

Role of caprin-1 in carcinogenesis (Review)

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Abstract. RNA-binding proteins serve an essential role in post-transcriptional gene regulation. Cytoplasmic activation/proliferation-associated protein-1 (caprin-1) is an RNA-binding protein that participates in the regulation of cell cycle control-associated genes. Caprin-1 acts alone or in combination with other RNA-binding proteins, such as RasGAP SH3-domain-binding protein 1 and fragile X mental retardation protein. In the tumorigenesis process, caprin-1 primarily functions by activating cell proliferation and upregulating the expression of immune checkpoint proteins. Through the formation of stress granules, caprin-1 is also involved in the process by which tumor cells adapt to adverse conditions, which contributes to radiation and chemotherapy resistance. Given its role in various clinical malignancies, caprin-1 holds the potential to be used as a biomarker and a target for the development of novel therapeutics. The present review describes this newly identified putative oncogenic protein and its possible impact on tumorigenesis.

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1. Introduction

RNA-binding proteins (RBPs) can directly interact with RNA or can be part of ribonucleoprotein complexes without direct contact with RNA (1). The presence of RNA-binding domains (RBDs) in proteins and AU-enriched regions in target RNAs is essential for the synergistic function of RBPs on their targets, which include mRNA, tRNA, rRNA, microRNA (miRNA) and non-coding RNA (ncRNA). Transient or stable interactions of RBPs with RNAs are crucial for RNA regulatory processes. RBPs are involved in post-transcriptional gene regulation (PTGR) primarily through the formation of functional units termed ribonucleoprotein (RNP) complexes. mRNA-binding proteins and corresponding messenger RNPs are directly responsible for mRNA maturation and regulation; however, diverse ncRNA-targeted RBPs are also involved in the process of PTGR (2,3). RBPs can combine with miRNAs to form miRNPs, which are also involved in the regulation of mRNA translation and stability. According to an extensive classification of 1,542 human RBPs conducted by Gerstberger *et al* (1), approximately half of these RBPs can be grouped on the basis of their mRNA targets, and others may interact with different types of RNAs. Furthermore, approximately one-third of RBPs can bind to DNA and RNA (4). The diverse binding spectrum of RBPs indicates their diverse spectrum of function. Recent studies have demonstrated that RBPs often associate with a group of mRNAs encoding proteins with similar functions, forming an RNA operon (5). The different types of RBPs combine with the corresponding mRNAs at different times and in different positions inside cells, thereby meeting the need of the cell in a time- and location-dependent manner to adjust the regulation of target molecules. A particular mRNA can be bound by numerous different RBPs. RBPs can also act as a binding platform for

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Abbreviations: caprin-1, cytoplasmic activation/proliferation-associated protein-1; eIF2 α , eukaryotic initiation factor 2 α ; FMRP, fragile X mental retardation protein; G3BP1, RasGAP-SH3-domain binding protein 1; miRNA, microRNA; ncRNA, non-coding RNA; NTF2, nuclear transport factor 2; PD-L1, programmed death-ligand 1; PTGR, post-transcriptional gene regulation; RBD, RNA-binding domain; RBP, RNA-binding protein; RNP, ribonucleoprotein; SGs, stress granules; TIA-1, T-cell-restricted intracellular antigen-1

Key words: cytoplasmic activation/proliferation-associated protein-1, tumorigenesis, RNA-binding proteins, epigenetics

other factors and enzymes involved in mRNA regulation. RBPs are considered the most important regulators of PTGR. In addition to sustaining cellular metabolism, coordinating maturation, transportation, stability and degradation of all classes of RNAs through PTGR, RBPs serve a critical role in maintaining genome integrity (6,7) and responding to a variety of cellular stresses, thus ensuring cellular homeostasis (8,9). Considering the multifaceted effects of RBPs, dysfunctional RBPs can initiate various pathological changes, including neurodegenerative disorders, cardiovascular diseases and certain types of cancer (10-12).

