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Circular RNAs: new genetic tools in melanoma

Jamal Hallajzadeh[1], Elaheh Amirani[2], Hamed Mirzaei**,[2], Rana Shafabakhsh[2], Seyyed M Mirhashemi[3], Mehran Sharifi[4], Bahman Yousefi[5], Mohammad A Mansournia[6] & Zatollah Asemi*,[2]

[1]Department of Biochemistry & Nutrition, Research Center for Evidence-Based Health Management, Maragheh University of Medical Sciences, Maragheh, Iran

[2]Research Center for Biochemistry & Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

[3]Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran

[4]Department of Hematology & Oncology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

[5]Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[6]Department of Epidemiology & Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

*Author for correspondence: Tel.: +98 315 546 3378; Fax: +98 315 546 3377; asemi_r@yahoo.com

**Author for correspondence: h.mirzaei2002@gmail.com

Melanoma is the most lethal form of skin cancer. New technologies have resulted in major advances in the diagnosis and treatment of melanoma and other cancer types. Recently, some studies have investigated the role of circular RNAs (circRNAs) in different cancers. CircRNAs are a member of long noncoding RNA family mainly formed through back-splicing and have a closed loop structure. These molecules affect several biological and oncogenic cascades in diverse ways via acting as microRNA sponge, interacting with RNA-binding proteins and acting as a transcription regulator. In this review, we made an insight into the impact of circRNA dysregulation in the melanoma tumorigenesis based on the presented evidences.

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Melanoma, the cancerous growth of melanocytes, is the most aggressive form of all skin cancers [1]. This cancer is more common in men, with worse survival rate than women [2,3]. Recently, its incidence, morbidity and mortality are increasing worldwide. The American Cancer Society estimated that in 2019 melanoma was the fourth most common cancer in men and the fifth most common cancer in women [4]. There are multiple distinct categories of melanocytic neoplasms which are different in cell of origin, role of ultraviolet radiation, clinical and histological indications, mutation pattern, predisposing germ line alterations and sites of metastasis [5]. Based on the primary site of neoplasm and morphologic aspects of the early growth phase, melanoma divided into four main types: superficial spreading melanoma (50–75%), nodular melanoma (15–35%), lentigo malignant melanoma (5–15%) and acrallentiginous melanoma (5–10%) [6,7].

Recent investigations and new technologies have resulted in major advances in the diagnosis and treatment of this cancer. In addition to conventional therapies for melanoma such as surgical intervention and radiation therapy, other treatment options including chemotherapy, immunotherapy, genetically targeted therapy and nanotechnology have been used [8–10]. Although melanoma is treatable in its early stages, it is still a therapeutic challenge and advanced malignant melanoma carries a poor prognosis. Patients with stages II and III have a 10-year survival rate of 77 and 69%, respectively [11]. One of the main problems in the treatment of melanoma is low response rate to the present treatment modalities due to inherent resistance of melanoma cells to chemotherapeutic agents [12]. Melanoma arises from a complex interaction between environmental and genetic factors. A well-established risk factor for melanoma development is exposure to ultraviolet radiation, which induces cellular stress signaling, DNA damage and disrupts DNA repair systems [13,14]. Multiple pathogenic mutations in melanoma affect genes involved in key signaling pathways that control proliferation (mitogen-activated protein kinase [MAPK], NF1, NRAS, and BRAF) replicative

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lifespan (cell cycle [cyclin-dependent kinase inhibitor 2A {CDKN2A}], telomerase reverse transcriptase [TERT]), metabolism and growth (KIT and PTEN), cell identity (AT-rich interaction domain 2 [ARID2]) and resistance to apoptosis [TP53]) [15]. It has been showed that variants of some genes, in other words, microphthalmia-associated transcription factor (MITF) and melanocortin 1 receptor (MC1R) result in a moderately elevated risk of melanoma development [16]. In recent years, a great progress has been made in understanding the role of epigenetic mechanisms involved in the regulation of gene expression including methylation, chromatin remodeling and modification and the various functions of noncoding RNAs (ncRNAs) in melanoma pathogenesis [17].

