Functions of circular RNAs and their potential applications in gastric cancer (Review)

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Abstract. As the fifth most common cancer and the fourth leading cause of cancer-related death in the world, gastric cancer (GC) poses a potential threat to human health. However, there is still a lack of effective means for the early screening and treatment of GC, and therefore, GC remains a difficult disease to overcome. With the continuous in-depth research on circular RNAs (circRNAs), an increasing body of evidence indicates that circRNAs play an important role in a wide variety of diseases, particularly cancer. Proliferation, invasion and metastatic spread of cancer cells are strongly associated with abnormal circRNA expression. Hence, circRNAs are considered a candidate biomarker for GC diagnosis and prognosis, and a target for cancer treatment. The focus has been on the association of GC with circRNAs, thus it is necessary to briefly review and summarize the relevant research to provide the research findings across the area to researchers, and to indicate the direction for future research. The present review provides an overview on the biogenesis and functions of circRNAs in GC, predicting their possible clinical application as ideal biomarkers and potential targets of treatment in GC.

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Contents

1. Introduction

A growing number of studies have demonstrated that a significant fraction of non-coding RNAs (ncRNAs) exist in various mammals, including humans (1-4). The ncRNAs are composed of constitutive and regulatory ncRNAs. The regulatory ncRNAs are involved in the regulation of gene expression and are classified as small non-coding RNAs (<200 bp) and long ncRNAs (lncRNAs; >200 bp) based on nucleotide fragment length.

In 1976, circular lncRNAs or circRNAs were first discovered in plant viruses (1). Subsequently, circRNAs were also detected in the cytoplasm of eukaryotic cells, yeast mitochondria, humans and rats (2-4). Therefore, circRNAs are widely distributed in nature. However, circRNAs have received insufficient attention in the following decades due to the widespread hypothesis that circRNAs are a byproduct of abnormal RNA splicing. Following rapid development of high-throughput sequencing and bioinformatic technologies, a large number of circRNAs have been discovered to play a critical role in some pathways, and attention has gradually been paid to their structures and functions by the academic community (5).

As the fifth most common cancer and the fourth leading cause of cancer-associated death in the world, gastric cancer (GC) is an important disease with >1,000,000 new cases and an estimated 769,000 deaths globally in 2020 alone, which equates to 1 in every 13 deaths due to stomach cancer (6). In the past decades, researchers have been exploring the treatment of GC (7). Although the development of chemotherapy technology has improved the survival quality of patients

with GC, the mortality rate of the disease remains high, which is attributed to the lack of effective early diagnostic tools (8). Overall, >80% of Chinese patients are diagnosed at advanced stages, and it is more difficult to cure advanced GC. Development of accurate, rapid and sensitive diagnostic methods, and effective and precise targeted therapies are the top priorities for the treatment of GC.

With further in-depth research on the function and mechanism of circRNAs, increasing evidence has indicated that circRNAs play a crucial role in various diseases, particularly cancer. Tumor cell proliferation, migration, invasion and metastatic spread are associated with the unnatural expression patterns of circRNAs (1,5). Therefore, circRNAs show potential value for the diagnosis, treatment and prognosis of GC. In the present review, the biogenesis and classification of circRNAs, as well as their biological properties and functions, are systematically introduced. The precise role and internal mechanism of circRNAs in GC, with a focus on their potential clinical value as biomarkers and therapeutic targets, are also reviewed.

2. Biogenesis and classification of circRNAs

The majority of circRNAs originate from back-splicing of precursor mRNAs and can be classified into four categories depending on their origin: i) Exonic circRNAs (ecircRNAs), which consist exclusively of single or multiple exons; ii) circular intronic RNAs (ciRNAs), which are intron-derived, iii) exon-intron circRNA (ElciRNAs), which contain both exons and introns; and iv) tRNA intronic circRNAs (tricRNAs), which are derived from the linear intron of tRNA precursors (7).