Cancer is a complex and heterogeneous disease, and is classically considered to be caused by genetic alterations that result in the activation of oncogenic signaling pathways and/or loss of tumor suppressor mechanisms (13). As RBPs serve a pivotal role in PTGR, it is not surprising that abnormal changes to RBPs can cause alterations of cancer-associated signaling pathways. Furthermore, as RBPs regulate multiple targets in various PTGR steps, small changes in their expression and/or activity can induce a large-scale alteration of downstream regulatory networks, potentially initiating cancer development (13). A wide range of mechanisms underlie RBP alteration-induced oncogenesis, including changes to alternative splicing and polyadenylation, and changes in RNA stability, subcellular localization and translation (13). In order for tumor cells to achieve survival, proliferation, metastasis and resistance to anticancer therapeutics, they must make adaptive changes to the gene expression. Regulating transcribed mRNA or PTGR is the most effective and rapid mechanism for doing so, and it has a pivotal role in tumorigenesis. Tumor cells can change the expression of target mRNAs and feedback regulators (miRNA and ncRNA) through the regulation of RBPs. The abnormal expression of RBPs has been detected in numerous types of tumor, and different RBPs act at different steps of mRNA metabolism. For example, Sam68 participates in alternative splicing, producing a variety of tumor-promoting mRNA variants (14); eukaryotic translation initiation factor 4E is involved in directing ribosomes to the 5'-cap of mRNAs and enhances the expression of specific mRNAs that regulate certain tumorigenesis-associated processes, such as proliferation [c-Myc and cyclin-dependent kinase (CDK)2], metastasis (matrix metalloproteinase 9) and angiogenesis (vascular endothelial growth factor) (15), while embryonic lethal abnormal visual-like RNA binding protein 1 regulates the stability and translation efficiency of tumor-related mRNAs (16). Cytoplasmic activation/proliferation-associated protein-1 (caprin-1) is an RBP that is essential for cell proliferation. As caprin-1 is closely associated with control of the cell cycle, alteration of caprin-1 is involved in oncogenesis, which has been demonstrated in multiple experimental cancer studies (17-20). It is important for the study of cancer and its therapeutic development to fully understand the biological function of caprin-1 and the association between its alteration and oncogenesis.

2. Caprin-1 and RBPs

Caprin-1 is a ubiquitously expressed and highly conserved cytoplasmic phosphoprotein. The gene is located on the long arm of human chromosome 11 (11p13), encoding a 709-amino acid protein, with a molecular weight of 116 kDa. Caprin-1

is part of the conserved caprin family, which consists of two members, caprin-1 and caprin-2, both of which contain two highly conserved regions, homologous region-1 and -2 (21). High expression of caprin-1 was initially identified in dividing cells of the thymus, and was also known to be upregulated in activated T or B lymphocytes, and hematopoietic progenitors. Caprin-1 expression has been reported to be low in slowly dividing cells, such as those of the kidney or muscles, but high levels have been detected in the brain (21). Caprin-1 is considered to be an RBP, as it possesses RNA binding characteristics, i.e., the arginine-glycine-glycine (RGG) motif and the RG enrichment region (18). Using RNA-sequencing technology, 6,064 mRNAs (>1,000 reads) were identified as caprin-1 binding targets in the CD3 and CD28 antibody-activated human T lymphoma cell line (Jurkat). Table I presents a partial list of caprin-1 target mRNAs divided into six categories according to their biological function: Cell structure, RNA metabolism, RNA translation, signaling transduction, ubiquitylation, and growth factors and growth factor receptors (Wang *et al*, unpublished results). Caprin-1 can affect cell survival and growth through selectively binding a variety of mRNAs that are involved in cell growth, differentiation and migration, including c-Myc and cyclin-D2 (20,22-25). c-Myc serves a central role in the transition from the G₁ to the S phase of the cell cycle, and cyclin D2 functions as a regulatory subunit of the kinases CDK4 or CDK6, whose activity is required for the G₁ to the S phase transition (26,27). Cells without caprin-1 expression exhibit delays in the transition from the G₁ to the S phase of the cell cycle (17). Therefore, it is speculated that caprin-1 may serve an important role in tumorigenesis.

