Circular RNAs in leukemia (Review)

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Abstract. Circular RNAs (circRNAs) have been demonstrated to be biomarkers in human cancers. CircRNAs are majorly recognized in the transcript formation of eukaryotic genes. Research has also revealed that circRNAs regulate gene expression at the transcriptional, post-transcriptional, and translational levels. Notably, there have been studies demonstrating that they contribute to the improvement of various diseases, including cancer. In this regard, they have potential applications in the diagnosis and treatment of cancer. In circRNA studies of blood fluids, plasma circRNAs have been identified as biomarkers in human cancers. For instance, the acute myeloid leukemia-associated hsa_circ_0004277 has been reported to be a biomarker in targeted treatments. This links with circRNAs being highly expressed in hematopoietic tissue; in haematopoiesis, the cell states are controlled by the main regulators and the complex circuits of the RNA family. In particular, circRNA serve a role in cellular processes including self-renewal, apoptosis and proliferation. In the current review, the aim was to explain the role of the defined pathogenic circRNAs derived from leukemia fusion genes and of hsa_circ_0004277 in leukemia cells.

Contents

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1. Introduction

Non-coding RNAs (ncRNAs), which comprise long non-coding RNAs (lncRNAs), short microRNAs (miRNA/miRs) and circular RNAs (circRNAs), constitute the majority of total RNAs in the eukaryotic transcriptome (1,2). CircRNAs were first identified in viruses in 1970, and subsequently in eukaryotic cells (3,4). CircRNAs are a relatively large group of RNAs that form stable closed circles. A major proportion of ncRNAs and circRNAs are involved in the regulation of transcriptional and post-transcriptional gene expression (5). CircRNAs are produced from the back-splicing of intronic and/or exonic RNA (2). They serve a significant role in cancer development, metastasis and response to treatment (6). The specificity of circRNA in disease states and the stability of circRNA in body fluids indicate that they may be used molecular markers in the diagnosis of cancer (6-9). A high number of circRNAs have been identified following the development of sequencing and bioinformatics analysis techniques (10-12). In particular, abnormal expressions of circRNAs have been identified in leukemia. For instance, hsa_circ_0035381, hsa_circ_0004136 and hsa_circ_0058058 are reportedly upregulated while hsa_circ_0017446 and hsa_circ_0004277 are downregulated in acute myeloid leukemia (6). In the present review, the aim was to explain the role of defined pathogenic circRNAs derived from leukemia fusion genes [mixed lineage leukemia-ALL1 fused gene from chromosome 9 (MLL-AF9) and promyelocytic leukemia-retinoic acid receptor α (PML-RARA)] and hsa_circ_0004277 in leukemia cells.

2. Characteristics of circRNAs

CircRNAs are highly diverse, originating from any region of the genomic subsequences (exon–intron circRNAs, intronic circRNAs, exonic circRNAs) (2,12-16). The majority of the circRNAs are generated from one or more excess exons (17-20). The exonic circRNAs predominantly reside in the cytoplasm (21,22). They have a more stable structure than linear RNAs, with 5'-3' polarities and no polyadenylation tails (10). CircRNAs can be degraded by RNA exonuclease or ribonuclease (RNase) R (23). CircRNAs are enriched in exosomes (24).

It is established that circRNAs are relatively common in eukaryotic transcriptomics and are stable in intracellularly in the cytoplasm and in the blood (7). CircRNAs can be secreted into body fluids or developed in exosomes, and as such have

emerged as major biomarkers for cancer diagnosis (8,24,25). It has been demonstrated that the expression of circRNA is specific, and that the molecules serve as miRNA sponges to regulate gene expression (5,26-28). CircRNAs may have biological activities by acting as miRNA sponges and/or by binding with RNA-binding proteins (RBPs) and translation peptides (5,24,29,30). In the study of cancer, an ongoing aim is to identify potential biomarkers that are differentially expressed between healthy and cancerous tissues. In this regard, there are studies indicating that circRNAs are associated with the initiation and development of cancer (31-33).

