

The mechanism of non-coding RNAs in medulloblastoma (Review)

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Abstract. Medulloblastoma (MB) is one of the most common malignant tumors of the central nervous system in children. Although surgery, radiotherapy and chemotherapy have resulted in considerable progress in the treatment of this disease, the prognosis of patients with MB remains very poor. Therefore, highly specific molecular targeted treatment, which can improve the therapeutic efficacy and reduce the side effects of MB, has become a research hotspot. In recent years, non-coding RNAs (ncRNAs), which were initially considered to be transcriptional noise, have been shown to possess regulatory functions. A series of ncRNAs have been identified, including microRNAs and circular RNAs, which affect the expression of specific genes in a variety of tumors. These genes lead to the formation of a specific complex of proteins or they directly participate in protein synthesis in order to regulate the occurrence and development of tumors. The aim of the present review article was to summarize the recent research studies that have explored the ability of ncRNAs to regulate the occurrence and development of MB.

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1. Introduction

Medulloblastoma (MB) is a malignant tumor, which exhibits the highest incidence and mortality amongst central nervous

system tumors (1). This disease predominately affects children. According to the 2016 World Health Organization's redefined classification of central nervous system tumors, MB is divided into four types as follows: Wnt-activated MB, Sonic hedgehog (SHH)-activated MB, group-3 MB and group-4 MB (2), of which, the latter two are the most common types. The prognosis of different subtypes varies considerably. The 5-year overall survival (OS) rate of Wnt-activated MB can reach 95%, whereas group-3 exhibits the worst prognosis (45-60%), and group-4 and SHH-activated MB have an intermediate OS (75-80%) (3,4). Since MB is commonly located in the cerebellum, the main symptoms and signs are caused by intracranial hypertension and hydrocephaly, which may be secondary to direct tumor compression or obstruction of cerebrospinal fluid circulation (5). At present, the treatment of MB is primarily based on surgery, radiotherapy and chemotherapy. Although MB is sensitive to radiotherapy and chemotherapy, excessive treatment usually gives rise to serious secondary side effects such as infection, peripheral neuropathy, ototoxicity and myelosuppression in children, who are typically in the developmental stage (6,7). Tumor cells can spread to the spinal cord along the cerebrospinal fluid circulation pathway and ~30% of patients will develop early tumor spread (8). Concomitantly, since MB exhibits a high degree of malignancy, it commonly relapses after surgery. The efficacy of traditional treatment remains poor. Therefore, the investigation of the molecular mechanism responsible for MB development and the identification of novel therapeutic targets are crucial for the treatment and prevention of this disease.

Approximately 80% of the genes found in the human genome possess transcriptional activity, whereas only 2% of the RNA produced by transcription encodes proteins (9,10). The remaining RNA that does not encode proteins is referred to as non-coding RNA (ncRNA) (9,10). Based on their functions, ncRNA molecules are divided into housekeeping RNAs and regulatory RNAs (11). According to the length of the gene, they are divided into short ncRNAs (sncRNAs) and long ncRNAs (lncRNAs). By using 200 nt as the cut-off, sncRNAs may be further subdivided into PIWI-interacting RNAs (piRNA), small nuclear RNAs (snRNA), small nucleolar RNAs (snoRNA) and microRNAs (miRs/miRNAs). Similarly, lncRNAs can be divided into long intergenic non-coding RNAs, natural antisense transcripts, enhancer RNAs (eRNAs), partially unparallelled lncRNAs and circular RNAs (circRNAs), which possess specific structural motifs (Fig. 1) (12,13). At

