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Go-Ichi-Ni-San 2: A potential biomarker and therapeutic target in human cancers

Shan DD *et al.* GINS2: A novel target in human cancers

Abstract

Cancer incidence and mortality are increasing globally, leading to its rising status as a leading cause of death. The Go-Ichi-Ni-San (GINS) complex plays a crucial role in DNA replication and the cell cycle. The GINS complex consists of four subunits encoded by the GINS1, GINS2, GINS3, and GINS4 genes. Recent findings have shown that GINS2 expression is upregulated in many diseases, particularly tumors. For example, increased GINS2 expression has been found in cervical cancer, gastric adenocarcinoma, glioma, non-small cell lung cancer, and pancreatic cancer. It correlates with the clinicopathological characteristics of the tumors. In addition, high GINS2 expression plays a pro-carcinogenic role in tumor development by promoting tumor cell proliferation and migration, inhibiting tumor cell apoptosis, and blocking the cell cycle. This review describes the upregulation of GINS2 expression in most human tumors and the pathway of GINS2 in tumor development. GINS2 may serve as a new marker for tumor diagnosis and a new biological target for therapy.

Key Words: Go-Ichi-Ni-San; Go-Ichi-Ni-San 2; Cancer; Biomarker; Clinicopathological characteristics; Molecular mechanism

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Core Tip: The Go-Ichi-Ni-San (GINS) complex plays a crucial role in DNA replication and the cell cycle. The GINS complex consists of four subunits encoded by the GINS1, GINS2, GINS3, and GINS4 genes. This review explores the differential expression of GINS2 as a novel target in human cancers. GINS2 is upregulated in most tumors and can influence tumorigenesis and progression through competing endogenous RNA effects and signaling pathways. Therefore, GINS2 may become a new target for the diagnosis and treatment of many cancers.

INTRODUCTION

Cancer ranks as the second leading cause of death worldwide, and the burden of cancer is growing, with approximately 9.6 million deaths due to cancer in 2018. Unfortunately, many cancer patients worldwide do not have access to timely, high-quality diagnosis and treatment (World Health Organization, <https://www.who.int/cancer/en/>). It is therefore crucial to more fully understand how cancer develops and to identify new markers for its diagnosis and new targets for its treatment.

In 2003, Takayama *et al*^[1] described Go-Ichi-Ni-San (GINS) for the first time. The GINS complex is conserved in eukaryotic cells and is essential for DNA replication. When the DNA replication fork is opened, GINS is required to maintain the association between the microchromosome maintenance protein (MCM) and Cdc45 in the large replicator complex^[1]. The GINS complex acts as a replicative helicase that unlocks the double-stranded DNA prior to the moving replication fork^[2]. The GINS complex consists of four subunits encoded by the GINS1, GINS2, GINS3, and GINS4 genes. GINS2, also known as Psf2, is located in regions 2 and 4 of the long arm of chromosome 16 with a length of 1196 bp^[2], as shown in Figure 1. Recent results suggest that GINS2 expression is upregulated in many diseases, especially tumors, and adversely affects prognosis, such as in patients with cervical cancer (CC)^[3], breast cancer (BC)^[4,5], gastric adenocarcinoma^[6], glioma^[7], non-small cell lung cancer (NSCLC)^[8,9], and pancreatic cancer^[10,11].

In this review, we reviewed associated reports and searched the PubMed database from February 2008 to April 2022 using the keywords “GINS2” and “cancer.” After excluding articles from letters, case reports, reviews, meta-analyses, or conference reports, 55 articles describing the expression of GINS2 in human cancers and its relevance to clinical features, as well as the pathways of GINS2 in tumors, were included for further analysis. It is reasonable to assume that GINS2 may become a marker in cancer diagnosis and a biological target for prognosis.