3. Biogenesis and function of circRNAs

CircRNAs are divided into three groups: Exonic circRNAs, intronic circRNAs and exon-intron circRNAs. Throughout the formation of all types of circRNAs, characteristic sequences are preserved. Sequences from the downstream and upstream regions enable the formation of mature circRNAs following-back-splicing by covalently linking in the reverse direction (34). While the effect of back-splicing is less significant for linear RNAs due to their durability and half-life, circRNAs are present in excess in cells (35). The first back-splicing mechanism works due to complementary intron matches that serve a role in the formation of exonic circRNA (17). CircRNA may interact with other RNA molecules and DNA, including mRNA and lncRNA (36,37).

CircRNAs are associated with various diseases, including cancer in particular (31,38-40). It is established that there is an association between circRNA and miRNA in various cancers (30,31). CircRNAs act as miRNA sponges, RBP sponges and transcription and translation regulators. CircRNAs have important functions in the regulation of gene expression (5,14,41,42). Reportedly there is deregulation of the splicing mechanisms in acute myeloid leukemia (AML), leading to abnormalities in the expressed circRNAs in leukemia cells; in turn, the altered circRNAs can have functions in leukemogenesis (6).

It has been shown that circRNAs can bind to miRNA as RNA sponges, and by influencing miRNA activities, may increase gene expression and contribute to the development of tumours (5,43-45). In particular, it has been reported that circRNAs can increase or suppress the development of cancer genes associated with migration, differentiation, proliferation and carcinogenesis by suppressing miRNA species (46). For instance, among the first circRNAs to be identified, CiRS-7, contains an miR-7 binding site and acts as an miR-7 sponge, thus reducing the effect of miR-7 on its target mRNAs (47,48). Overexpression of ciRS-7 in colorectal cancer cells has been reported to eliminate the tumor suppressor function of miR-7 (49).Circ-ZNF609 is also a cancer-associated gene, being observed to inhibit proliferation in colorectal cancer cells (50).

4. CircRNAs-F-circRNAs in leukemia

CircRNAs have been studied in hematopoietic malignancies in primary patient samples. In bone marrow from patients, Salzman *et al* (10) determined that hyperdiploid B-linage acute lymphoblastic leukemia (ALL) in childhood could rearrange chromosomal regions using an RNA-seq method. Furthermore, they conducted research on the rearrangement in specialized genomic exon regions subject to RNA splicing. In the ALL patients, they identified hundreds of genes that could produce circRNAs. Fusion genes encoded by abnormal chromosomal translocations have been demonstrated to be associated with malignant haematological diseases. Chromosomal rearrangements in tumour cells affect ncRNA levels through the formation of fusion-circRNAs (f-circRNAs) (51).

There are inherent chromosomal translocations in various types of leukemia. A recurrent translocation is PML-RARA in patients with acute promyelocytic leukemia (APL) (52). Recently, studies on circRNA expression in AML have been conducted. Guarnerio *et al* (6) demonstrated that circRNAs are derived from the transcription of fusion genes that occur from chromosomal translocations. Indeed in various studies, circRNAs have been associated with many cancers, including AML with MLL-AF9 and promyelocytic leukemia with PML-RARA. Many are established as f-circRNAs. Abnormal expression of circRNAs may be the result of distant interrelated introns and introns of translational genes that contain repeating sequences complementary to each other. Novel back-splicing events are supposed to support their formation into abnormal circRNAs (53).

A previous review noted that cancer-associated fusion genes may cause the expression of f-circRNAs, including the pro-proliferative, proto-oncogenic f-circPR and f-circM9_1 (6). You and Conrad (54) determined differently expressed f-circRNAs in APL and AML. Such is in accordance with f-circRNAs being established to serve an active role in haematological events (53). Li *et al* (53) reported that hsa_circ_0004277 in AML patients was downregulated.