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present, the involvement of ncRNAs in tumor cell regulation remains unclear. However, numerous studies have investigated various applications based on their functions. For example, miRNAs regulate the stability of transcripts in order to silence genes at the post-transcriptional level (14). circRNAs can be used as miR molecular sponges that participate in adjustment of cell biological function by affecting the functions of miRNAs (15). eRNAs and binding transcription factors form complexes to promote interactions between gene enhancers and promoters (16). In recent years, certain studies have provided significant evidence on the structure and function of ncRNAs. It has been demonstrated that some short ncRNAs, including circRNA, can not only regulate cell function through the aforementioned pathways, but also directly encode various regulatory proteins (17-19). Mounting evidence has shown that ncRNAs can regulate the growth of central nervous system malignant tumors, including gliomas (11,20,21). In addition, it has been shown that the expression levels of various ncRNAs are significantly different between MB and normal cerebellar cells (22). Therefore, it was hypothesized that deregulated expression of ncRNAs may serve as a marker and/or therapeutic target for MB. Currently, research in this field focuses on the mechanisms of miRNAs has revealed the functions of a large number of miRNAs. However, there are relatively fewer studies on the mechanisms of circRNA and other ncRNAs, which are equally important. This article focuses on the research progress of the role of ncRNAs in MB. In addition, this paper also reviews some of the studies that are expected to be translated into clinical therapeutic and diagnostic targets. The aim of the present article was to review the above content to show the potential of ncRNA in the clinical application of MB.

2. miRNAs in MB

miRNAs belong to the ncRNA family, which usually includes classes of RNA molecules of 18-25 nucleotides in length. These motifs are highly conserved across different species (11). miRNAs were initially identified in *Caenorhabditis elegans* in 1993 (23). Since then, research on this topic has been gaining increasing popularity, with a wealth of studies assessing the roles of numerous miRNAs in almost all types of diseases. The current point of view suggests that the main function of miRNAs is to form RNA-induced silencing complexes (RISCs), which include the Argonaute family protein in the cytoplasm (14). RISCs act on the downstream encoding RNAs or ncRNAs to affect cell metabolism at the post-transcriptional level (Fig. 2) (14). It has been shown that the expression levels of specific miRNAs differ on the type and stage of the tumor (24-26). The specific expression patterns of miRNAs determines the development of tumors. Therefore, miRNAs have a wide range of applications for early diagnosis, targeted treatment and prognostic assessment of the tumors.

The analysis of the miRNA expression levels in tissues derived from normal cerebellum and MB has shown similarities with regard to deregulated miRNA expression between MB and other malignancies (22). The first report that examined the expression of specific miRNAs in MB was performed in 2008 by Pierson *et al* (27), in which miR-124 expression was predicted to participate in the regulation of the

MB prognostic marker cyclin-dependent kinase 6 (CDK6). Subsequent experiments confirmed that miR-124 expression was decreased in MB and that it affected the expression levels of CKD6 in tumor cells (27). Ferretti *et al* (28) compared the expression levels of specific miRNAs in normal brain and MB tissues. It was found that miR-18a, miR-19a, miR-21 and miR-25 expression levels in MB were significantly higher than those in normal brain tissues. Concomitantly, the expression levels of the majority of miRNAs, such as miR-9 and miR-125a, were downregulated in tumor samples. These downregulated miRNAs may possess tumor suppressive functions (28). The same is true for cancer and neural stem cells (29). miRNA microarray data analysis from the Gene Expression Omnibus database demonstrated that the expression levels of 22 miRNAs were upregulated in MB, and 26 miRNAs were downregulated (30). It has also been shown that the expression levels of certain miRNAs in MB do not differ from those in normal cerebellum cells. Differential expression of miRNAs has been used as an identification marker of MB molecular subtypes. For example, it was shown that miR-148a expression was specifically enriched in the Wnt-activated MB subtype (31). High expression of the miR-17-92 cluster was observed in SHH-activated MB (32). Zhu *et al* (33) demonstrated that the expression levels of miR-181a-5p and miR-125b-5p were increased in group-3 MB. However, 12 miRNAs, including miR-18a, miR-135b and miR-660, were overexpressed in group-4 MB (34). These differentially expressed miRNAs were expected to be key indicators for the identification of specific MB-associated markers. Visani *et al* (35) indicated that there were differences in miR-196B-5P and miR-200B-3P expression between adults and children. Their study suggested that miRNAs may be involved in the development of MB, but not in the differences noted in the biological responses of adults and children with MB. An increasing number of studies have confirmed that the differences in the expression of these miRNAs can affect specific biological processes of MB cells, such as proliferation, migration, invasion and apoptosis. For example, miR-10b is specifically overexpressed in MB cells and it can promote proliferation by mediating the downregulation of the expression of the apoptotic protein Bcl-2 (36). Therefore, miR-10b overexpression can induce apoptosis and inhibit colony formation (36). In SHH-activated MB, the expression of the miR-17-92 cluster regulates N-myc proto-oncogene overexpression (32). Northcott *et al* (32) confirmed that miR-17-92 clusters can promote proliferation of tumor cells and enhance the invasion of MB cells *in vitro*. Grunder *et al* (37) demonstrated that miR-21 overexpression negatively regulated the expression of the transfer inhibitory factor programmed cell death protein 4 in MB compared with that observed in normal tissues, thereby increasing the expression levels of the downstream invasion medium proteins mitogen-activated protein kinase kinase and JNK, which promote tumor cell invasion. Yang *et al* (38) analyzed the miRNA expression profiles in 29 patients with MB and screened this group for miR-192 expression, which was downregulated in tumor cells. The results of their study confirmed that miR-192 inhibited the proliferation and anchorage capability of MB cell lines by regulating the downstream target genes dihydrofolate, integrin α -V precursor, integrin β -1/3 precursor and cluster of