EXPRESSION PROFILES OF GINS2 IN CANCERS

Numerous studies have investigated the expression levels of GINS2 in human tissues. The results show that GINS2 expression is increased in most tumors compared to normal tissues and correlates with various clinicopathological features. It has been demonstrated that GINS2 is expressed at higher levels in tumor tissue than in adjacent normal tissue, such as in CC^[3], gastric adenocarcinoma^[6], glioma^[7], NSCLC^[8,9], pancreatic cancer^[10,11], and thyroid cancer (TC)^[12,13]. Specifically, analysis of potential correlations between GINS2 expression levels and clinicopathological features has indicated that high GINS2 expression levels are closely associated with tumor size^[6,10], tumor nodal metastasis (TNM) stage^[6,8], pathological grade^[7] and vascular permeation^[10]. These conclusions imply that GINS2 may act as a tumor promoter. A summary of data obtained from published studies is provided in Table 1. In addition, in conjunction with the online database GEPIA, we show in Figure 2 the GINS2 gene expression and prognosis in the tumors mentioned in Table 1, which further complements the information in Table 1.

MOLECULAR PATHWAYS INVOLVED IN GINS2

In most tumors, elevated levels of GINS2 expression can increase malignant features such as tumor cell proliferation^[3-9,11-18], migration^[8,13,14], invasion^[8,13], epithelial-mesenchymal transition (EMT)^[8,10], anti-apoptosis effects^[7,9,12-16,18,19] and cell cycle arrest^[7,9,11,12,15-19], as shown in Figure 3, which are related to the many mechanisms GINS2 is involved in, as shown in Figure 4 and Table 2.

BC

BC has high morbidity and mortality rates. However, there is still no cure, and patients diagnosed at a late stage often have a poor survival rate, and therefore it is crucial to better understand the mechanisms of breast cancer development^[20]. **Matrix metalloproteinases (MMPs) are zinc (Zn²⁺)-dependent endopeptidases involved in the remodeling of the extracellular matrix** during physiopathological processes^[21]. MMPs play an important role in development, wound healing, tissue remodeling and

angiogenesis, with angiogenesis playing a key role in the growth and development of tumors^[22]. MMP9 is one of these MMPs and belongs to the gelatinase family^[23]. It degrades gelatine and collagen types IV, V, XI and XVI in tissue remodeling and has a significant impact on tumor invasion and metastasis^[24]. Peng *et al*^[4] found that knockdown of GINS2 in breast cancer resulted in a significant reduction in MMP9, and GINS2 may regulate the invasive and stem cell-like properties of breast cancer cells through MMP9. The above findings suggest that the expression of GINS2 may be closely related to the prognosis and survival of BC patients.

Bladder cancer

Bladder cancer has a high incidence of cancer of the urinary system, and 150000 people die of bladder cancer each year^[25]. Targets for the effective diagnosis and treatment of bladder cancer are vital. Tian *et al*^[26] found that GINS2 mRNA was a downstream target of miR-22-3p in bladder cancer cells and that knockdown of GINS2 suppressed the phenotype of tumor cells. Similar results were found in bladder cancer cells by Dai *et al*^[27].

Colon cancer

The incidence and mortality rate of colon cancer remain high and pose a substantial global burden^[28]. Exploring new targets for colon cancer is particularly critical. In cells, protein tyrosine phosphatases (PTPs) have a vital role in regulating tyrosine phosphorylation levels and numerous physiological processes^[29]. PTP4A1 belongs to the tripartite PTP subclass (PTP4A1/2/3)^[30]. Hu *et al*^[31] found that GINS2 interacted with PTP4A1 to regulate the proliferation and apoptosis of colon cancer cells. This finding indicates that GINS2 may be a potential new molecular target for colon cancer.

Ovarian cancer

In 2018, the worldwide incidence of ovarian cancer (OC) was 6.6 per 100000^[32]. Zhan *et al*^[14] found that miR-502-5p can inhibit GINS2 expression through the activity of a

competing endogenous RNA, which inhibits OC progression by suppressing OC cell growth and promoting apoptosis. In summary, GINS2 can be used as a downstream molecule to influence OC development, and GINS2 may be a new OC target.

Glioma

Gliomas are the most commonly occurring primary malignancies in the brain, with significantly higher recurrence and mortality rates^[33]. In addition, the prognosis of patients is poor, methods to significantly improve patient survival are lacking, and research into the mechanisms of glioma is urgently needed. Minichromosome maintenance complex component 2 (MCM2) belongs to the minichromosome maintenance protein complex and consists of 6 highly conserved proteins (MCM2-7)^[34]. ATM is an important upstream signaling molecule that controls the cell cycle and phosphorylates and activates CHEK2 during DNA replication or upon stimulation by other substances, halting the cell cycle^[35-37]. Shen *et al*^[7] used laser confocal microscopy to reveal the relationship between MCM2 and ATM in glioma cells. Additionally, it was reported that inhibition of GINS2 expression reduced cell proliferation and tumorigenicity and that GINS2 could block the cell cycle by regulating MCM2, ATM, CHEK2 and other downstream molecules^[7]. GINS2 could be a prognostic indicator and potential therapeutic target for glioma.

