Molecular Biology Reports (2020) 47:9913–9920
https://doi.org/10.1007/s11033-020-05949-8

REVIEW

MiR-196: emerging of a new potential therapeutic target and biomarker in colorectal cancer

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Received: 12 July 2020 / Accepted: 23 October 2020 / Published online: 1 November 2020

Abstract

Deregulation of microRNAs, as key elements in colorectal cancer (CRC) pathogenesis, is correlated with various stages of this cancer. miR-196 is involved in the initiation and progression of a verity of malignances, especially CRC. miR-196 in CRC cells could target different types of genes with oncogenic and/or tumor suppressor function such as HOX genes, GATA6, SOCS1, SOCS3, ANXA1, DFFA, PDCD4, ZG16 and ING5. Therefore, these genes could be up or down-regulated in cells and subsequently change the capacity of CRC cells in terms of tumor development, progression and, response to therapy. Comprehension of miR-196-associated aberrations underlying the CRC pathogenesis might introduce promising targets for therapy. Additionally, it seems that miR-196 expression profiling, especially circulatory exosomal miR-196, might be useful for diagnosis and prognosis determination of the CRC patients. In this review, at first, we summarize the roles of miR-196 in different types of cancers. After that, a detailed discussion about this miRNA and also their targets in CRC pathogenesis, progression, and response to treatment are represented. Moreover, we highlight the potential utilization of miR-196 and its targets as therapeutic targets and novel biomarkers in early detection and prediction of prognosis in CRC patients.

Keywords Colorectal cancer (CRC) · MicroRNA-196 · Therapy · Biomarker

Introduction

Colorectal cancer (CRC) is the third and the second most commonly occurring cancer in men and women, respectively. It is estimated that in 2018 more than 1.8 million new CRC cases and about 881,000 deaths have occurred [1]. In spite of many advances in treatment, CRC, among different types of cancers, is still in second place in terms of mortality; also, the 5-year survival rate of CRC is about 12.5%, especially in the last stages [2, 3]. Because CRC is often a silent disease, many people do not have complaints until the disease reaches end stages; while, early detection might cause 5-year survival to reach greater than 90% [2, 3]. About 90% of patients with metastatic cancer represent resistance to therapy; therefore, detection of disease in early stages and finding new targets for CRC therapy can play a pivotal role in improving the outcome of patients [4]. In all, identifying novel diagnostic, prognostic, and therapeutic biomarkers opens new landscapes in CRC management. Amongst various biomarkers, microRNAs (miRNAs) have emerged as a new potential type of cancer-specific biomarkers in CRC [5, 6]. The miRNAs constitute a novel class of small non-coding single strand regulatory RNAs (about 18–22 nucleotides long) that play important roles in different aspects of cellular biology such as cell differentiation, proliferation, cell cycle progression, migration, inflammation, apoptosis, and tissue homeostasis. These molecules

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play central roles in posttranscriptional gene modulation by binding to the 3′-untranslated regions (3′-UTR) of specific mRNAs, which subsequently results in cleavage or translational repression of mRNAs [7, 8]. The aberrant expression level of miRNAs is reported in several different diseases such as malignancies; mechanistically, these tiny molecules are involved in the pathogenesis of cancers [9, 10]. According to a preponderance of evidence these regulatory genes, based on the nature of their targets in cells, are categorized to oncogene miRNAs (OncomiRs) and/or tumor-suppressor miRNAs (TS-miRNAs) in cancer cells [11, 12]. Numerous reports have shown that the expression of specific miRNAs is upregulated or downregulated in CRC compared to their normal counterparts, suggesting that miRNAs can contribute to oncogenesis, tumor development and progression [13, 14]. The specific pattern of dysregulated miRNAs expression may be utilized as a biomarker in CRC management because these molecules are stable in tumor tissue and body fluids [5]. Nowadays, several studies reported that cell-free miRNAs (known as circulating miRNAs) have been found in various body fluids of CRC patients which could be considered not only as diagnostic and prognostic biomarkers but also some of these miRNAs introduce promising targets for cancer therapy [15, 16]. Aberrant expression of miR-196 and the contribution of this regulatory RNA in the progression of malignancies especially CRC has unraveled in various tumors [17, 18]. mir-196 family encompasses 3 genes in different location including miR-196a1 (on chromosome 17), miR-196a2 (on chromosome 12) and miR-196b (on chromosome 7). Mature forms of miR-196a1 and 2 are the same but they have one nucleotide difference with miR-196b [18]. These miRNAs family located between HOX gene clusters. HOX genes encode conserved homeodomain transcription factors that are implicated in stem cell differentiation, organization of the human body plan during embryogenesis, and also in oncogenesis [19, 20]. By considering the different target genes, miR-196 manifests different functions in different cancers i.e. oncogenic or tumor suppressor function. In this review, at first, we summarized the roles of miR-196 in different types of cancers. Then, a detailed discussion about this miRNA including their targets in CRC pathogenesis is illustrated and, finally, miR-196 and their target genes as putative diagnostic, prognostic, and therapeutic targets in CRC patients were highlighted.

