Long non-coding RNA CASC2 suppresses malignancy in human gliomas by miR-21

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A B S T R A C T

Long non-coding RNAs (lncRNAs) are aberrantly expressed in many diseases including cancer. LncRNA CASC2 (cancer susceptibility candidate 2) has been characterized as a tumor suppressor in endometrial cancer and colorectal cancer. However, the role and function of CASC2 in human gliomas remain unknown. In this study, we confirmed that CASC2 was lowly expressed in glioma tissues as well as in U251 and U87 glioma cell lines. Overexpression of CASC2 inhibited the malignancy of glioma cells, including proliferation, migration, and invasion, and promoted cell apoptosis. MicroRNA-21 (miR-21) has been reported to be overexpressed in human glioma tissues and cell lines, which is responsible for the malignant progression of glioma. We found that upregulated CASC2 decreased the expression of miR-21 significantly and there is a reciprocal repression between CASC2 and miR-21 in an Argonaute2-dependent manner. Furthermore, bioinformatics, luciferase reporter assays and pull-down assay confirmed that miR-21 binds to CASC2 in a sequence-specific manner. Introduction of miR-21 largely abrogated CASC2-mediated inhibition of glioma cell proliferation, migration, and invasion, and promotion of cell apoptosis. This study demonstrated that CASC2 plays a tumor suppressive role in glioma via negative regulation of miR-21, which may be a novel therapeutic target for treating gliomas.

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1. Introduction

Gliomas represent the major type of primary brain tumors and are often associated with fatal outcome because of their highly invasive growth pattern and frequent resistance to therapies [1]. A growing number of researches have been focused on exploring the molecular modulatory network involved in the development of glioma as well as investigating the effective therapeutic targets. Recently, various long non-coding RNAs (lncRNAs; >200 nt), including CRNDE, MEG3 and HOTAIR, have been identified as new modulators in the origination and progression of gliomas [2–4]. These lncRNAs could be employed as novel therapeutic targets.

Cancer susceptibility candidate 2 (CASC2), a lncRNA whose gene is located at chromosome 10q26, was originally identified as a down-regulated gene in endometrial cancer and acted as a tumor suppressor gene as well. Genomic and cDNA sequence comparisons revealed the presence of three alternatively spliced CASC2 transcripts (CASC2a, CASC2b and CASC2c) that share the first three exons but contain different downstream exons [5]. Exogenous expression of CASC2a in undifferentiated endometrial cancer cells significantly inhibited the clonal growth [6]. However, little is known about the expression levels of CASC2 in gliomas as well as whether it is involved in the gliomagenesis. Among the non-coding RNAs, microRNAs (miRNAs, ~22 nucleotides) have been extensively studied and their central role in diverse cellular and developmental processes has also been well documented. Aberrant expression of miRNA genes could cause severe human diseases such as cancer [7]. Using high-throughput profiling of miRNA expression, miR-21 was identified as being strongly elevated in various malignant tumors including colorectal, breast, and hepatocellular carcinoma [8,9]. In glioma tissues and cell lines, a growing body of literature reported that miR-21 was overexpressed as well. Knockdown of miR-21 inhibited gliomagenesis by regulating multiple genes associated with cell proliferation, apoptosis, migration and invasion, suggesting that miR-21 could be acting as an oncopogene in glioma cells [10–13].

In this study, we show that CASC2 is lowly expressed in glioma tissues and cell lines, which may act as a tumor-suppressor gene to suppress malignancy of glioma cells, including proliferation, migration, and invasion, and to promote cell apoptosis. MiR-21 was found to target CASC2 in a sequence-specific manner and there is a reciprocal repression between miR-21 and CASC2 possibly induced by RNA-induced silencing complex (RISC). The negative regulation of miR-21 by CASC2...
may partly account for CASC2-mediated inhibition of glioma cell proliferation, migration, and invasion, and promotion of cell apoptosis.

2. Materials and methods

2.1. Clinical specimens

All human specimens were obtained from the Department of Neurosurgery, Shengjing Hospital of China Medical University (Shenyang, China). Glioma specimens were divided into two groups: grade I–II glioma group (n = 12) and grade III–IV glioma group (n = 12) according to the 2007 WHO classification of tumors in the central nervous system. Human brain materials obtained from surgeries of brain trauma and epilepsy were used as negative control. All specimens were immediately frozen in liquid nitrogen following surgical resection. Informed consent for the use of specimens was obtained from all participants before surgery and approval was obtained from the Institutional Review Board at Shengjing Hospital of China Medical University and the hospital ethical committee.