3. Caprin-1 and cancer

Caprin-1 selectively binds to c-Myc and cyclin D2 mRNAs, which accelerates cell progression through the G₁ phase into the S phase, enhances cell viability and promotes cell growth, indicating that it may serve an important role in tumorigenesis (17). This hypothesis is supported by increasing experimental and clinical evidence. Caprin-1 and associated regulatory factors (including miRNAs) are abnormally expressed in tumor tissues and tumor cell lines. For instance, miR-1 (24) and miR-223 (22) were revealed to be downregulated in renal carcinoma cells and breast cancer cells, respectively, resulting in a significant increase in the expression level of caprin-1. The overexpression of caprin-1 may contribute to the growth and invasion of tumor cells. Abnormal expression of caprin-1 was also observed in patients with osteosarcoma and in osteosarcoma cell lines (23). Increased expression of caprin-1 can promote tumor growth and lung metastasis from primary tumors, and shorten survival time (23). Tylophorine directly binds with caprin-1 and accelerates degradation of the RNP formed by caprin-1 and RasGAP SH3-domain-binding protein (G3BP), downregulates c-Myc and cyclins D1/D2, and ultimately inhibits the growth of the tumor (20). Our recent studies revealed the high expression of caprin-1 in clinical specimens from glioblastoma patients. The degree of caprin-1 expression was associated with clinical classification (28). Recently, a study by Casey *et al* (29) that focused on c-Myc, indirectly identified caprin-1 to be associated with certain immune checkpoint proteins. c-Myc has been

Table I. Caprin-1-targeted mRNAs in activated Jurkat cells^a.

Function	Gene	Gene ID	Fold enrichment
Cytoskeleton	Myosin heavy chain	MYH9	10.60
	Talin-1	TLN1	14.97
	Spectrin β chain	SPTBN2	11.95
	Filamin-B	FLNB	9.87
Receptors	Interleukin-17 receptor A	IL17RA	16.84
	Tetraspanin-27	CD82	10.82
	Interleukin-27- α	IL27RA	9.04
	Fibroblast growth factor receptor 4	FGFR4	7.75
Signaling	T-cell activation NFKB-like protein	NP_640332	15.56
	TNFR1-associated DEATH domain protein	TRADD	11.07
	Phospholipase C- β 3	PLCB3	10.81
	Protein phosphatase 1 regulatory 14B	PPP1R114B	9.48
RNA translation/metabolism	p21ras, PI3-kinase, MAPK		
	Eukaryotic translation factor 4 γ 1	eIF4-G1	10.83
	Pre-mRNA processing splicing factor 8	PRPFS	8.89
	40S ribosomal protein S19-binding protein 1	RPS19BP1	8.69
	Polyadenylate-binding protein 1	PABPC1	5.02
Growth factor-associated	G3BP1, FXR1, FXR2		
	Wnt-8b	WNT8B	15.56
	Fibroblast growth factor-binding protein 3	FGFBP3	12.21
	Insulin-like growth factor II receptor	IGF2R	8.45

^aCaprin-1 immunoprecipitation + RNA-sequencing from Jurkat cells stimulated with anti-CD3 and anti-CD28 antibodies. ID, identifier.

demonstrated to directly bind to the promoters of two immune checkpoint protein genes, the innate immune regulator CD47 and the adaptive immune checkpoint protein programmed death-ligand 1 (PD-L1), thus regulating their expression on the surface of tumor cells.

4. Caprin-1 may function as a complex with other RBPs

In biological microenvironments, protein molecules do not act alone; they function through intracellular networks formed by interactions with other proteins. According to published experimental results, caprin-1 can directly bind with G3BP1 (18), fragile X mental retardation protein (FMRP) (30) and Japanese encephalitis virus core protein (31). G3BP is a classic RBP, containing one nuclear transport factor 2-like function domain (NTF2), one acidic amino acid region, one RBD and one C-terminal RGG/G-enriched sequence. The direct combination of G3BP1 and caprin-1 is formed through the NTF2 domain of G3BP1 interacting with amino acids 352-380 of caprin-1 (18). The RBD region and RGG/G-enriched sequence can selectively bind mRNA. FMRP is another important RBP, and its deficiency can induce fragile X syndrome (32). FMRP contains two Agenet-like functional regions, two heterogeneous nuclear ribonucleoprotein K homology functional regions and one RGG region. The FMRP 427-442 amino acid sequence can interact with the caprin-1 231-245 amino acid sequence (30), while the Agenet-like region, KH functional region and RGG region have the mRNA binding function.