miR-196 in cancer

Numerous works have reported that dysregulation of the miR-196 family in several types of malignancies is associated with carcinogenesis; that is, this event is involved in tumor development, progression, and clinicopathological status [18, 21, 22]. A bulk of the currently available evidence has unveiled that the miR-196 has an oncogenic role and is upregulated in cancers such as head and neck squamous cell carcinoma, HNSCC [23], oral [24], gastric [25, 26], pancreatic [27], ovarian [28], cervical [29, 30], osteosarcoma [31], non-small-cell lung carcinoma, NSCLC [32], glioblastoma [33], hepatocellular carcinoma, HCC [34], and esophageal [35]. On the other hand, some of the experiments have pointed out the tumor suppressor function of this miRNA and downregulation of that in cancers such as melanoma [36], breast [37], B-cell lineage acute lymphoblastic leukemia [38], chronic myeloid leukemogenesis [39], glioblastoma [40], and cervical cancer [41]. Overexpression of miR-196 could promote cell proliferation and invasion, lymph node metastasis, and resistance to therapy (radio or chemo-therapy) and also suppressed apoptosis by targeting important genes in different types of cancers [18, 22]. In Table 1, we summarized miR-196 alteration and its experimentally verified target genes in different types of cancers. After that, we presented some functional studies that provided insight into the role of miR-196 and their target genes in the pathogenesis of different types of cancers and subsequently their applications in cancer management.

In HCC cells, upregulation of miR-196 led to induction of cell migration, invasion and tumor cell growth through directly targeting of FOXP2, and FOXO1 genes [34]. This miRNA could stimulate cell proliferation and invasion by suppressing CDKN1B, FOXO1, and NTN4 in cervical cancer [30] and CDKN1B, FOXO1, and HOXA9 in NSCLC [42]. Study in human glioma stem cells (GSCs) revealed that upregulation of FOXO1, a target of miR-196a, upregulates expression of PID1, thereby inhibiting GSC tumorigenicity and growth. Consistently, via upregulation of MIIP, miR-196a causes inhibition of migration and invasion activities in GSCs [43].

According to several pieces of evidence, the ANXA1 gene may have tumor suppressor or oncogenic function depending on the particular type of cancer [44]. Downregulation of ANXA1 by miR-196 in head and neck, pancreatic, esophageal cancer, and osteosarcoma is correlated with tumor progression and enhancing of radioresistance [45, 46]. In considering the interaction between long noncoding RNA (lncRNA) growth arrest-specific 5 (GAS5) and miR-196, downregulation of this lncRNA and consequently increased tumor progression has indicated in several types of cancers; on the other hand, restoring expression of this gene inhibited tumor growth, migration, and invasion. Wang et al. demonstrated that miR-196a could suppress the expression of GAS5 in esophageal cancer [47]; in contrast, concerning glioma [43], ovarian [28], and cervical cancer [48], investigators acquired vice versa results i.e. miR-196 can be downregulated by GAS5. Zhao and coworkers with work on ovarian cell lines introduced a new approach in ovarian cancer treatment; they revealed that ectopic expression of GAS5

Table 1 mir-196 alteration and its experimentally verified targets in different types of cancers