For the cyclization of ecircRNAs, there are three possible mechanisms: Lariat-driven circularization, intron pairing-driven circularization and RNA-binding protein (RBP)-driven circularization. In the lariat-driven circularization model, the downstream splice donor binds covalently to the upstream splice acceptor, resulting in a lariat structure containing one or more exons. The lariat undergoes splicing processing to form ecircRNA (9). Intron pairing-driven circularization is facilitated through base-pairing of the intron sequences bordering the circularised exon. RBP-driven circularization occurs through the binding of RBPs such as quaking and FUsed in Sarcoma to exon-flanking introns. The dimerization of RBPs promotes proximity of the two flanking introns to each other, leading to cyclization (10). Some ecircRNAs contain multiple exons, while others contain only one, depending mainly on the splice site.

The biogenesis of ciRNAs depends on several key sites, including 7-nucleotide, GU-rich element near the 5'-splice site and 11-nucleotide, C-rich element near the branchpoint site. The 5' splice site of the intron can form a loop structure after binding to the branchpoint site, and then ciRNAs can be formed by further processing. Researchers have identified a large number of ciRNAs in the nucleus and found little enrichment of ciRNAs for microRNA (miRNA/miR) target sites (11).

The cyclization process of ElciRNAs is similar to that of ecircRNAs, except that its introns are retained. ElciRNAs are mainly found in the nucleus. tricRNA is derived from the cleavage of pre-tRNA by the tRNA splicing endonuclease (TSEN) complex; the TSEN complex excises the pre-tRNA intron at the bulge-helix-bulge motif, promoting the pre-tRNA to become mature tRNA, and the excised intron portion is cyclized to tricRNA (12).

3. Biological properties of circRNAs

circRNAs are characterized by stability, conservatism and diversity. Unlike linear RNAs, circRNAs form a loop structure without a 5'-terminal cap structure and a 3'-terminal poly(A) tail, which makes them more stable and resistant to nucleic acid exonucleases (13). circRNAs are widely present in various organisms such as fungi and protozoa, and show a high degree of evolutionary conservation. In addition, they are diverse and >25,000 circRNAs have been detected in human fibroblasts (14). Furthermore, circRNAs are also found in various body fluids such as blood and saliva, which greatly facilitates the development of circRNA biomarkers for early disease detection, clinical diagnosis and prognosis.

4. Biological functions of circRNAs

circRNAs act as miRNA sponges. miRNAs are small non-coding RNAs transcribed from miRNA genes, which suppress the translation or result in the degradation of their target mRNAs by interacting with the 3'-untranslated region (UTR), open reading frame, or 5'-UTR of target mRNA. It has been reported that miRNAs play a vital role in the development of diseases, such as depression and cancer (15). The competitive endogenous RNA hypothesis explains the interaction between circRNA and miRNA. circRNA binds to miRNA through the miRNA response element, thus preventing miRNA-mRNA binding, and relieving the repressive effect of miRNA on target gene expression (16). For example, circ_PGPEP1 can reverse the oncogenic effect of miR-1297, and promote GC progression by binding miR-1297, which positively inhibits the expression of transcription factor E2F3 (17).

circRNAs interact with proteins. RBPs are a class of proteins that bind RNA to regulate processes such as splicing and translation. RBP binding sites on the surface of circRNA can specifically bind RBPs to form the RNA-protein complex, thereby blocking RBPs from binding to mRNAs for transcription and translation to inhibit the expression of specific genes. Cyclin-dependent kinases 2 (CDK2) is an important factor in cell cycle regulation, enabling the cell cycle to proceed in an orderly manner. circFOXO3 combines CDK2 and p21 proteins to form a ternary complex, leading to cell cycle disruption (18). In addition, circRNA can also interact with CCHC-type zinc finger nucleic acid binding protein (CNBP), nucleosome remodeling factor complex and other proteins to regulate life activities (19).

circRNAs encode proteins. circRNAs are traditionally defined as ncRNAs, yet studies have demonstrated that some circRNAs are also capable of encoding proteins that play vital roles in numerous biological processes. For example, circular neuroligin RNA (circNlgn) encodes Nlgn173 in the heart, a protein isoform that causes proliferation of cardiac fibroblasts and reduced cardiomyocyte viability, and circNlgn expression

is upregulated in congenital heart disease with cardiac overload (20). circMAPK1 encodes a polypeptide 109 amino acids in length that is localized in the cytoplasm and inhibits cancer cell proliferation, migration and invasion, thereby acting as a tumor suppressor (21). Owing to the lack of 5' cap and 3' poly(A) tail, circRNA initiates the translation process through the mediation of internal ribosome entry sites (IRES) or N-methyladensine (m6A) residues. IRES form secondary structures of RNA sequences, which recruit ribosomes and allow translation to be triggered (22). The m6A not only initiates and promotes the translation of circRNA, but also enhances the formation of translatable circRNA (23).