2.2. Cell culture

Human U251 and U87 glioma cells, and human embryonic kidney cell line HEK-293 were obtained from Chinese Academy of Medical Sciences (Beijing, China). U87 glioma cells and HEK-293 cells were cultured in Dulbecco’s modified Eagle medium (DMEM)/high glucose supplemented with 10% FBS. U251 cells were cultured in DMEM/F12 medium supplemented with 10% FBS. All cells were maintained in a humidified incubator at 37 °C with 5% CO2. Primary normal human astrocytes (NHA) were purchased from the ScienCell Research Laboratories (Carlsbad, CA, USA) and cultured under the instructed condition by the manufacturer.

2.3. Cell transfection

Human CASC2 gene (NR_026939) was ligated into pCMV/MCS/RFP/Neo vector (GenePharma, Shanghai, China). The empty vector was used as a negative control (NC). Glioma cells at approximately 50–70% confluence were transfected using Opti-MEM I and Lipofectamine2000 reagents (Invitrogen, CA, USA) according to the manufacturer's instructions after 24 h of culture. Stable cell lines were created by selection with Geneticin (G418; Invitrogen, CA, USA) and their transfected efficiencies were assessed by quantitative real-time PCR (qRT-PCR). Furthermore, the miR-21 agonist (agomir-21), negative control of agomir (agomir-NC), miR-21 antagonist (antagomir-21), and negative control of antagomir (antagomir-NC; GenePharma, Shanghai, China) were transiently transfected into U251 and U87 glioma cells or cell lines which stably overexpressed CASC2 according to the manufacturer’s instructions, respectively. The levels of hsa-miR-21 in the transfected cells were verified by qRT-PCR.

2.4. RNA and miRNA isolation and quantitative RT-PCR

Total RNA was isolated from the glioma tissues and NHA, U251, and U87 cells using Trizol reagent (Life Technologies Corporation, Carlsbad, CA, USA). The RNA concentration was determined by 260/280 nm absorbance using a Nanodrop Spectrophotometer (ND-1000, Thermo, USA). cDNA from total RNA was generated using a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, CA, USA). cDNA from miRNAs was generated using a TaqMan miRNA Reverse Transcription kit (Applied Biosystems, Foster City, CA, USA). qRT-PCR was conducted using TaqMan gene expression assays of CASC2 and GAPDH or TaqMan Universal Master Mix II with TaqMan microRNA assays of miR-21 and U6 (Applied Biosystems, Foster City, CA, USA) using the ABI 7500 Fast Real-Time PCR System (Applied Biosystems). PCR cycling conditions were 2 min at 50 °C, 10 min at 95 °C and then 40 cycles of 15 s at 95 °C and 1 min at 60 °C. The primers of CASC2 (Hs00289594_m1), GAPDH (Hs03929097_g1), hsa-miR-21-5p (Assay ID: 000397) and U6 (Assay ID: 001973) were synthesized from the Applied Biosystems. GAPDH and U6 were used as endogenous controls for CASC2 and miR-21 expressions, respectively. Expressions were normalized to endogenous controls and fold change in gene expression was calculated as 2^(-ΔΔCt).

2.5. Cell proliferation assay

U251 and U87 cells were seeded in 96-well plates at the density of 2000 cells/well. 10 μL of Cell Counting Kit-8 (Beyotime, Jiangsu, China) solution was added into each well and cells were incubated for 1.5 h at 37 °C. Absorbance at 450 nm was recorded using the SpectraMax M5 microplate reader (Molecular Devices, USA). Five replicate wells were set up in each group and five independent experiments were performed repeatedly.

2.6. Apoptosis detection

Apoptosis was assessed using Annexin V-FITC/PI double staining kit (Beyotime, Jiangsu, China). Cells were harvested and stained with Annexin V-FITC and PI according to the manufacturer’s instructions. Cell samples were analyzed on flow cytometry (FACScan, BD Biosciences).