Cancer type	Alteration of miR-196	Target gene	Sample size	References
Head and neck cancer	Up regulation	ANXA1 and HOX family, MAMDC2 , CDKN1B and ING5	16, 80	[23, 82]
Laryngeal cancer	Up regulation	SOCS2, CDKN1B	113, 20	[83, 84]
Oral cancer	Up regulation	HOXB8, CDKN1B, NME4	36, 39	[85, 86]
Gastric cancer	Up regulation	CDKN1B, RDX	36, 109	[87, 88]
	Down regulation	RAD23B	–	[89]
Pancreatic cancer	Up regulation	NFKBIA, CADM1, ANXA1	–, 20	[90, 91]
Esophageal cancer	Up regulation	GAS5, ANXA1	86, 46	[47, 92]
HCC	Up regulation	FOXP2, FOXO1	84, –	[34, 93]
Ovarian cancer	Up regulation	HOXA9, HOXA5	195, 10	[28, 50]
Cervical cancer	Up regulation	NTN4, FOXO1, CDKN1B, HOXC8	92, 45	[94, 95]
	Down regulation	HOXB7	–	[41]
NSCLC	Up regulation	GATA6, FOXO1, CDKN1B, HOXA9, HOXA5	40, 34	[32, 49]
Glioma	Up regulation	FOXO1	50	[43]
Glioblastoma	Up regulation	IκBα, ZMYND11	132, 20	[96, 97]
Melanoma	Down regulation	HOXB7, HOXC8	–, 8	[36, 53]
Osteosarcoma	Down regulation	ANXA1, SNHG3, HOXC8	32, 127	[46, 58]
Breast cancer	Up regulation	HOXC8	25	[37]

HCC hepatocellular carcinoma, *NSCLC* non-small-cell lung carcinoma

repressed ovarian cancer development via directly targeting of miR-196a and consequently upregulated the HOXA5 expression and finally reduced tumorigenicity [28]. Similarly, miR-196a could induce cell proliferation and metastasis by HOXA5 regulation in NSCLC [49].

Other lines of evidence also have shown the interaction between miR-196 and HOX gene family cluster including HOXA9 and HOXA10. A particular study unraveled that negative regulation of HOXA9 by miR-196b contribute to invasion activities in recurrent epithelial ovarian cancer (EOC), while upregulation of HOXA10, which has a positive correlation with miR-196a, is closely associated with the incidence of ovarian cancer [50, 51]. In lines, a positive correlation between expressions of HOXB9 and miR-196a exists in HNSCC [52]. Also, in their study pinpointed that knock-down of both HOXB9 and miR-196a inhibits cell migration and invasion, adhesion to fibronectin (only in miR-196a knock-down), and proliferation (only in HOXB9 knock-down) [52]. Experimenters documented that in cervical cancer [41] and melanoma [36], on the one hand, the HOXB7 gene is overexpressed and has a negative correlation with miR-196, whilst on the other hand, HOXC8, another target of miR-196, is respectively downregulated and upregulated in cervical cancer [41] and malignant melanoma [53]. All in all, these findings manifest the oncogenic function of miR-196 in cervical cancer and tumor suppressor function in melanoma tumors.

The results of previous studies inform us that circulating miR-196 could be utilized as a diagnostic and prognostic biomarker in different types of cancers. For instance, higher levels of circulating (plasma) miR-196 in patients with precancerous lesions/early gastric adenocarcinoma than that healthy controls was associated with metastatic or progression of the disease and bad outcome [54]. Regarding the serum as the sample, the combination of miR-196b/LCN2/TIMP1 might be a promising biomarker set for the recognition of high-grade pancreatic ductal adenocarcinoma (PDAC) precursor lesions in individuals at risk of familial pancreatic cancer, FPC [55]. According to the Liu et al. study on serum samples of patients with pancreatic cancer, miR-16 and miR196a in combination with CA199 would increase the detection rate of disease (85.2%) in early-stage (stage I) [56]. Overexpression of miR-196a in the serum of patients with cervical intraepithelial neoplasia (CIN) is associated with CIN grade and progression [57]. The findings of other experiments mirrored that overexpression of miR-196a/b in serum has an association with decreased overall survival, short-disease free survival, and tumor aggressiveness of osteosarcoma patients [58].

miR-196 as a therapeutic target in CRC

Convergent lines of evidence has uncovered that miR-196 in CRC cells could target different types of genes with oncogenic and/or tumor suppressor function, therefore these genes could be up or down-regulated in cells and ultimately could change the capacity of CRC cells in tumor

development, progression and response to treatment (Fig. 1). Conceivably, understanding these aberrations might lead toward the identification of a promising target for CRC therapy.