Other examples of regulation of gene expression by circRNA. ElciRNAs localized in the nucleus, such as circEIF3J and circPAIP2, can bind to the U1 small nuclear ribonucleic proteins (snRNPs) to form the ElciRNA-U1 snRNP complex, which combines with RNA polymerase II and enhances the activity of enzymes, thus positively regulating gene transcription (24). CircRNAs can also compete with mRNAs for expression. Some genes can be transcribed, which later produce both mRNAs and circRNAs. When the spliceosome components are silenced, circRNA expression increases, while mRNA expression decreases, and the opposite occurs when the spliceosome components are activated (25).

5. Methods for circRNA identification

RNA sequencing (RNA-seq) is often used in circRNA identification, and the accuracy and comprehensiveness of its recognition depend on the rigor and reliability of the algorithm. The commonly available algorithms include CircRNA_finder (https://github.com/orzechoj/circRNA_finder), Find_CIRC (https://github.com/marvin-jens/find_circ), CIRCexplorer (github.com/YangLab/CIRCexplorer), CIRI (https://sourceforge.net/projects/ciri/files) and MapSplice (http:/www.netlab.uky.edu/p/bioinfo/MapSplice). Among them, Find_CIRC is characterized by the highest sensitivity, MapSplice has the highest accuracy and CircRNA_finder has the fastest calculation speed (1). Hence, the joint use of different algorithms can effectively reduce the false-positive rate (26). The mapper used by the algorithm (e.g. Bowtie2 or STAR) can also influence the false-positive rate (27). In addition, the identification of circRNA by RNA-seq requires a sufficiently large sequencing depth, i.e., at least 100 bp of sequencing to obtain sufficient read lengths to enable the confident prediction of circRNAs based on read- spanning backsplice junction region (28).

Microarray technology is an important tool for identification of circRNAs, which requires less bioinformatic expertise and is more efficient at detecting circRNAs compared to RNA-seq (29,30). Arraystar, Inc., has created the first commercial microarrays for human, mouse and rat circRNAs, containing >10,000 circRNAs. Li *et al* (30) integrated 87,935 circRNA sequences and designed microarray probes targeting the back-splice site of each circRNA for its expression analysis, and a number of the circRNAs detected by this microarray could be validated by reverse transcription-quantitative PCR (RT-qPCR) or RNA-seq.

RNase R is a 3'-5' ribonucleic acid exonuclease from the *Escherichia coli* ribonucleotide reductase superfamily that degrades most linear RNAs, to which circRNA is resistant, so circRNA can be identified and enriched by RNase R. After enrichment, circRNA can be further verified by RT-qPCR and northern blotting (1). In addition to the aforementioned methods, droplet digital PCR, fluorescence *in situ* hybridization and NanoString technology are also applied in the identification and validation of circRNAs (31).

6. circRNA and GC

Expression of circRNAs in GC. Aberrant expression of circRNA in GC greatly contributes to carcinogenesis and development of GC. With the development of bioinformatics, researchers have identified a number of distinguishing circRNAs expressed in GC tissues, blood and gastric juice compared with normal samples. Luo *et al* (32) performed RNA-seq analysis of GC tissues and adjacent normal tissues, and identified 85 differentially expressed circRNAs, of which 52 were upregulated and 33 were downregulated in GC tissues. Wang *et al* (33) identified 145 circRNAs that were differentially expressed in cancerous and non-cancerous tissues, with 67 upregulated and 78 downregulated in GC tissues. Shen *et al* (34) distinguished 950 differentially expressed circRNAs by microarray, among which 347 were upregulated and 603 were downregulated in GC tissues. Chen *et al* (35) reported 180 differentially expressed circRNAs by RNA-seq, of which 82 were upregulated and 98 were downregulated in GC tissues, and ~80% of the circRNAs were from protein-coding genes. Shao *et al* (36) identified 308 differentially expressed circRNAs by microarray, of which 107 were upregulated and 201 were downregulated in GC tissues. Dang *et al* (37) screened the expression profiles of circRNAs in GC tissues using circRNA chip and found that 713 circRNAs were differentially expressed in GC tissues and normal tissues, of which 191 were upregulated and 522 were downregulated in GC tissues.