The existence of the caprin-1/G3BP1/FMRP-containing RNP was further confirmed by the recent crystallographic study by Wu *et al* (33). Crystal structures of a fragment of caprin-1 (residues 132-251) revealed that tight homodimerization can be formed through the combination of the HR1 regions of two molecules of caprin-1, creating a large and highly negatively charged concave surface, which acts as a protein-binding groove. This dimeric caprin-1 structure can be used as a scaffold to further combine with G3BP and FMRP to form a macromolecule polymer platform for more complex functions. Theoretically, two molecules of caprin-1 can combine with two molecules of G3BP1 and two molecules of FMRP. The resulting macromolecule polymer does not affect the integrity of the RNA-binding region of each component or their ability to bind mRNAs. Further precise research on the caprin-1/G3BP1/FMRP complex may have great potential to aid in developing novel and more effective anticancer drugs.

5. Caprin-1 may initiate carcinogenesis via stress granules

With increasing experimental evidence, the importance of SG in cancer has been awarded unprecedented attention. Our previous study demonstrated the presence of caprin-1 in RNA transport granules and stress granules (SGs) (18). These results indicated that caprin-1 may be involved in carcinogenesis through the formation of SGs. As illustrated in Fig. 1, there are numerous types of RNA-containing granule in the

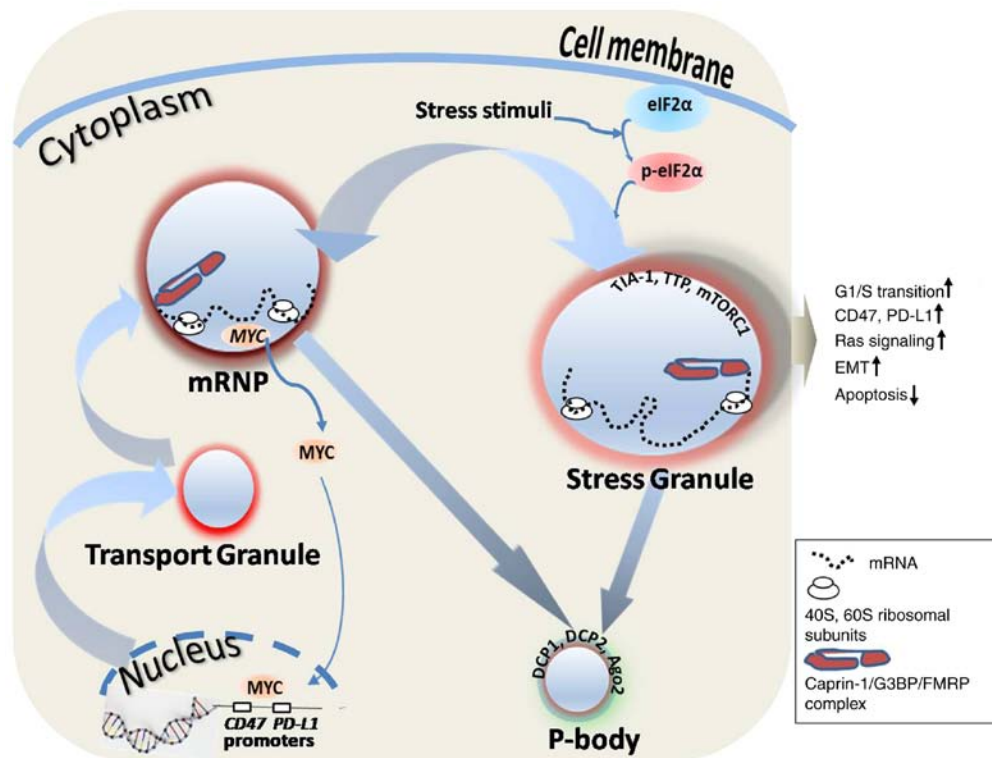


Figure 1. RNA granules and caprin-1-associated tumorigenesis. Caprin-1 mRNA is produced in the nucleus and transported into mRNP or the SG through the transport granule, and finally degraded in the P-body. Caprin-1-associated tumorigenesis takes place primarily through affecting SG-mediated tumorigenic characteristics and the MYC-mediated immune checkpoint. eIF2 α can be activated by various stress stimuli and induces SG formation, thereby leading to tumorigenic characteristics, such as increased transition from the G₁ to the S phase of the cell cycle, increased Ras signaling pathway, EMT and decreased apoptosis. Caprin-1 can also indirectly enhance the expression of immune checkpoint proteins, such as CD47 and PD-L1, through MYC, which is one of the regulatory targets of caprin-1. Caprin-1, cytoplasmic activation/proliferation-associated protein-1; mRNP, mRNA protein complexes; SG, stress granule; P-body, processing body; eIF2 α , eukaryotic translation initiation factor 2 α ; EMT, epithelial to mesenchymal transition; PD-L1, programmed death-ligand 1; TIA-1, T-cell-restricted intracellular antigen-1; TTP, tristetraprolin; mTORC1, mammalian target of rapamycin complex 1; DCP, decapping enzyme; Ago2, argonaute 2; G3BP, GTPase-activating protein (Src homology 3 domain) binding protein; FMRP, fragile X mental retardation 1.