Prominent body of evidence has unveiled that upregulation of miR-196 in CRC is associated with tumor development and progression. Contrarily, Stiegelbauer et al. claimed that miR-196b suppression results in a considerable increased CRC cell migration, invasion and, metastases formation in mice model; also, this suppression was remarkably related with metastases and poor outcomes in 2 independent CRC patient cohorts. Additionally, the result of this experiment showed a negative correlation between miR-196b and HOXB7 [59]. HOXB7 is involved in migration, invasion, and metastasis of tumor cells and also poor prognosis in patients with a verity of different types of carcinomas such as breast, pancreatic, cervical, and gastric [60, 61]. In the same vein, Liao and collaborators signified that HOXB7 upregulation in CRC is associated with poor prognosis and enhancement of cell proliferation, tumorigenesis, and G0–G1 to S-phase transition in CRC cell lines [62]. On the contrary, Stiegelbauer et al. reported that ectopic overexpression of miR-196b gives rise to the opposite results on the HOXB7 expression, cell migration, and invasion capability, which provide us a new target for CRC treatment [59]. The level of HOXB8, reported by Shen et al., is extremely transcripted in normal circumstances but is lowered in the CRC tissues because of a negative association with miR-196 [63]. Relatedly, there is a negative correlation between level of miR-196a and some of HOX genes (HOXA7, HOXB8, HOXC8, and HOXD8) [64]. Intriguingly, both oncogenic and tumor suppressor tasks have been attributed to HOX genes in CRC. By way of example, overexpression of HOXB8 increases epithelial-to-mesenchymal transition (EMT) by activating STAT3, reflecting the oncogenic function of HOXB8. In this sense, expression restoration of HOXB8 suppresses cell proliferation, invasion, and metastatic ability [65]. Reportedly, HOXC8 and HOXD8 genes exert their tumor suppressor function in CRC by improving cellular adhesion and significantly reducing cell growth, migration, anchorage-independent growth, and colony formation [66–68].

Of note, Fantini and colleagues stated that the upregulation of miR-196b in CRC samples is associated with less severe clinicopathological characteristics; evidently, this finding emanated from the fact that GATA6 is directly suppressed by miR-196b. Overexpression of GATA6, a transcription factor responsible for positive regulation of the Wnt/β-catenin pathway, in CRC is correlated with worse prognosis such as liver metastasis and poor overall survival. Therefore, they suggested that the ectopic expression of miR-196b as an antagonist of GATA6 could be a therapeutic strategy in CRC treatment [69].

Ren et al. for the first time indicated recurrent miR-196b gene amplification in more than 57% of CRC tissue samples; concordantly, expression of this miRNA was