Differences in circRNA expression in GC tissues were often associated with sex, tumor diameter, degree of differentiation, T stage, distant metastasis, Tumor-Node-Metastasis (TNM) stage, lymph node metastasis, carcinoembryonic antigen and carbohydrate antigen 19-9 levels (38,39).

circRNAs in GC and molecular mechanisms. Numerous circRNAs have been found to be involved in GC cell proliferation, migration, invasion and apoptosis (Table SI) (1).

circRNA regulates the progression of gastric carcinogenesis mainly through its role as an miRNA sponge. As aforementioned, miRNA can repress target gene expression, and circRNA can deregulate this repressive effect. When miRNAs act on cancer genes, circRNAs can affect the relevant cancer pathways accordingly. If the miRNA target gene is a proto-oncogene, circRNA tends to promote the differentiation and proliferation of cancer cells, while if the miRNA target gene is an anti-oncogene, circRNA usually inhibits carcinogenesis. Numerous studies on the mechanism of the circRNA-miRNA-mRNA network in GC have appeared in the last 3 years (Table SI). For example, Zhang *et al* (40) found that knockdown of circular nuclear receptor interacting protein 1 (circNRIP1) inhibited the proliferation, migration and invasion of GC cells, and the study confirmed that

circNRIP1 bound miR-149-5P, thus promoting the expression level of AKT1 and acting as a cancer promoter through the AKT1/mTOR pathway. The expression of circular RNA thrombospondin-1 (circTHBS1) was increased in GC and it was associated with a poor prognosis. Mechanistically, circTHBS1 sponged miR-204-5p to promote the expression of inhibin subunit βA (41). By contrast, Rong *et al* (42) showed that circPSMC3 expression was downregulated in GC tissues and plasma, and that circPSMC3 exerted tumor-suppressive effects by binding to miR-296-5p to regulate the expression of phosphatase and tensin homolog.

In addition to binding miRNAs, circRNAs can also bind directly to proteins to produce cancer-promoting or cancer-suppressing effects. For example, Yang *et al* (19) showed that circular RNA human antigen R (circ-HuR) can bind to CNBP, thus inhibiting CNBP binding to HuR promoter, downregulating HuR and ultimately exerting oncogenic effects. Zang *et al* (43) showed a tumor suppressor function of circEIF4G3 in GC through binding to δ-catenin protein to promote its tripartite motif containing 25-mediated ubiquitin degradation, and revealed its role as a promising prognostic biomarker and therapeutic target for GC.

Some circRNAs can also encode cancer-related proteins. As aforementioned, circMAPK1 can encode MAPK1-109aa, which inhibits the malignant biological behavior of cancer cells (21).

In addition, circRNA can act on promoters and regulate carcinogenesis by affecting gene expression. For instance, Ding *et al* (44) reported that circular RNA-downstream neighbor of SON (circ-DONSON) recruits the nucleosome remodeling factor complex to Sox4 promoter, initiates Sox4 transcription, and promotes proliferation, migration and invasion of GC cells. Jie *et al* (45) showed that circular RNA mitochondrial ribosomal protein S35 recruit histone acetyltransferase KAT7 to the promoters of FOXO1 and FOXO3a, and then activate FOXO1 and FOXO3a transcription, and inhibit the proliferation and invasion of GC cells.

circRNAs act as biomarkers of GC. Biomarker means 'a biological molecule found in blood, other body fluids or tissues, which could be a marker of a normal or abnormal process, or of a condition or disease', and it can distinguish diseased individuals from normal individuals (46). Biomarkers are relatively diverse chemically. Proteins, nucleic acids and glycans could all serve as biomarkers. As aforementioned, circRNA has higher stability than linear RNA, is conserved across species and is widely distributed in blood and various tissue fluids. These properties make circRNA a suitable choice for a biomarker. In patients with GC, researchers often sample plasma or GC tissue to detect circRNAs, and their role as diagnostic and prognostic markers is displayed in Table SII (1,47,48).