cell cytoplasm, including RNA transport granules, SGs and processing bodies (P-bodies). RNA transport granules are responsible for transporting mRNA to specific subcellular structures. For example, actin and microtubules are located at the leading edge of the cell membrane in the direction of fibroblast and tumor cell movement, which is closely associated with the invasive growth and metastasis of tumor cells. Caprin-1 is present in RNA transport granules (18), which are located at tubulin-enriched sites, such as mid-bodies, actin-enriched podosomes (34,35), the leading edge membrane of moving T lymphocytes (Wang *et al*, unpublished data) and migrating fibroblasts (36). Caprin-1 and G3BP1 can combine with FMRP and coexist in RNA transport granules. P-bodies are the site of RNA degradation; they contain multiple molecules that are responsible for mRNA degradation, surveillance, translation inhibition and RNA-mediated gene suppression. P-bodies also include marker proteins decapping mRNA, RNA degradation enzyme 1 and RNA degradation enzyme 2, GW182 (another RBP), argonaute 2, RNA-induced silencing complex and miRNAs. SGs are formed in response to cells undergoing different stress stimuli and are a conserved mechanism to reduce stress-associated damage and promote cell survival. SGs contain translationally stalled mRNAs, translation initiation factors, 40S and 60S ribosomal subunits, translation of suspended enzymes, specific RBPs and signaling molecules (37,38). The majority of classic SGs are

produced by stress-induced phosphorylation of eukaryotic translation initiation factor 2 α (eIF2 α). Caprin-1, G3BP, T-cell-restricted intracellular antigen-1 (TIA-1), TIA-1-related protein, tristetraprolin (TTP) and FMRP can all induce the biogenesis of SGs. Caprin-1 combines with G3BP1 and/or TIA-1 and coexists in the classic SGs. However, high expression of caprin-1, G3BP, TIA-1, TTP or FMRP alone can induce the formation of SGs, even when there is no stress stimulus signal (18,39-43). SGs function to preserve RNAs against harmful conditions; they also serve a decisive role in facilitating further storage, translation reprogramming or degradation of untranslated mRNAs (38,44,45). The association between RNA granules and caprin-1-associated tumorigenesis is illustrated in Fig. 1.

SG formation is part of the integrated stress response, which is a process that receives information from different 'stress sensors' and acts with cells to adapt to stress stimuli (46). These sensors are usually kinases that can phosphorylate serine/threonine residues of eIF2 α . The tumor microenvironment is characterized by tissue hypoxia, high levels of reactive oxygen species and insufficient nutrients. These conditions can activate the cell stress response and promote SG formation, inducing tumor cells to adapt to the environment quickly and to alter metabolic pathways, thus maintaining their rapid growth. The existence of this mechanism has been validated in various clinical investigations. The presence of SGs has been verified in numerous types of human cancer, including glioblastoma,

Table II. Experimental evidence of caprin-1-associated human malignancies.

