified from human peripheral whole blood (Memczak et al., 2015) and urine of prostate cancer patients (Vo et al., 2019). These indicate body fluid detection as a promising application for profiling human circRNAs in a noninvasive manner. In addition, circRNAs are extensively present in exosomes (Li et al., 2015a), and circRNA detection by capturing tissue/disease-specific exosomes can predict disease occurrence and progression. These all indicate that circRNA level changes caused by environmental chemical exposure may be detected in body fluids or exosomes. However, there are many chemicals that have not found suitable circRNAs as biomarkers for diagnosis. As there is no standard method for circRNA detection, there may be certain limitations for clinical application. Nevertheless, it is undeniable that circRNAs have potential applications as diseases biomarkers in environmental chemical exposure.

Diseases caused by chemical exposure are often chronic by nature, and this process is often accompanied by abnormal expression of circRNAs. Therefore, early effective intervention for preventing and treating chemical exposure-related diseases may be an effective therapeutic strategy. Studies have shown that small interfering RNA (siRNA) or CRISPR–Cas9 can successfully affect the expression of endogenous circRNAs (Boeckel et al., 2015; Memczak et al., 2013; Zheng et al., 2016), thereby achieving interventional regulation. However, there are also significant drawbacks. The low-efficiency interference of siRNA and the off-targeting of CRISPR–Cas9 may affect special circRNAs resistance. Artificial circRNAs may be another good strategy. Jost et al. (2018) constructed of overexpressed artificial circRNAs, which contained the miR-122 binding site, and could inhibit viral protein production in an HCV cell culture system by sequestering miR-122 during the viral life cycle. This indicates that circRNAs may be a promising tool in molecular medicine and novel therapeutic targets for chemical exposure-related diseases.

In conclusion, we discussed the generation and function of circRNAs, and how their abnormal expression may affect disease occurrence. Furthermore, we discussed the possible molecular mechanisms underlying the roles of circRNAs in regulating the development and progression of environmental chemical exposure-induced diseases. The dysregulation of circRNA expression, possible regulation of DNA methylation, and transmission of exosome-dependent pathways together affect the disease status. These reports enhance our understanding of the role of circRNAs in various diseases and demonstrate that circRNAs have promising applications as disease biomarkers and novel therapeutic targets for diseases caused by exposure to environmental chemical pollution. However, investigating the contribution of circRNAs to the occurrence and development of chemical exposure-related diseases is still in its infancy. Therefore, future research can focus on two aspects: identification of specific circRNAs involved in various diseases, which should provide a basis for developing targeted therapy; and characterization of the quantitative relationship between chemical exposure and gene interactions, which should enable intervention at early stages of disease to prevent disease progression. The elucidation of these unaddressed issues should provide the foundation for the development of novel therapeutic strategies and diagnostic criteria.

Author contributions

Xiaohua Zhu conceived and designed the project. Dong Li wrote the paper with input from the authors. Zeqin Li, Yan Yang and Youping Li participated in the discussion and revision. Xianyin Zeng and Xiaogang Du modified the grammar and increased the readability of the review.

Declaration of competing interest

The authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

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