Existing studies have demonstrated the high value of some circRNAs in the diagnosis of GC. In GC tissues, circ_0066444, hsa_circ_0000467 and hsa_circRNA_102958 were upregulated and were used as diagnostic biomarkers (47). In GC plasma, circ_0004771 expression was detected to be upregulated, and it was expressed at different levels in patients with GC, patients with post-operative GC and patients with recurrence of GC, indicating that plasma circ_0004771 can be used as a biomarker for the diagnosis and dynamic monitoring of GC (48). In addition, a number of circRNAs with downregulated expression were also detected in GC tissues, including hsa_circ_0000181, hsa_circ_0001445, hsa_circ_0005758, hsa_circ_0005556, hsa_circ_0065149, hsa_circ_0067582, hsa_circ_0001811, circ_0049447, hsa_circ_0006470 and hsa_circ_0001874 (49). In plasma, hsa_circ_0006848 and hsa_circ_0001811 expression was found to be downregulated (50). The aforementioned studies confirmed the great potential of circRNAs as diagnostic biomarkers for GC.

circRNA has also shown great promise in the prognosis of GC. Tang *et al* (51) revealed that the expression of circ-KIAA1244 was lower in GC tissues than that in normal controls, and clinical analysis showed that its expression level was associated with TNM stage, lymph node metastasis and overall survival time of patients. circ-KIAA1244 can be considered a prognostic biomarker for GC, with an area under the curve value of 0.7481 (51). In addition, as aforementioned, some circRNAs, including hsa_circ_0001445, hsa_circ_0000467, hsa_circ_0005556, hsa_circ_0065149, circ_0004771, hsa_circ_0067582 and hsa_circ_0001874, are not only used as diagnostic biomarkers, but also have a suggested role in the prognosis of GC (48).

Therapeutic potential of circRNAs in GC. circRNA is involved in a variety of biological processes in cancer development, including cell proliferation, migration and invasion. The use of circRNA as a major target for GC therapy is receiving increasing attention.

Tumor suppressor circRNAs offer new options for the treatment of GC. As aforementioned, a number of circRNAs can inhibit tumors as miRNA sponges. Liu *et al* (52) synthesized circRNAs targeting miR-21 *in vitro*, and these sponges were able to prohibit cancer cell proliferation through relevant pathways, suggesting that synthetic circRNAs are a promising therapeutic strategy. Some drugs, such as lidocaine, can also increase the expression of tumor suppressor circRNAs; for example, upregulating circ_ANO5 in GC cells and regulating the circ_ANO5/miR-21-5p/leukemia inhibitory factor receptor axis to inhibit tumor growth (53). By contrast, cancer-promoting circRNAs are viable therapeutic targets. For circRNAs that promote the proliferation, spread and invasion of cancer cells, a therapeutic process can be achieved by inhibiting their expression. Piwecka *et al* (54) successfully knocked out Cdr1as from mice to achieve the relevant functional deletion, suggesting the feasibility of eliminating cancer-promoting circRNAs in patients with GC to attain cancer suppression. Cancer-promoting circRNAs were inhibited by drugs, such as gambogic acid, which downregulates circular RNA_arfGAP with SH3 domain, ankyrin repeat and PH domain 2 (circ_ASAP2) expression, isoproterenol, which reduces circular RNA plasmacytoma variant translocation 1 (circPVT1) expression in GC cells, and bupivacaine, which inhibits cancer progression by reducing circ_0000376 expression and exerts antitumor effects (55).