2.7. Cell migration and invasion assay

Migration and invasion of U251 and U87 cells in vitro were assayed using Transwell chamber (Costar, Corning, NY, USA) with polycarbonate membrane (6.5 mm in diameter, 8 μm pore size). In the migration assay, the transfected cells were resuspended in 100 μL serum-free medium at a density of 5 × 10^5 cells/mL and added in the upper chamber. 600 μL of DMEM/high-glucose or DMEM/F12 medium supplemented with 10% FBS was added to the lower chamber. After incubation for 48 h, the cells on the upper membrane surface were mechanically removed. Cells that had migrated or invaded to the lower side of the membrane were fixed with methanol and stained with 20% Giemsa. Stained cells were counted under a microscope in five randomly chosen fields and the average number was calculated. In the invasion assay, the Transwell membrane was coated with 80 μL of Matrigel solution (500 ng/mL; BD, Franklin Lakes, NJ, USA) and incubated at 37 °C for 4 h, the remaining steps were similar to the migration assay.

2.8. Bioinformatics prediction and luciferase reporter assay

The potential microRNA binding sites of CASC2 predicted by computer-aided algorithms were obtained from microRNA.org-target program (www.microRNA.org). The putative miR-21 target binding sequence in CASC2 and its mutant of the binding sites were synthesized and cloned downstream of the luciferase gene in the pmirGLO luciferase vector (Promega, Madison, WI, USA). HEK-293 cells were seeded in 96-well plates for 24 h, and cells at 50–70% confluence were co-transfected with wild-type or mutated pmirGLO-CASC2 reporter plasmid and agomir-21 or agomir-NC. The luciferase activity was measured 48 h after transfection using the Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA).

2.9. Pull-down assay with biotinylated miR-21

U251 and U87 cells were transiently transfected with biotinylated miR-21, miR-21-Mut and negative control of miR-21 (GenePharma, Shanghai, China), harvested and lysed 48 h after transfection. 50 μL of the samples were aliquoted for input. The remaining lysates were incubated with Dynabeads M-280 Streptavidin (Invitrogen, CA, USA) according to the manufacturer’s protocol. In brief, the washed beads were treated in RNase-free solutions and incubated with equal volume
of biotinylated miR-21 for 10 min at room temperature in binding and washing buffer on a rotator. Then, the beads with the immobilized miR-21 fragment were incubated with 10 mM EDTA pH 8.2 with 95% formamide at 65 °C for 5 min. The bound RNAs were purified using Trizol for the qRT-PCR analysis.

2.10. Pull-down assay with biotinylated DNA probe

The biotinylated DNA probe complementary to CASC2 IncRNA was synthesized (GenePharma, Shanghai, China), dissolved in binding and washing buffer, and incubated with DynaBeads M-280 Streptavidin (Invitrogen, CA, USA) at room temperature for 10 min to generate probe-coated beads according to the manufacturer’s protocol. Then, U251 and U87 cell lysates were incubated with the probe-coated beads, and the RNA complexes bound to these beads were eluted and extracted for qRT-PCR analysis. The CASC2 pull-down probe sequence was 5′-Bio-GAGGAGCCATCGCAATCACAAT-3′; and random pull-down probe sequence used as negative control was 5′-Bio-AGCTTAGACTGTAGAGC-3′.

2.11. RNA immunoprecipitation

U251 and U87 cells were lysed using a complete RNA lysis buffer containing protease inhibitor and RNase inhibitor from an EZ-Magna RIP RNA-binding protein immunoprecipitation kit (Millipore, Billerica, MA, USA). RNA immunoprecipitation was performed following the manufacturer’s protocol. 100 μL of whole cell lysate was incubated with RIP immunoprecipitation buffer containing magnetic beads conjugated with human anti-Argonaute2 (Ago2) antibody (Millipore), and negative control normal mouse IgG (Millipore). Samples were incubated with Proteinase K buffer and then immunoprecipitated RNA was isolated. The RNA concentration was measured by a NanoDrop (Thermo Scientific) and the RNA quality assessed using a bioanalyzer (Agilent, Santa Clara, CA, USA). Furthermore, purified RNA was subjected to qRT-PCR analysis to demonstrate the presence of the binding targets using respective primers mentioned above.