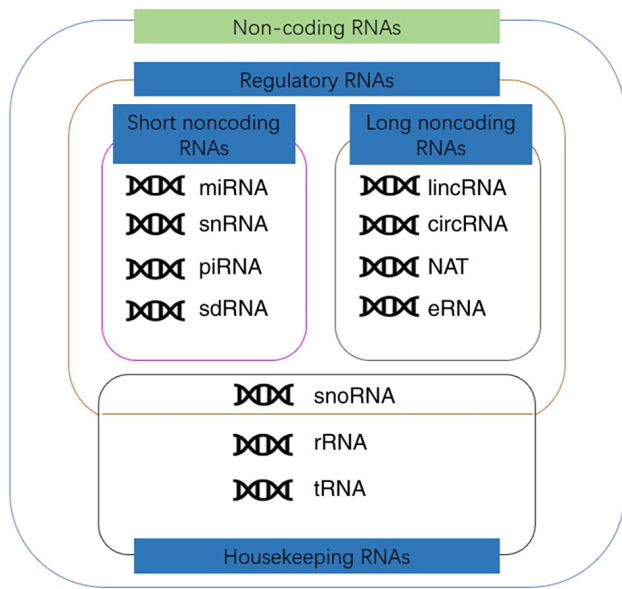


Figure 1. Classification of non-coding RNAs. miRNA, microRNA; snRNA, small nuclear RNA; piRNA, PIWI-interacting RNA; sdRNA, snoRNA derived small RNA; lincRNA, Large intergenic noncoding RNA; circRNA, circular RNA; NAT, natural antisense transcript; eRNA, enhancer RNA; snoRNA, small nucleolar RNA; rRNA, ribosomal RNA; tRNA, transfer RNA.

differentiation (47). This finding was also confirmed in a nude mouse xenograft model, suggesting that miR-192 is a type of metastasis inhibitory factor (38). In MB, the natural antisense transcript HOTAIR of lncRNA HOX competitively binds to miR-1 and miR-206 and causes upregulation of Yin Yang 1 protein expression. This pathway promotes the malignant phenotype of MB (39). Senfter *et al* (40) demonstrated that the loss of miR-4521 expression led to the activation of the proto-oncogene forkhead box protein M1 (FOXO1) in MB. Kumar *et al* (41) indicated that miR-217 promoted tumor growth by negatively regulating the target genes sirtuin 1, Roundabout1, FOXO3 and SMAD7. Early diagnosis and prognostic assessment are important steps in the treatment of MB. Currently, the detection of miR expression offers an alternative to imaging data. Li *et al* (42) demonstrated that miR-449a expression was downregulated in MB of all subtypes, with the exception of Wnt-MB. This suggests the potential applications of this miR in the diagnosis of Wnt-MB (42). Pezuk *et al* (43) examined the expression levels of Polo-like kinase family members and their associated miRNAs (miR-100, miR-126, miR-219 and miR-593) in 32 clinical samples of MB in association with disease prognosis. The results indicated that patients with higher expression of miR-100 and lower expression of miR-126 and miR-219 had improved OS (43). Although increasing evidence has suggested that miR-targeted therapy is of considerable value, miRNA-targeting for the treatment of MB remains under investigation. Some targeted treatments for specific miRNAs have been shown to inhibit the development of the malignant phenotype of MB cells. For example, overexpression of miR-34a can reduce the expression of transmembrane protein δ -Like1 in MB to inhibit tumor cell proliferation and induce apoptosis (44). De Antonellis *et al* (44) demonstrated