Circ-HIPK2 has been indicated to serve a role as a transcription coactivator in nuclear bodies and is considered to have important functions in the formation and development of AML (55,56). Li *et al* (57) demonstrated that expression of circ-HIPK2 affected ATRA-induced differentiation of APL cells. In addition, the expression of circ-HIPK2 was lower in AML cells compared with APL cells, and overexpression of circ-HIPK2 increased differentiation in NB4 cells (APL cells with PML-RARA). Therefore, HIPK2 appeared to be required for differentiation of ATRA-induced APL cells. This suggests that circ-HIPK2 may be a biomarker in APL cells.

There are many chromosomal translocations in several types of leukemia. These chromosomal translocations may occur due to the instability of the tumour cells' genome. The abnormal chromosomal translocations leading to the rearrangement of non-homologous chromosomes brings two separate genes together, giving rise to the production of a fusion genome. Chromosomal translocations can encode such oncogenic fusion proteins in tumor formation, these proteins may be a cause of cancer (58).

While fusion of circular RNA (f-circRNA) occurs, gene fusions can also cause defects in mRNA. For example, PML-RARA and MLL-AF9 genes are fused, and thus form f-circM9 and f-circPR. Knockout of f-circM9 and f-circPR can increase apoptosis in cancer cells and increase drug sensitivity to agents such as arsenic (6). These data indicate that f-circM9 and f-circPR have a role in haematological malignancies (Fig. 1). Guarnerio *et al* (6) documented that expression of f-circRNAs (f-circPR and f-circM9) in leukemia increased

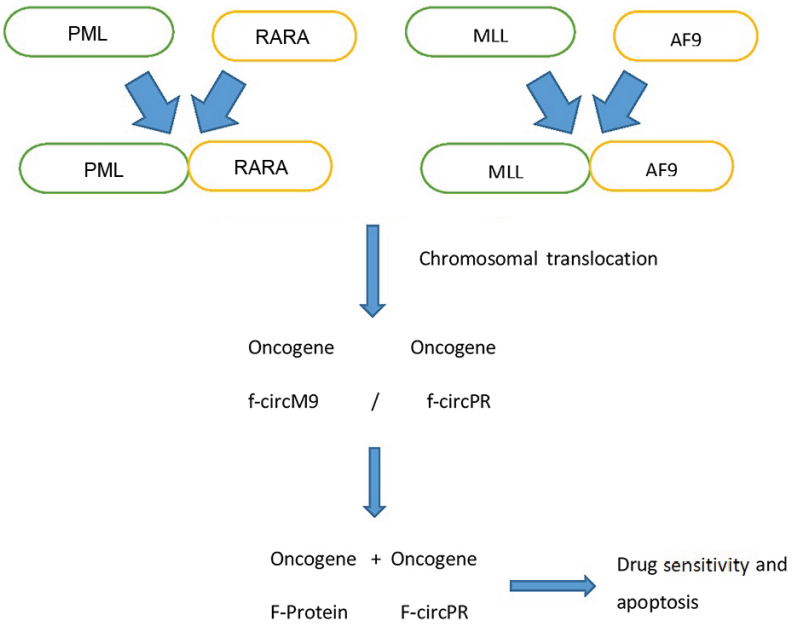

Figure 1. Roles of the PML-RARA and MLL/AF9 fusion genes in the apoptosis and drug of sensitivity of leukemia cells. PML-RARA and MLL-AF9 genes become fused, and f-circM9 and f-circPR are formed. Knockout of f-circM9 and f-circPR may increase apoptosis and drug sensitivity. PML-RARA, promyelocytic leukemia-retinoic acid receptor α; MLL-AF9, mixed lineage leukemia-ALL1 fused gene from chromosome 9; F- fusion; circ, circular RNA.

cell proliferation and clonogenicity. They also showed that the phenotype of cells with silenced f-circRNA was reversed. Thus, these f-circRNAs may have pro-proliferative and proto-oncogenic properties in leukemia. Indeed, it has been documented that f-circRNAs (produced from PML-RARA and MLL-AF9 fusion genes) have a role in the survival of leukemia cells (6).