A group of RNAs that could not encode any proteins are known as ncRNAs. Primarily, ncRNAs are regulators of gene expression and exert their function at the post-transcriptional level. They also have a key role in epigenetic control [18]. Increasing evidence suggest that different kinds of ncRNAs for example, microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) including circular RNAs (circRNAs) exert considerable impact on several molecular mechanisms in a variety of diseases [19–22]. Following miRNAs and lncRNAs, circRNAs enrich the RNA world. CircRNAs are a different class of endogenous ncRNAs family that mainly result from back-splicing, a noncanonical form of alternative splicing [23]. In human cells, circRNAs comprise more than 10% of all transcripts [24]. Unlike linear mRNAs, 5′ and 3′ ends in circRNAs have been bonded together, forming covalently closed-loop structures [25]. Recent findings have demonstrated the circRNAs as stable and endogenous species. They also found out that circRNAs are extensive in mammalian cells. The circRNAs show tissue/cell/developmental stage-specific pattern for expression [26]. CircRNAs have different lengths and these molecules are able to form from each site in the genome [27]. CircRNAs can be classified into five groups based on their genomic proximity to the counterpart gene. The first type is sense or exonic, which comes from a linear transcript on the same sequence and has the ability to alternatively splice isoforms. The second type is intronic circRNAs deriving from an intron and the third type is antisense formed when circRNAs overlap one or more exons on the opposite sequence. The next type is intragenic or bidirectional which is produced when circRNA is transcribed from same gene locus of the linear sequence. The last type is intergenic, formed when circRNAs are located between the genomic intervals of two genes [28,29]. The exact function of most circRNAs remains largely unexplored, but some functional circRNAs have identified to play an important role in regulating the genes by different mechanisms such as regulation of splicing and transcription, sponging miRNAs and proteins. Hence, they are highlighted as a new class of important regulators [30,31]. CircRNA–miRNA axis is involved in several cancer-related pathways such as apoptosis, vascularization, invasion and metastasis [28,32]. Emerging studies showed that deregulation of circRNAs has been implicated in the pathogenesis of multiple diseases, especially various cancers [33,34].

During these last years, our knowledge regarding the function of circRNAs in cancers has been expanded. Several circRNAs such as cerebellar degeneration-related 1 (CDR1) antisense RNA (CDR1-AS) can bind to miRNA-7 in different binding sites and inhibit its gene regulation [35–37]. In a study, Hanniford *et al.* investigated the role of circRNA in the metastatic model of melanoma [37]. They indicated that the silencing of CDR1-AS, as an miR-7 regulator, could be used as a hallmark in the progression melanoma. LINC00632 as an lncRNA could lead to CDR1-AS depletion that results in induction of invasion via miR-7-independent, IGF2BP3-mediated mechanism both *in vitro* and *in vivo*. Their results indicated that the levels of CDR1-AS reflect cellular states related to distinct therapeutic responses. These findings suggested CDR1-AS has functional, predictive and prognostic roles and it plays a crucial function in metastasis [37].

MiR-7 can negatively regulate a variety of molecules and pathways involved in cancer such as cell growth, proliferation and invasion and also it is considered as a promising target in cancer therapy [38]. Further, circRNAs affect the cancer biogenesis by interacting with RNA-binding proteins and acting as a transcriptional regulator of diverse proteins [39]. In addition, dysregulation of certain circRNAs may contribute to tumor metastasis by activating epithelial–mesenchymal transition (EMT) process [40]. At this point, when it is established that melanoma is a highly metastatic cancer with a poor prognosis and a high degree of resistance to medical treatment, increasing studies have explored the role of epigenetic pathways in melanoma tumorigenesis and treatment. However, the role of lncRNAs and miRNAs in melanoma has been reviewed in some details [41–43], a remaining question is about the role of circRNAs in melanoma carcinogenesis. In this review, we summarize advance research regarding the involvement of circRNA regulation and functions in melanoma.