2.12. Statistical analysis

Data are presented as mean ± standard deviation (SD) and analyzed using SPSS 13.0 software (SPSS, Chicago, USA) with the Student’s t-test or one-way ANOVA. Differences were considered to be significant when \( P < 0.05 \).

3. Results

3.1. Down-regulated expression of CASC2 in glioma tissues and cell lines

The expression levels of IncRNA CASC2 in control brain, grade I–II and grade III–IV glioma tissues as well as in NHA, U251, and U87 cells were analyzed by qRT-PCR. As shown in Fig. 1, CASC2 expression levels were significantly down-regulated in glioma tissues and two glioma cell lines compared with the average expression levels in control brain tissues and NHA (\( P < 0.05 \)). Furthermore, the expression levels of CASC2 were reduced with the rising pathological grades of gliomas.

3.2. CASC2 inhibited cell proliferation, migration, and invasion, and promoted apoptosis of glioma cells

The CASC2 was stably overexpressed in glioma cell lines (3.73-fold in U251 cells, 4.16-fold in U87 cells, Fig. 2A) to assess the potential functional role. As shown in Fig. 2B, over-expression of CASC2 resulted in a significantly decreased proliferation of U251 and U87 glioma cells compared to the respective NC group (\( P < 0.05 \)). The effects of CASC2 IncRNA on the migratory ability and invasiveness of glioma cells were checked by Transwell assays. As shown in Fig. 2C, over-expressed CASC2 impeded the migratory ability by roughly 42% in U251 cells and by roughly 45% in U87 cells. Corresponding effects on invasiveness were also observed in a parallel invasion assay, which indicated a significant reduction of invasion in U251 and U87 cells compared with the respective NC group (\( P < 0.05 \)). Moreover, Fig. 2D showed that up-regulated CASC2 significantly promoted the apoptosis in both U251 and U87 cells compared with the NC group (\( P < 0.01 \)).

3.3. CASC2 is a target of miR-21

Several recent reports have confirmed that IncRNA may function as a competing endogenous RNA (ceRNA) or a molecular sponge in modulating the concentration and biological functions of miRNA[14,15], suggesting that there might be an inverse correlation between expression of IncRNA and miRNA. To explore the potential targeted miRNA of CASC2, bioinformatics analysis (miRanda) of miRNA recognition sequences was performed and the result revealed that several miRNA binding sites were presented in CASC2 cDNA. Fig. 3A indicated that the stable overexpression of CASC2 significantly reduced the expression level of miR-21 (\( P < 0.01 \)). Moreover, the binding site of miR-21 to CASC2 was highly conserved among species (Fig. 3B). To further investigate whether CASC2 was a functional target of miR-21, dual-luciferase reporter assay was performed. The results showed that overexpressed

![Fig. 1](image1.png)  **Fig. 1.** CASC2 was lowly expressed in human glioma tissues and cell lines. Expression levels of CASC2 were determined by qRT-PCR in control brain tissues, glioma tissues with pathological grades from I–II to III–IV and NHA, U251, and U87 glioma cells. Data were presented as mean ± SD from three independent experiments. **\( P < 0.01 \).**
Fig. 2. Overexpressed CASC2 inhibited cell proliferation, migration, and invasion, and promoted apoptosis of glioma cells. (A) CASC2 expression levels were evaluated using qRT-PCR in pGCMV/CASC2-transfected U251 and U87 cells. (B) CCK-8 assay was performed to determine the proliferation of U251 and U87 cell lines stably overexpressing CASC2. (C) Transwell assay was performed in U251 and U87 cells stably overexpressing CASC2 to investigate changes in cell migration and invasiveness. (D) The apoptotic percentages of U251 and U87 cells stably overexpressing CASC2 were detected by flow cytometry. UL, necrotic cells; UR, terminal apoptotic cells; and LR, early apoptotic cells. Data were presented as mean ± SD from five independent experiments. *P < 0.05, **P < 0.01. Scale bar represents 20 μm.
miR-21 significantly decreased luciferase activity of wild-type pmirGLO-CASC2 compared with the miR-21-NC group, and miR-21 did not affect the mutated pmirGLO-CASC2-Mut luciferase activity (\(P_{b}0.01\); Fig. 3C, D). Furthermore, we applied a biotin–avidin pull-down system to find out whether miR-21 could pull down CASC2. As shown in Fig. 3F, CASC2 was pulled down by miR-21 as analyzed by qRT-PCR, but the introduction of mutations that disrupted the putative miRNA recognition site between CASC2 and miR-21 led to the inability of miR-21 to pull down CASC2, indicating that the recognition of miR-21 to CASC2 is in a sequence-specific manner. We also used inverse pull-down assay to test whether CASC2 could pull down miR-21, using a biotin-labeled specific CASC2 probe. MiR-21 was precipitated as analyzed by qRT-PCR (Fig. 3G). Taken together, these data demonstrated that miR-21 could directly bind to CASC2 at the miRNA recognition site.