The f-circRNAs expressed in human leukemia cells have been associated with disease formation (59). However, the f-circRNA does not cause leukemia alone. Combined expression of F-circM9 and MLL-AF9 fusion protein have been reported to increase proliferation; notably only cells expressing the fusion protein exhibited increased colonies. The expression of f-circRNAs may provide protection for tumour cells in standard leukemia therapy, including against arsenic trioxide, and may also provide survival benefit to leukemic cells during standard leukemia treatment with cytarabine (59).

5. Hsa_circ_0004277 and leukemia

Hsa_circ_0004277 is located in the region of chromosome 10: 1125950-1126416. WDR37 is the gene symbol of hsa_circ_0004277 (60). WDR37, located on the same chromosome, is the linear isoform of Hsa_circ_0004277 (53). This family is associated with apoptosis, signalling pathways and cellular events including the cell cycle (60). Wei *et al* (53) identified hsa_circ_0004277 as a target and biomarker in the treatment of AML. When the circRNA-miRNA-mRNA interaction for hsa_circ_0004277 has been examined by bioinformatics analysis, it has provided insight into the underlying mechanism of its function in AML. For instance, while hsa_circ_0035381, hsa_circ_0004136 and hsa_circ_0058058 are upregulated, the hsa_circ_0017446 and hsa_circ_0004277 are downregulated in AML (53). Newly diagnosed cases of AML have been found to exhibit downregulated hsa_circ_0004277, while, the expression of hsa_circ_0004277 was increased in complete remission cases, and the level once again downregulated in relapsed/refractory cases. These results indicate that hsa_circ_0004277 may be used as a diagnostic marker and therapeutic target in AML (53).

6. Conclusions and perspectives

In the current review, we sought to summarize the formation of circRNAs and their characteristics and functional properties, and the roles of the defined pathogenic circRNAs derived from the leukemia fusion genes and hsa_circ_0004277 in leukemia cells. Studies on circRNAs for clinical diagnosis and treatment are viewed as a guide for translational and clinical medical developments. Considering the functions and mechanisms of circRNAs, they may be considered among the main topics of cancer research. Research on these molecules may provide insight into the fundamental molecular events involved. The use of circRNAs as diagnostic biomarkers in cases of cancer metastasis may be clinically significant. Different cirRNA expression profiles correlate with clinical features, including tumor stage and recurrence of metastasis, supported by recent RNA-seq studies (61,62). Additionally, circRNAs are established as being markedly more stable than linear RNAs.

Different expression profiles of circRNAs have been identified in studies on tissues and blood. The expression of circRNAs is different from that of miRNAs and lncRNAs. By combining with various biomarkers, it is possible to model for prognosis and increase the accuracy and specificity of diagnosis (63,64). The consequences of molecular circuits that control cellular differentiation in the hematopoietic system are a topic of study. In haematopoiesis, differentiated cell states can be controlled by transcriptional circuits linked to each other (65). Recent study of f-circRNAs has revealed the oncogenic roles of abnormal circRNAs in leukemogenesis (51). Studies have also shown that

circRNAs may be molecular markers in tumours and affect cell death.

CircRNAs have potential in targeted cancer therapy, in that they may be used as a sponge for binding to abnormally expressed regulatory RNAs and proteins (e.g., RBPs), to thus reduce oncogenic activities (66). For instance, certain f-circRNAs have been found to be resistant to chemotherapy in leukemia patients. The knocking out of f-circM9 expression in leukemia cells can lead to apoptosis. In another example, while hsa_circ_0004277 showed low expression in newly diagnosed AML patients, no difference was determined in patients following treatment. In patients with recurrent disease, hsa_circ_0004277 has been observed to be downregulated (6). For this reason, hsa_circ_0004277 may be a diagnostic marker in AML. The overall stability of the circRNAs may be useful in indicating diseases that can be identified by body fluids.

In conclusion, considering the functions and mechanisms of circRNAs, they may be among the main topics in cancer research. In particular, circRNAs may be a diagnostic marker for leukemia. An improved understanding of circRNA biology may provide a guide for novel therapeutic targets.

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Competing interests

The authors declare that they have no competing interests.

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