Melanoma carcinogenesis: signaling pathways

Molecular studies have indicated that melanoma is a heterogeneous disease arising from different factors. Over the past decade, many biological pathways, genetic alterations and epigenetic regulation affecting melanoma

development have been identified [44,45]. MAPK is the pathway with the highest oncogenic and therapeutic relevance for this disease. Activation of MAPK signaling by oncogenic mutations has been found in more than 80% of melanoma cases [46,47]. For instance, mutation in BRAF induces activation of MAPK-signaling cascade and downstream protein kinases (MEK and ERK), which results in increased proliferation of melanoma cells and oncogene activity [48]. Another remarkable pathway in melanoma development is mediated by MITF, which controls the transcription of multiple genes, and a number of signaling molecules including PKC, cAMP, MEK and Wnt/β-catenin. This transcription factor finally modifies multiple cellular processes including differentiation, proliferation, survival and motility [49].

Nuclear factor-kB (NF-kB) as a transcription factor can induce and modulate the expression of many genes that are engaged in the immune response. Recently, hyperactivity of NF-kB has reported in several cancers including melanoma. These findings show that overactivation of NF-kB may be caused by upstream dysregulated signaling pathways including PI3K/Akt/mTOR, NIK and Ras/Raf. All of them indicated the key function of NF-kB in tumorigenesis [50]. Under normal condition, the above-mentioned pathways regulate the basic cell functions such as cell cycle, survival and metabolism. In melanoma, genetic alterations and other factors lead to the constitutive activation of these pathways and loss of cellular homeostasis [51]. Moreover, some of these cascades such as Ras/Raf, PI3K/Akt/mTOR, Wnt/β-catenin and several others are implicated in the promotion of EMT by which melanocytes lose their epithelial characteristics and acquire mesenchymal phenotypes [52]. In addition, altered expression of miRNAs has been associated with the development of melanoma [53]. Diverse miRNAs can disrupt or facilitate many processes in melanoma carcinogenesis including cellular proliferation (miR-31, miR-375, miR-376c, miR-196b), apoptosis (miR-21, miR-15b, miR-182, miR-1246), tumor suppressor p53 signaling (miR-18b, miR-34a), invasion (miR-182, miR-211, miR-196a, miR-143-3p) and EMT (miR-205, miR-211) [53,54].

CircRNAs & cancer

There are many different circRNAs that are expressed in cancer tissues. Previously, through microarray analysis and RNA sequencing technologies, the abnormal expression of a wide variety of circRNAs in different kinds of carcinomas such as lung cancer [55], gastric cancer [56], osteosarcoma [57], hepatocellular carcinoma [58] and retinoblastoma [59] and several other types of tumors has been indicated. Due to identification of a large number of circRNAs associated with cancer, the clinical significance of circRNAs and their roles in cancer diagnosis setting and prognosis evaluation get more attention. Using miRNA-binding sites, many circRNAs show miRNA sponging features. MiRNA sponge prevents the regulatory effect of miRNAs on downstream target genes. This feature may either promote cancer progression or suppress tumorigenesis depending on the expression of miRNA targets [32,60]. For instance, CDR1-AS, one of the most studied circRNAs, which is also known as ciRS-7, sponges miR-7 and thus suppresses its activity [36,61]. MiR-7 is involved in various cancer-associated signaling cascades through downregulation of the expression of epidermal growth factor receptor (EGFR) and downstream protein kinases including ERK, Akt, STAT3 [62,63], mammalian target of rapamycin (mTOR) [64], Raf-1 proto-oncogene [65], cyclin-dependent kinase 1 (CDK1) [66], p21-activated kinase-1 (PAK1) [67] and focal adhesion kinase (FAK) [68] which are key oncogenic factors. In melanoma cells, it was found that miRNA-7 was downregulated and reestablishment of its expression could reverse drug resistance to BRAF inhibitors, markedly decrease the expressions of EGFR, insulin-like growth factor-1 receptor (IGF-1R) and CRAF and further suppress the activation of MAPK and PI3K/AKT pathway [69]. CircRNAs deriving from homeodomain-interacting protein kinase (HIPK) *loci* are another group of important circRNAs that modulate cellular proliferation and viability mainly by sponging multiple miRNAs specifically miRNA-124 [70]. Appropriate activity of miR-124 is implicated for the inhibition of cell invasion and cancer metastasis in lung adenocarcinoma [71], osteosarcoma [72] and breast cancer [73]. In addition, by sponging miRNAs, certain circRNAs promote the EMT signaling pathway that plays a key role in cancer progression and other adult pathologies through lowering of E-cadherin and increasing N-cadherin and vimentin [74]. Interaction between circRNAs and RNA-binding protein such as Quaking (QKI) protein, Argonaute (AGO) and Muscleblind (MBL) leading to the formation of RNA–protein complex is another mechanism by which some circRNAs can affect tumorigenesis process [75]. Moreover, several circRNAs can enhance the expression of their precursor genes that may suppress or promote cancer progression [76].