inhibition of tumor growth in a nude mouse MB model by administration of adenoviral vectors carrying miR-34a. The minichromosome maintenance protein (MCM2-7) complex has the ability to influence DNA transcription and replication. CDK6, which is part of the MCM2-7 complex, is overexpressed in one-third of MB cases. Therefore, it may be used as a specific marker of disease prognosis. Silber *et al* (45) established a nude mouse model of heterotopic transplanted tumor with D425 cells, which were infected with lentiviruses containing miR-124. The results indicated that miR-124-targeted CDK6 and effectively inhibited tumor growth (45). However, the development of high-efficiency miR-targeted drugs that can be applied clinically requires further exploration due to the limitations of the current technologies.

3. circRNAs in MB

In 1991, Nigro *et al* (46) reported the identification of a new type of RNA, termed circRNA, which was formed by exons. Salzman *et al* (47), sequenced 15 types of normal or cancerous cells using RNA-seq, including a fetal pulmonary fibroblast line and a leukemia cell line. A total of 80 types of circRNAs were identified (47). Following this study, circRNAs became a research hotspot. It has been shown that circRNAs are widely expressed in eukaryotes. They possess rich, stable, highly conserved and non-randomized motifs (48). Of the annotated circRNAs, 99% require cutting of the exon at the 3' and 5' splicing sites. The majority of the circRNAs contain 2-3 exons. Subsequently, the 3' end of the clipped segment is spliced with the 5' end to form a ring. Due to this special circular structure, circRNAs exhibit high stability compared with linear RNAs and are affected to a lesser extent by RNases (49-52). It has also been reported that circRNAs are widely expressed in the brain (49).

Currently, the prevailing hypothesis is that the main role of circRNAs is to combine with corresponding miRNAs through conserved sites. Subsequently, circRNAs act as molecular sponges of miRNAs and regulate various cellular functions (53-58) (Fig. 3). circRNAs are often dysregulated in a variety of malignant tumors, including glioma (59-61). These molecules are involved in regulation of tumor growth, suggesting that they may be important regulators in the development of MB. Lv *et al* (62) selected 4 pairs of normal cerebellum and MB tissue samples for gene sequencing and identified 33 differentially expressed circRNAs in MB tissues. The upregulation of two of these circRNAs, which were identified as circular-spindle and kinetochore associated complex subunit 3 (circ-SKA3) and circ-DTL, reverted the malignant phenotype of MB (62). A previous study observed significantly higher expression levels of circ-SKA3 in MB compared with the corresponding expression noted in normal tissues. This was achieved by detecting the expression levels of specific circRNAs that were differentially expressed in MB. The expression levels of the downstream target miR-383-5p were determined by luciferase assay. Subsequent experiments indicated that miR-383-5p expression was influenced by low expression of circ-SKA3 in tumor cells. Following restoration of miR-383-5p expression by silencing circ-SKA3, the expression levels of the downstream FOXO1 protein were also