To elucidate whether there was a negative correlation between CASC2 and miR-21, the expression levels of CASC2 were detected by qRT-PCR. As shown in Fig. 4A, agomir-21, the agonist of miR-21, markedly up-regulated miR-21 expression in U251 and U87 glioma cells (\(P_{b}0.01\)). Antagomir-21, the antagonist of miR-21, significantly down-regulated miR-21 in U251 and U87 glioma cells (\(P_{b}0.01\); Fig. 4B). Agomir-21 decreased the expression level of CASC2 and antagomir-21 induced the inverse results in U251 and U87 glioma cells (\(P_{b}0.01\); Fig. 4C, D). We have shown that overexpressed CASC2 significantly reduced the miR-21 expression in Fig. 3A. Taken these results together, it has been reasonable to infer that there might be a reciprocal repression feedback loop between CASC2 and miR-21.
To clarify whether RISC might be involved in the reciprocal repression between CASC2 and miR-21, RNA immunoprecipitation experiments were performed using antibody against Ago2, a key component of RISC complex. Fig. 4E and 4F indicated that both CASC2 and miR-21 were in Ago2-pulled down pellet.

3.5. Overexpression of miR-21 largely reversed CASC2-induced inhibitory effects on glioma cells

Having confirmed that CASC2 was a target of miR-21, the role of miR-21 in IncRNA CASC2-induced inhibition on glioma cells remains unclear. Fig. 5A and B showed that up-regulated miR-21 in U251 and U87 glioma cells, which stably overexpressed CASC2, largely reversed the inhibitory effect of CASC2 on cell proliferation, migration and invasion. Moreover, overexpression of miR-21 largely suppressed the cell apoptosis promoted by CASC2 (Fig. 5C). These results strongly suggested that miR-21 played a crucial role in CASC2-induced inhibitory effects on glioma cells.

4. Discussion

Recently, accumulated evidence on IncRNA has indicated that dysregulation of IncRNA may not only affect the regulation of the eukaryotic genome, but also provide a growth advantage to malignant cells, resulting in progressive and uncontrolled tumor growth [16,17]. Our research provided evidence that lowly expressed CASC2 in glioma tissues and cell lines functioned as a tumor suppressor gene. CASC2 was identified as a target of miR-21 and there was a reciprocal repression between each other. CASC2 functions as a tumor-suppressor to suppress the malignancy of glioma cells in large part through the negative regulation of miR-21.

CASC2 was first identified in the loss of the heterozygosity region of chromosome 10q26 with a low frequency of mutation in endometrial cancer. CASC2 was expressed in a lower level in various tumor tissues such as endometrial cancer, colorectal cancer, malignant melanoma, and kidney and renal carcinoma tissues, than that in normal tissues. In AN3CA endometrial cancer cell line, CASC2 behaved as a tumor suppressor in that exogenous expression of CASC2 inhibited cell proliferation as well as colony formation [5,6]. A number of cytogenetic and molecular analyses revealed that there were very frequent and extensive losses of regions of chromosome 10 (10pter-q11 and 10q24-q26) in human glioblastomas [18]. To explore whether CASC2 might be correlated to the tumorigenesis of glioma, we detected the expression levels of CASC2 in glioma tissues, and U251 and U87 glioma cells. The results indicated that CASC2 was significantly down-regulated compared with control brain tissues and NHA. The function of CASC2 was also investigated in our experiment. The data indicated that CASC2 inhibited cell proliferation, migration, and invasion, and promoted the apoptosis of U251 and U87 glioma cells. In glioma tissues and cells, the down-regulated CASC2 may also act as a tumor suppressor gene, which was in accordance with the reports about CASC2 in other tumor tissues [5,6].