Roles of circRNAs in melanoma development & progression

Advances in RNA-sequencing techniques and bioinformatics tools have provided the possibility for discovery of various circRNAs and their roles in melanoma. One study identified 9300 different circRNAs in conjunctival

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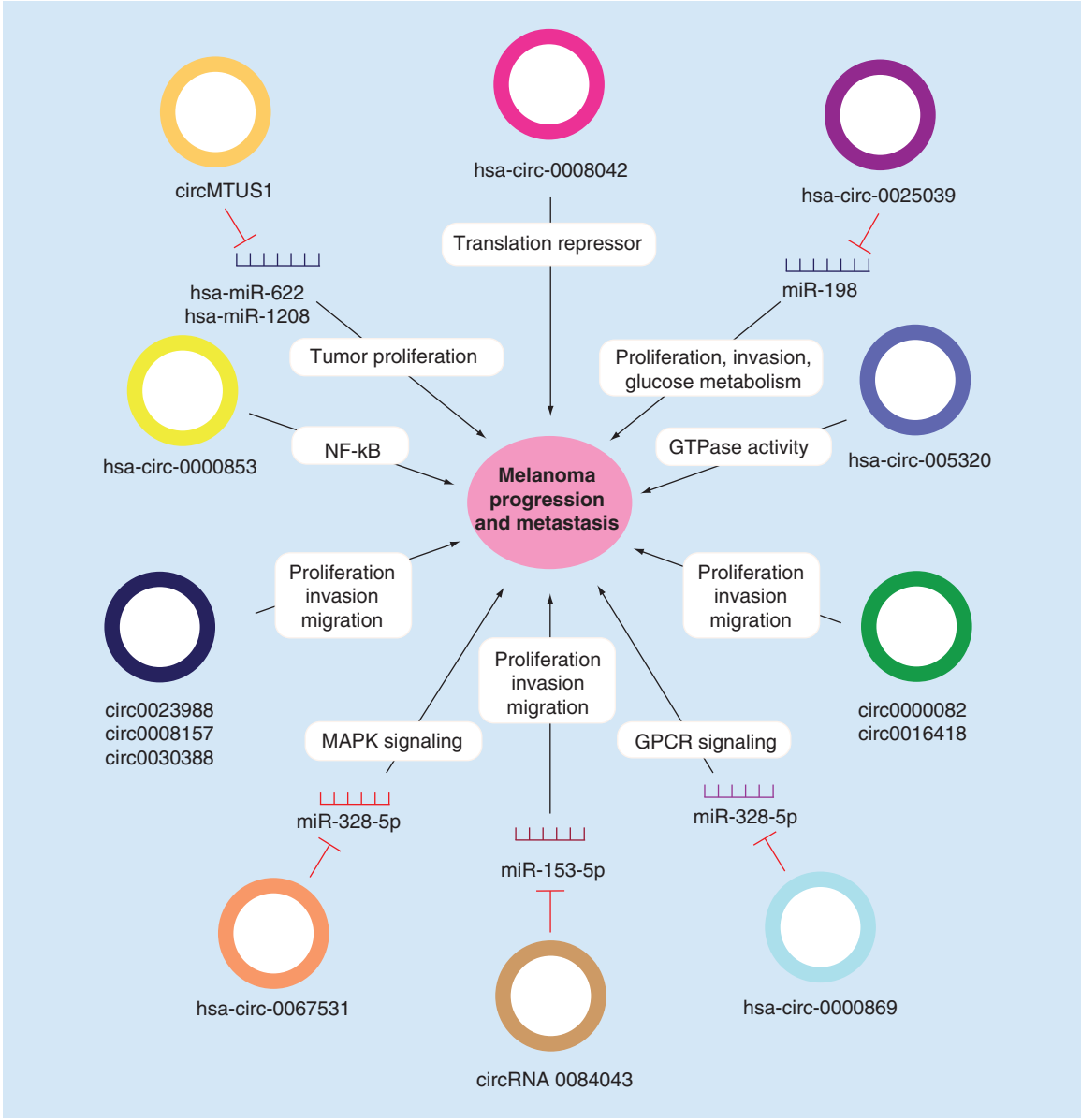