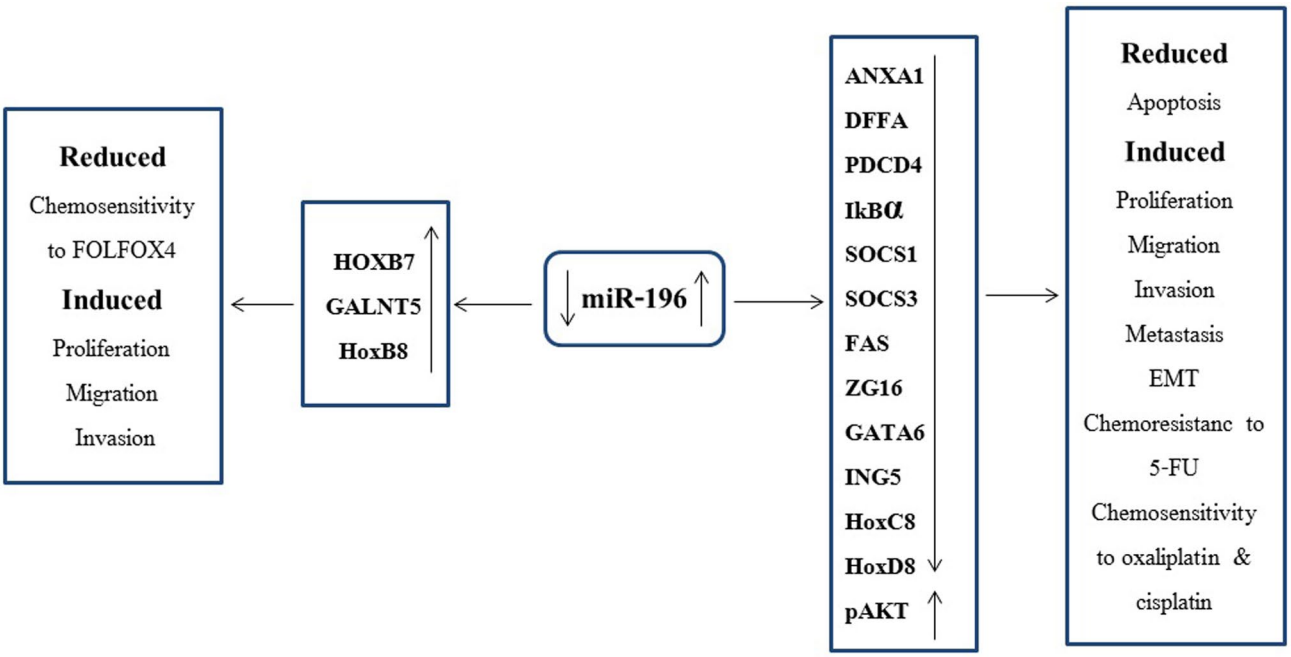

Fig. 1 Aberrant expression of miR-196 in CRC cells could lead to dysregulation of several target genes and subsequently change tumor development and progression

intensely higher in tissues with amplification compared with those without gene amplification. Further to this, they reached the conclusion that overexpression of miR-196b creates chemoresistance of CRC cells to 5-fluorouracil (5-FU) and promotes stemness via increasing spheroids formation ability and stem cell factors expression. In-depth analysis displayed that inhibition of SOCS1 and SOCS3 (negative regulators of STAT3 signaling pathway) via miR-196b is the underlying mechanism of these outcomes. In this way, they ascertained that restoring the expression of miR-196b could suppress chemotherapeutic resistance and cancer stem cell properties [70]. These results about the association between miR-196b overexpression and increased resistance to 5-FU were approved by Che et al. [71]. However, the finding obtained by Schimanski et al. was at odds with previously-mentioned studies in terms of the effect of miR-196 on response to chemotherapy. In detail, in this study, overexpression of this miRNA in CRC cells was associated with increased sensitivity to platin derivatives such as oxaliplatin and cisplatin; although, there was not any significant association between miR-196a and response to 5-FU and irinotecan. Besides, they concluded that overexpression of miR-196a increases the pro-migratory phenotype by activation of the PI3K-AKT-mTOR pathway through increasing phosphorylation of AKT [64].

Dysregulation of apoptosis-related genes namely ANXA1, DFFA, PDCD4, and FAS as one class of miR-196 targets is involved in oncogenesis and cancer progression of CRC cells [72, 73]. Fawzy et al. exhibited that overexpression of miR-196a increased tumor cell proliferation and metastasis by targeting ANXA1, DFFA, and PDCD4 [73]. Mo et al. proved that miR-196b by targeting of the FAS gene could repress apoptosis; inferably, administration of anti-miR-196b transfection to CRC cell lines (SW480 and HT29) might increase cell apoptosis and augment 5-FU-induced apoptosis in HT29 cell line [72]. These results substantiate that exploitation of anti-miR-196b could be a potential therapeutic strategy for CRC treatment. A study applied on CRC cell lines (SW620 and HCT116) demonstrated that miR-196a could directly target IκBα gene, therefor highlight miR-196a knockdown as a therapeutic approach because inhibits cell proliferation, migration, invasion, and metastasis by repression of NF-κB pathway and eventually increases CDH1 (E-cadherin) and inhibits of CDH2 (N-cadherin) and FN1 (fibronectin) [74].

A significant decreation of ZG16 in CRC is associated with poor prognosis. The expression of this gene reversely associated with the expression of LGR5, a CRC stem cell marker that is upregulated in CRC tissues. Chen et al. displayed that downregulation of ZG16 increases cell growth and stemness of CRC cells; in turn, this gene is regulated by miR-196a which is upregulated in CRC cells [75]. Hence, the upregulation of ZG16 via suppression of miR-196a might provide a hopeful therapeutic approach for CRC.