Type of cancer	Type of evidence	(Refs.)
Hepatocellular	Tissue microarray and IHC of specimens from 239 patients	(53)
	Human HepG2 and Hep3B cell lines	(20,47)
Osteosarcoma	Tissue microarray and IHC of specimens from 59 patients	(23)
	Human SaOS-2 and U2OS xenograft model	(23,49)
Breast	PET imaging study of SaOS-2/Caprin-1 vs. 143B model	(54)
Melanoma	Human MCF-7, T-47D and MDA-MB-231 vs. MCF-10A	(20,22,47)
	Human BT-474 and MDA-MB-453 xenograft model	(45)
	Proteomic analysis of human BLM melanoma cells	(55)
Glioblastoma	Human C6 and U87MG glioma cell lines	(48)
Prostate	Human PC-3 and LnCaP cell lines	(20,47)
Cervical	Human HeLa cell line	(20,47)
Gastric	Tissue microarray and IHC of specimens from 262 patients	(56)
	Human NUGC-3, HGC-27 and MGC80-3 cell lines	(20,56)
Pancreatic	Human H1299 xenograft model	(57)
Colon	Human PANC-1, BxPC3, S2-013, SUIT-2, COLO357, HPAF, MIA-Paca2, Capan2 and AsPC-1 cell lines	(20,58)
Leukemia	Human DLD-1, SW480 and HCT116 xenograft model	(20,59)
	Human U-937 and human leukemic Jurkat T cells	(20)

IHC, immunohistochemistry; PET, positron emission tomography.

hepatocellular carcinoma and osteosarcoma (47-50). In addition, radiation therapy and chemotherapy can stimulate tumor cells to form SGs, which can result in resistance to treatment (46). A variety of approved chemotherapeutic agents have been indicated to induce SG, resulting in reduced therapeutic efficacy (46,51). Therefore, it can be hypothesized that blocking SG production may effectively kill tumor cells. Experimental evidence supports the hypothesis that the inhibition of SG formation can enhance cell mortality and inhibit tumor growth (52).

In addition to roles in cell mortality and tumorigenesis, SGs are also associated with tumor metastasis. In tumor xenograft animal experiments, SG-producing osteosarcoma cells were more resistant to treatment and were able to migrate to the lungs with greater ease, while inhibiting SG formation via G3BP1 limited tumor invasion and prevented metastasis *in vivo* (49). Dissemination of tumor cells can enhance metastasis. Bone marrow-derived tumor cells from patients with breast cancer have been revealed to contain SGs, and these SGs contribute to cell survival of disseminated tumor cells (45).

6. Clinical perspectives on caprin-1

As demonstrated in Table II, caprin-1 has been reported to be involved in almost all types of human malignancy, although the majority of the evidence obtained thus far comes from *in vitro* settings. Given its pivotal role in the PTGR of cell cycle control-associated genes, caprin-1 and/or caprin-1-containing complex act as an amplifier to drive tumorigenesis (17,18). The clinical significance of caprin-1 will be elucidated along with the progress of the corresponding investigations.

Although being able to use caprin-1 as a therapeutic target in clinical practice may be a distant prospect, there are a number of established associations between caprin-1 and clinical cancer science: i) Caprin-1 acts as a biomarker for the clinical diagnosis of certain malignancies (53,54). Considering the close association between the expression level of caprin-1 and tumorigenesis, high expression levels of caprin-1 can be used as an indicator of certain malignancies. Caprin-1 mRNA and/or protein levels can be determined using molecular biology and liquid biopsy techniques in tissue or peripheral blood samples (28,55). ii) The degree of caprin-1 expression can be used to predict the prognosis of malignancies (23). iii) Caprin-1 and complexes can be used as a target for the development of cancer therapeutic drugs, such as specific short hairpin RNAs to knockdown caprin-1 expression, or specific peptides to block the formation of caprin-1/G3BP1/FMRP complexes (20,56-59).

7. Conclusions

Caprin-1 forms part of RNP complexes and directly interacts with mRNAs, and is therefore defined as an RBP. Caprin-1 acts alone or combines with other RBPs to participate in the regulation of cell cycle control-associated gene expression. Caprin-1 selectively interacts with c-Myc and cyclin D1/D2 mRNAs activating cell proliferation and upregulating the expression of immune checkpoint proteins CD47 and PD-L1. Through the formation of SGs, caprin-1 is also involved in the process of tumor cell adaption to adverse conditions, such as radiation and chemotherapy. Given its role in various clinical malignancies, caprin-1 holds the potential to be used as a biomarker and target for the development of novel therapeutics.

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Availability of data and material

The datasets used/analyzed in the present study are available from the corresponding author upon reasonable request.

Authors' contributions

ZSY, HQ, HG, JL and BW collected data. LJD and BW contributed to the writing of the manuscript. All the authors 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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