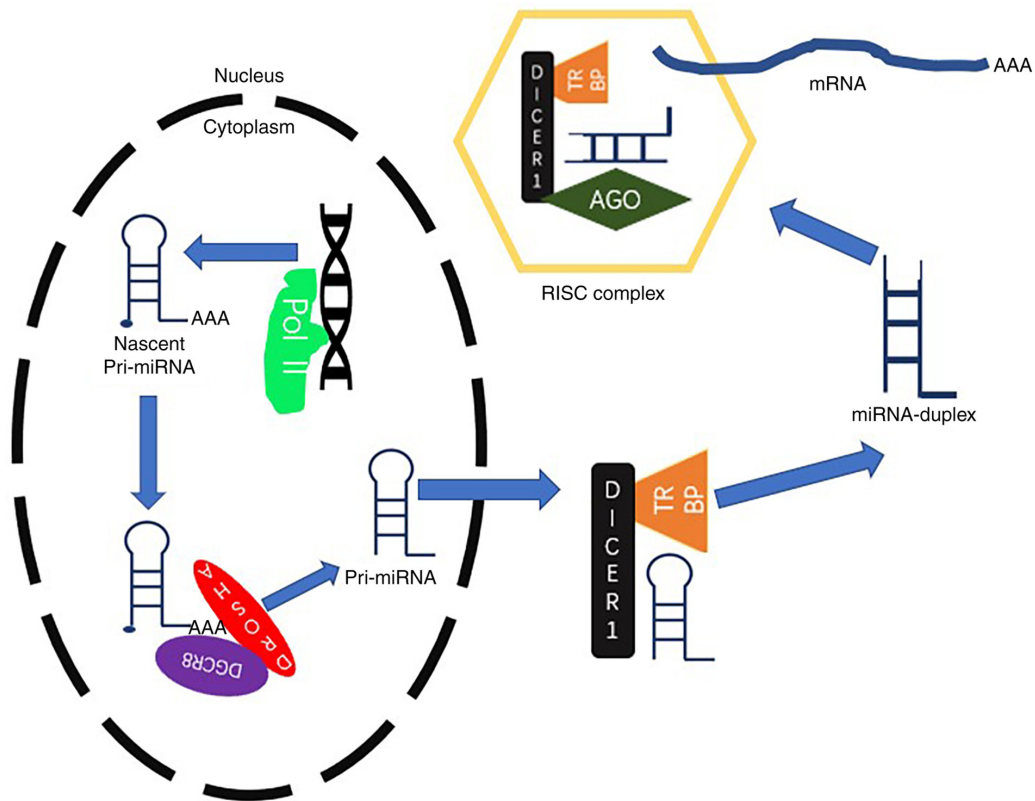


Figure 2. Generation and role of miRNAs: First, nascent pri-miRNAs are generated by related genes mediated by pol II, and then the poly A-tail and m7G-PPNmN cap are removed in the nucleus by shearing of the DROSHA-DGCR8 complex to form precursor miRNAs. After the pri-miRNA translocates to the cytoplasm, DICER1 complex modifies it during a second round of processing and produces miRNA-duplexes containing the mature miRNA strand. Finally, the miRNA binds to the AGO-containing RISC complex to inhibit mRNA function. miRNA, microRNA; pri-miRNA, primary miRNA; RISC, RNA-induced silencing complex; DGCR8, DiGeorge syndrome critical region 8; pol II, RNA polymerase II; TRBP, Tar RNA-binding protein.