Figure 1. Various factors related to circular RNAs and their impact on the development of melanoma. The main suggested mechanism by which circRNAs involved in melanoma included miRNA sponging, which finally controls several key cellular processes and regulate tumor proliferation, invasion, migration and metabolism.
circRNA: Circular RNA; miRNA: MicroRNA.

melanoma tissues compared with adjacent normal tissues [77]. Bian *et al.* [78] reported that FOXM1 exons are able to produce the Circ_0025039. The upregulation of this circRNA is associated with some melanoma-related processes including inducing the cell growth, glucose metabolism and invasion via regulating CDK4 and sponging miR-198. In a melanoma xenograft model, silencing of this circRNA decreased the tumor volumes and weight. Additionally, increased miR-198 expression and decreased CDK4 were also observed in melanoma. Another upregulated circRNA is CircMTUS1, which may serve as an oncogene by binding to hsa-miR-622 and hsa-miR-1208 to regulate several tumor-related pathways, including those promotes cell proliferation in conjunctival melanoma. Recent findings showed that this circRNA might promote tumor progression through regulating MAPK pathway and Wnt/β-catenin cascade. Further investigation indicated that silencing of circMTUS1 suppressed melanoma proliferation *in vitro* and *in vivo* [77]. In addition, it was demonstrated that in oral mucosal melanoma, hsa_circ_0005320, hsa_circ_0067531 and hsa_circ_0008042 were significantly upregulated in primary tumor and metastatic lymph

Table 1. List of circular RNAs that are involved in the melanoma.

CircRNA	Type of melanoma	Expression change	Function	Possible mechanism	Ref.
circMTUS1	Conjunctival melanoma tissues and cell lines	Up	Promote tumor proliferation	Sponging hsa-miR-622 and hsa-miR-1208	[77]
hsa_circ_0025039	Malignant melanoma tissues and cell lines	Up	Promote cell proliferation, colony formation ability, and invasion and glucose metabolism.	Sponging miR-198 regulation of CDK4 expression	[78]
hsa_circ_0005320	Oral mucosal melanoma tissues	Up	GTPase activity, GTP binding, septin complex.	Targeting a series of miRNA (predicted by bioinformatics databases)	[79]
hsa_circ_0067531	Oral mucosal melanoma tissues	Up	Activation of MAPK activity, ATP binding	Targeting miR-328-5p (predicted by bioinformatics databases)	[79]
hsa_circ_0008042	Oral mucosal melanoma tissues	Up	Translation repressor activity	–	[79]
hsa_circ_0000869	Oral mucosal melanoma tissues	Down	Regulation of G-protein coupled receptor protein signaling pathway	Targeting miR-328-5p (predicted by bioinformatics databases)	[79]
hsa_circ_0000853	Oral mucosal melanoma	Down	NF-kB signaling pathway	–	[79]
circRNA_0084043	Malignant melanoma tissues and cell lines	Up	Cell proliferation, invasion and migration	Sponging miR-153-3p and upregulating Snail expression	[81]
circ0000082 and circ0016418	Low- and high-metastatic melanoma cell line: WM35, WM451	Up	Proliferation and invasion of the WM451	Targeting a series of miRNA (predicted by bioinformatics databases)	[80]
circ0023988, circ0008157 and circ0030388	Low- and-high metastatic melanoma cell line: WM35, WM451	Down	Proliferation and invasion of the WM35 cells	Targeting a series of miRNA (predicted by bioinformatics databases)	[80]

The roles of circRNAs in the cellular processes. CircRNAs are able to regulate tumor proliferation, invasion, migration and metabolism that are involved in melanoma pathogenesis.
CircRNA: Circular RNA.