circRNAs play an important role in tumor drug resistance. circAKT3 expression was higher in cisplatin-resistant GC tissues than in cisplatin-sensitive GC tissues, and circAKT3

promoted the resistance of GC cells to cisplatin by targeting the miR-198/PIK3R1 axis (56). Circular RNA cullin 2 (circCUL2) regulates cisplatin resistance by modulating autophagy activation via miR-142-3p/ROCK2 circCUL2 (57). circ_0110805 knockdown enhances the sensitivity of GC cells to cisplatin. Mechanistically, circ_0110805 acted as a sponge of miR-299-3p and its targeted endothelial protein disulfide isomerase (58). circ-DONSON expression is elevated in cisplatin-resistant GC tissues and cells, and it facilitates cisplatin resistance in GC cells by regulating the miR-802/BMI1 axis (59). circ_0026359 enhances cisplatin resistance in GC by targeting the miR-1200/POLD4 pathway (60). hsa_circ_0081143 inhibits miR-646 expression and activity, and leads to upregulation of CDK6 to promote cisplatin resistance in GC (61). Circular RNA multiple C2-domains with two transmembrane regions 2 (circMCTP2) sensitizes GC cells to cisplatin by upregulating myotubularin-related protein 3 through binding of miR-99a-5p. Upregulation of circMCTP2 may be a new strategy against cisplatin resistance in GC (62). In cisplatin-resistant GC cells, circPVT1 and heparin binding growth factor (HDGF) mRNA expression was upregulated. However, miR-152-3p expression was downregulated. circ-PVT1 regulates HDGF expression by targeting miR-152-3p, thereby regulating chemoresistance and malignancy in GC (63). circular RNA vesicle-associated membrane protein-associated protein A promotes chemoresistance and malignant progression of GC through the miR-125b-5p/STAT3 signaling pathway (64). circ_ASAP2 regulates drug sensitivity and functional behaviors of cisplatin-resistant GC cells by the miR-330-3p/NT5E/circ_ASAP2 axis (65). circ-PVT1 promotes cisplatin resistance by regulating autophagy, invasion and apoptosis in GC cells through the miR-30a-5p/YAP1 axis (66). circ-PVT1 expression is upregulated in paclitaxel-resistant GC tissues and cells, and it promotes paclitaxel resistance in GC cells by binding miR-124-3p to regulate ZEB1 expression, suggesting a potential therapeutic strategy for GC (67). circ_0032821 contributes to oxaliplatin (OXA) resistance of GC cells by regulating SOX9 via miR-515-5p, while hsa_circ_0000144 enhances OXA resistance by sponging miR-502-5P and upregulating ADAM9 (68). circNRIP1 can bind miR-138-5p to enhance 5-fluorouracil (5-FU) resistance in GC cells, providing a new target of action to overcome hypoxia-induced 5-FU resistance (69). circular RNA carboxypeptidase M has a crucial role in 5-FU resistance by targeting protein kinase AMP-activated catalytic subunit alpha 2 (70). Considering the effects of circRNAs on resistance to various antitumor drugs, combining drug therapy with target-acting circRNAs might play an unexpectedly large role in the treatment of GC.

7. Conclusion and perspective

In the past, circRNAs were considered to be a byproduct of abnormal splicing, but recent studies have confirmed that circRNAs are involved in several functions of the body as important molecules. circRNA is stable, conserved, diverse and widely distributed in various body fluids. High-throughput analysis has revealed that a large number of circRNAs are dysregulated in GC. circRNAs participate in the proliferation, invasion and apoptosis of GC cells by acting as miRNA sponges, regulating transcription, binding proteins, encoding cancer-related proteins and affecting gene expression. On the one hand, these findings confirmed the significant potential of circRNAs as a diagnostic and prognostic biomarker for GC. On the other hand, circRNAs are expected to be a major therapeutic target for GC. Further studies on circRNAs will help improve the early diagnosis and survival of patients with GC.

However, our current understanding of circRNAs is still not sufficient, and there are still some issues in existing studies. Firstly, when it comes to circRNAs as biomarkers, the samples used in current studies are mainly GC tissues or plasma, thus there are some gaps in research using non-invasive samples such as urine and saliva as experimental materials. Secondly, for the specific mechanism of circRNAs in GC, most studies focus on circRNAs as miRNA sponges. Some other effects, such as circRNAs binding or encoding proteins are rarely explored. Thirdly, some circRNAs have been shown to modulate the resistance of GC cells to chemotherapeutic drugs and serve as targets for GC therapy; therefore, more clinical studies are needed to promote the clinical application of circRNAs. In addition, synthetic circRNAs have potential in GC therapy and deserve the attention of researchers. Last but not least, little is known about the specific causes of circRNA dysregulation, and few studies have discussed why circRNAs are upregulated or downregulated in patients with cancer.

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Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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