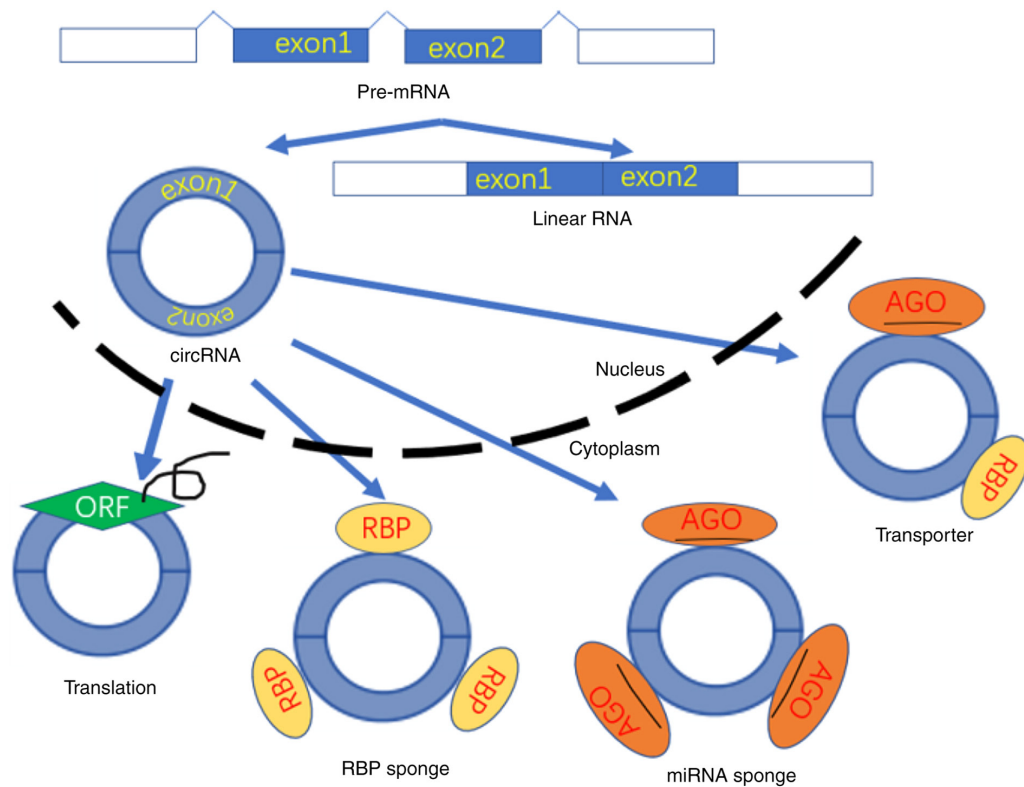


Figure 3. Generation and role of circRNAs: The spliced flanking introns bind to specific sites of the intron either by complementation or by RBPs to form a special ring structure. This then functions as a molecular sponge, or affects RBP and miRNAs in the cytoplasm. Certain circRNAs with an ORF can autonomously generate proteins that participate in regulation. circRNA, circular RNA; ORF, open reading frame; RBP, RNA binding protein.

affected and the proliferation, migration and invasion of the tumors were inhibited, whereas the induction of apoptosis was enhanced (63). Although current evidence suggests that circRNAs play an important role in the development of MB, additional studies are required to assess their specific mechanisms and potential applications in the clinical treatment of MB.

4. Other ncRNAs in MB

At present, the regulatory mechanism of ncRNA expression in MB has been primarily examined by assessing the expression levels of miRNAs and circRNAs. Pertinent ncRNA regulatory functions have not been thoroughly investigated. For example, eRNAs, which were identified relative more recently, play a regulatory role by forming a complex with RNA polymerase II DNA binding transcription factor and the RNA binding transcription factor that binds to the gene enhancer (64). Lin *et al* (65) investigated the binding of H3K27AC and bromodomain-containing protein 4 by chromatin immunoprecipitation assays in MB tissue matched samples. DNA methylation and transcription data were also provided to describe 28 cis-regulatory elements in MB. The results indicated that the differential regulation of enhancers was heterogeneous between subgroups (65). That is, eRNAs may play an important role in the phenotypic changes of MB. SPRY4 intronic transcript 1 (SPRY4-IT1) is a type of lncRNA with a length of ~706 bp. It has a hairpin structure and is expressed in gliomas. Shi *et al* (66) demonstrated that inhibition of SPRY4-IT1 affected the expression of MMP-2 in MB, and the migration of the MB cell line Daoy was decreased by this pathway.

5. Conclusions

MB is one of the most common types of central nervous system malignant tumors encountered in children, and it is characterized by a high incidence and a poor prognosis. Although significant progress has been made in exploring the development and pathogenesis of MB, the effects of currently available treatments are often unsatisfactory due to the propensity of the tumor for recurrence and metastatic spread, and the occurrence of serious complications. In recent years, it has been confirmed that several ncRNAs, such as miRNAs and circRNAs, are associated with the regulatory mechanisms involved in the occurrence and development of various tumors. It has also been shown that several ncRNAs, including miRNAs and circRNAs, regulate tumor metabolism and are involved in the development of MB. At present, a number of studies have been conducted on the regulatory mechanism of miRNAs in MB. It has been confirmed that miRNAs play an important role in the occurrence and development of MB. However, a limited number of studies have been performed on the mechanisms associated with the expression of other ncRNAs, including circRNAs, and the development of MB. It is considered that wider adoption of high-throughput microarray and second-generation sequencing technologies will enable the full investigation of ncRNA-associated mechanisms and their clinical applications in the diagnosis and treatment of MB.

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Availability of data and materials

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Authors' contributions

YNZ completed the primary writing and proofreading of the manuscript. KL made partial corrections to the original anuscript and made the figures. XSH performed the literature search. YWP directed the writing of the article and made partial revisions. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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