Emerging evidence suggests that IncRNAs may participate in the competitive endogenous RNAs (ceRNA) regulatory network and act as endogenous miRNA sponges to bind to miRNAs and regulate their function [14,19]. To find out whether CASC2 serves as a miRNA sponge, we performed the bioinformatics analysis to explore the potential
Fig. 5. Overexpression of miR-21 largely reversed CASC2-induced inhibitory effects on glioma cells. (A) Overexpression of miR-21 partly reversed CASC2-induced inhibition of proliferation in U251 and U87 cells determined by CCK-8 assay. (B) Overexpression of miR-21 largely reversed CASC2-induced suppression of migration and invasion in U251 and U87 cells detected by Transwell assay. (C) Overexpression of miR-21 partly reversed CASC2-induced apoptosis in U251 and U87 cells detected by flow cytometry. Data were presented as mean ± SD from five independent experiments. *P < 0.05, **P < 0.01. Scale bar represents 20 μm.
interactions between them and found that the expression of miR-21 was significantly suppressed in U251 and U87 glioma cell lines that overexpressed CASC2. Luciferase assay and biotin–avidin pull-down assay verified that miR-21 can bind to CASC2 directly by the putative miRNA response element (MRE). MRE was identified to be a highly conserved sequence by UCSC Genome Browsers, suggesting that MRE might be an important functional sequence element. Moreover, up-regulated expression of miR-21 could also suppress the CASC2 expression, whereas down-regulated miR-21 induced a reverse result, which suggested that there might be a reciprocal repression between CASC2 and miR-21. To better clarify the underlying mechanism of the miRNA/lncRNA trans-regulatory function, we performed RIP with anti-Ago2 antibody. The results provided in the present study support the involvement of RISC complex in this reciprocal repression process, which is consistent with the following literature. In gastric cancer, up-regulated HOTAIR acts as a ceRNA, which modulates the derepression of HER2 through competition for miR–331–3p binding in Agog2-containing ribonucleoprotein complex [15]. Loc285194 is a p53-regulated tumor suppressor, which executes the anti-cancer function in part through the repression of miR-211 in RISC complex [20].

The role of miR-21 has been well characterized as an oncogenic gene in cancer. In various human tumors, miR-21 is frequently overexpressed and plays a crucial role in oncogenesis, including the association with high proliferation, invasion, metastatic potential and low apoptosis [21,22]. In glioma cells, the overexpressed miR-21 is also implicated in the malignant progression, in which a number of miR-21 targets are involved. Inhibition of miR-21 by antisense oligonucleotides leads to inhibition of HNRPK and TAp63, known as the coactivator and homologue of p53 respectively, causing repressed growth, increased apoptosis, and invasiveness in A172 and LN229 glioma cells as well as human breast cancer MCF7 and human osteosarcoma U2OS cell lines [23]. Posttranscriptional regulation of Spry2 by miR-21 has an essential role in glioma invasion by controlling the strength and duration of Ras/MAPK signaling [24]. Down-regulation of miR-21 in U251 glioma cells leads to derepression of HNRPK and TAP63, known as the coactivator and homologue of p53 respectively, causing repressed growth, increased apoptosis, and promoted cell cycle arrest [25]. To verify the hypothesis that CASC2 functions via down-regulating the expression of miR-21, agomir-21 was used to up-regulate the miR-21 expression in glioma cell lines that stably overexpressed CASC2. The results indicated that up-regulated miR-21 largely reversed the cell proliferation, migration, invasion and apoptosis induced by CASC2. Therefore, it may highlight the significance of the interaction between microRNAs and lncRNAs in tumorigenesis that CASC2 suppressed malignancy of glioma mainly by inhibiting miR-21.

5. Conclusions

Lowly expressed CASC2 functions as a tumor suppressor gene in gliomas. CASC2 is a target of miR-21 and there is a reciprocal repression between them in an Ago2 dependent manner. Ectopic expression of CASC2 suppresses malignancy of glioma cells mainly by miR-21. Our research has provided a better understanding of the CASC2 function in glioma, which might facilitate the development of lncRNA-directed diagnostics and therapeutics against this disease.

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