nodes compared with paired adjacent normal tissues and nonmetastatic lymph nodes, whereas the expression of hsa_circ_0000869 and hsa_circ_0000853 were downregulated relatively. Gene Ontology and pathway analyses indicated that these identified circRNAs might play important roles in protein modification, protein binding and cellular metabolism in this cancer [79]. Circ0000082 and circ0016418 overexpressed in high- and low-metastatic cell lines of melanoma. In addition, a downregulation of circ0023988, circ0008157 and circ0030388 was also detected. Recent evidence revealed that knockdown of circ0023988, circ0008157 or circ0030388 remarkably increased the WM35 cell's propagation and invasion. Besides, the invasion and proliferation was inhibited by silencing the circ0016418 and circ0000082 in WM451 cells [80]. Moreover, it is has been reported that circRNA_0084043 remarkably overexpressed in melanoma and may play a sponge role for miR-153-3p for Snail upregulation, thereby, raised the invasion, propagation and migration of melanoma. Knocking down the circRNA_0084043 notably reduced the tumor growth between day 12 and day 21 in the melanoma xenograft model compared with the control group.

Also, expression of MMP2 (invasion markers), Ki-67 (proliferation-related) and Snail protein was reduced, while E-cadherin (a marker related to epithelial cells) was increased in circRNA_0084043 silent group [81]. The above-mentioned studies suggested that circRNAs might exert important carcinogenic roles in melanoma.

Prognostic value of circRNAs in melanoma

Several factors including increased thickness, ulceration and mitotic rate are strong independent predictors of survival in patients with stage I/II melanoma [82]. Diver molecular markers have been recently examined for their prognostic values in melanoma. Although a small number of studies have investigated the relationship between circRNAs and clinical pathological characteristics of melanoma, important findings have been obtained. Hsa_circ_0025039 is a circRNA, which its expression strongly associated with the pathological node status, metastasis and various clinical stages. Furthermore, melanoma subjects with hsa_circ_0025039 overexpression showed smaller survival

time comparing those with underexpressed has_circ_0025039. This data show that overexpression of this circRNA is associated with a poor prognosis [78]. Another important circRNA in this regard is circRNA_0084043. Evidence indicated high expression of this molecule in malignant melanoma patients. The expression of circRNA_0084043 is strongly related to various pathological stages including clinical stage of the disease, while it is not associated with others, for example, age, family history, sex and ulcer. The upregulation of this molecule could be related to poorer survival. Moreover, various analysis revealed that upregulation of circRNA_0084043 is an independent risk factor of overall survival for melanoma patients [81]. These findings proposed that along with other factors, circRNAs could be an important factor in determining the survival of patients with melanoma.

Conclusion

Evidence indicated that the expression of circRNAs altered during melanoma development, which suggests that circRNAs could play profound roles in this cancer. Some studies proposed various mechanisms for circRNA function in melanoma (Figure 1 & Table 1). The main suggested mechanism by which circRNAs involved in melanoma included miRNA sponging, which finally controls several key cellular processes and regulate tumor proliferation, invasion, migration and metabolism. Collectively, this evidence highlights the importance of circRNAs as new tools in biomedical applications for management of melanoma.

Future perspective

Nowadays, there is an essential need to identify novel biomarkers with superior diagnostic and prognostic performance compared with traditional parameters for management of different cancers specially melanoma. Given the abundance of circRNAs, their high stability and tissue-specific expression patterns, these molecules potentially can be used as promising biomarkers in the future. Certain circRNAs also represent to be associated with clinical pathological characteristics of melanoma. However, more efforts are warranted to elucidate the exact functions of circRNAs and their mechanism of action in melanoma.

Executive summary

- Melanoma is a prevalent disease with increasing incidence that is associated with various health public problems across the world.
- A variety of genetics and epigenetic mechanisms are involved in melanoma pathogenesis.
- Circular RNAs are epigenetic signals which could influence the spread, invasiveness and chemoresistance of melanoma cells.
- Various studies indicated that circular RNAs could be used as prognostic, diagnostic and therapeutic biomarkers in the treatment of melanoma.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Availability of data & material

The primary data for this study is available from the authors on direct request.

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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