In accordance with previous studies, Xin et al. showed that the downregulation of ING5 is correlated with CRC progression by means of upregulation of some important CRC-related proteins such as p-PI3K, p-Akt, and p-MEK. They also indicated that ING5 might directly be targeted by miR-196b; thus, downregulation of this miRNA and consequently upregulation of ING5 as a therapeutic approach could decrease tumor progression and expression of some proteins which have an oncogenic function [76].

miR-196 as a biomarker in CRC

Overwhelming evidence has revealed that miR-196 might be a promising biomarker in early detection and prediction of prognosis in CRC patients. Exosomes and particularly exosomal miRNAs are active participants in CRC carcinogenesis and progression. Two independent studies on serum exosomes demonstrated that miR-196b is upregulated in CRC patients and associated with liver metastases [77, 78]. Wu et al. disclosed that expression of miR-196b was significantly higher in metachronous liver metastases (MLM) compared with synchronous liver metastases (SLM) and non-liver metastases (NLM). High level of exosome-delivered miR-196b was positively related to the elevated levels of CA199 and CEA in CRC patients with MLM; in addition, these patients have shorter overall survival. Moreover, in these groups (MLM, SLM, and NLM), receiver operating characteristic (ROC) analysis underscored that area under the curve (AUC) of exosomal miR-196b-5p was higher than AUC of CEA and CA199 [77].

Xu and colleagues unveiled that circulatory miR-196b in the serum sample of patients with CRC was considerably higher, suggesting a specificity and sensitivity of 63 and 87.38%, respectively for CRC detection capability of this miRNA [79]. Some experiments also reported that patients with a high level of miR-196b compared with low levels of this miRNA have shorter overall survival and disease-free survival [79, 80]. Further, the higher level of miR-196b in certain studies was correlated with some clinicopathological features such as lymph node invasion and metastasis, advanced TNM stage, distant metastasis, site of origin of the primary tumor, and poor differentiation grade; nevertheless, this overexpression was not associated with some factors such as tumor size, gross type, depth of invasion, age and gender [63, 71, 79, 80].

Regarding ANXA1 (an apoptosis-related gene) as a target of miR-196a, Fawzy et al. uncovered that miR-196a overexpression and consequently downregulation of ANXA1 are correlated with worse prognosis including poor differentiation, increasing tumor size, and advanced

clinical stage [73]. Shen and collaborators illustrated that a high level of miR-196 and consequently suppressed expression of HOXB8, as one bona fide target of this miRNA, augments the sensitivity of CRC cells to FOLFOX4, mirroring miR-196 and HOXB8 could be utilized to predict sensitivity to chemotherapy with FOLFOX4 in CRC patients [63].

By sharp contrast, Stiegelbauer and coworkers came to the conclusion that inhibited expression of miR-196b is remarkably correlated with poor prognosis including high tumor grade, advanced clinical stage, distant metastasis, and shorter overall survival [59].

Shindo and colleagues ascertained that a panel of 3 miRNAs (miR-196b-5p, miR-378a-3p, and miR-486-5p) could possibly predict the efficacy of vaccine treatment in subjects with colorectal cancer to determine who have a better outcome following vaccination [81].

Conclusions

Concerning the high incidence and mortality rate of CRC, early detection, and treatment can remarkably reduce CRC fatality. Hence, identification of new biomarkers for diagnoses and prognoses and also therapeutic targets could help to the improvement of the outcome and management of patients with CRC. The dysregulation of miRNAs, as one of the key actors in CRC pathogenesis, is correlated with various stages of CRC. Abnormal expression of miR-196 is described in several malignant tumors; particularly, dysregulation of miR-196 is involved in the development and progression of CRC. Researchers discovered that miR-196 in CRC cells could target different types of genes with oncogenic and/or tumor suppressor function, therefore these genes could be dysregulated in cells and ultimately change tumor development, progression, and response to therapies. Conceivably, recognition of the miR-196 mechanism in CRC pathogenesis could render promising targets for cancer therapy. Additionally, it seems that the dysregulation of miR-196 might be useful as a diagnostic and prognostic biomarker in CRC patients.

Acknowledgements None.

Author contributions All authors were involved in whole work.

Funding No funding received.

Compliance with ethical standards

Conflict of interest The authors declare that they have has no conflict of interest.

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