Leukaemia

Leukaemia is a blood cancer that originates in the bone marrow and is one of the leading causes of death from tumors in humans. In 2016, there were 467000 new cases of leukaemia and 310000 deaths from leukaemia worldwide. Early detection of effective treatment options for leukaemia can help reduce mortality^[38]. Mitogen-activated protein kinase (MAPK) is a serine/threonine-protein kinase found in eukaryotic cells that can be activated by various internal and external stimuli. Upon activation, MAPK transmits extracellular signals to the nucleus and affects cellular functions by modulating the activity of transcription factors to alter the expression of related

genes^[39]. The p38MAPK signaling pathway is a member of the MAPK superfamily. Gao *et al*^[19] reported that GINS2 knockdown caused cell cycle arrest in chronic granulocytic leukaemia cells and acute promyelocytic leukaemia cells at the G2 phase through activation of p38MAPK.

ATM-Chk2 and ATM-Chk1 are key signaling pathways that mediate the DNA damage response, and activation of these pathways is critical for the coordination of checkpoint and DNA repair processes. The DNA damage response is crucial to both cancer progression and treatment. p53 oncogene mutations are a way to evade the oncogenic barrier during tumor progression^[40]. The findings of Zhang *et al*^[16] suggest that the ATM, Chk2 and p53 genes may play a role in the pathogenic signaling pathway of human acute promyelocytic leukaemia when the GINS2 gene is downregulated. The above studies suggest that GINS2 contributes to the diagnosis and treatment of leukaemia.

NSCLC

Lung cancer is the leading cause of cancer deaths, with NSCLC accounting for approximately 85% of all lung cancers^[41]. Patients with NSCLC are often at an advanced stage at the time of detection. A better understanding of the development and evolution of NSCLC is needed to improve this situation. GADD45A is a protein whose expression is regulated over the entire cell cycle, with levels of this protein at their highest in the G1 phase and significantly reduced in the S phase. p53 is a member of the GADD45 (growth arrest and DNA damage induction) family and is responsible for maintaining genomic stability. Wild-type p53 protein arrests cell proliferation, inhibits cell division at the G1 checkpoint and contributes to the repair of damaged DNA. p53 mutations predispose cells to cellular malignancy and tumor formation during the S-phase of damaged DNA. GADD45A-mediated G2-M arrest was found to be dependent on wild-type p53, which controls cell proliferation/apoptosis by regulating cell cycle phases^[42]. The results of Chi *et al*^[9] showed that GINS2 expression was increased in NSCLC tissues

and cell lines and could promote cell proliferation and inhibit apoptosis *via* the p53/GADD45A pathway.

Studies have shown that noncanonical nuclear factor-kappaB (NF-κB) transcription factors regulate several normal cellular and tissue processes, such as inflammatory responses, immunity, cell growth, and apoptosis^[43,44]. NF-κB is an important “transcription factor”, and aberrant activation of NF-κB signaling has been implicated in the pathogenesis of many diseases, especially tumors^[45-47]. Tumor necrosis factor-inducible protein 3 (TNFAIP3) encodes TNFAIP3 (also known as A20) and is a critical negative regulator of NF-κB signaling^[48]. Family members of transcription signal transducers and activators (STATs) have been identified as key proteins involved in cytokine signaling and interferon-related antiviral activity^[49-51]. Their signaling activities are involved in many normal physiological cellular processes, including proliferation, differentiation, apoptosis, and angiogenesis. However, aberrant STAT regulation can lead to various pathological events, such as malignant cell transformation and metastasis^[52]. Sun *et al*^[17] found that after GINS2 gene knockout, the expression of STAT1 and STAT2 proteins increased, which inhibited tumor migration and proliferation. The protein expression of TNFAIP3 increased, suggesting that TNFAIP3 participates in the activity of GINS2 and could be involved in the spread and migration of NSCLC.

Both the ⁶PI3K/Akt and MEK/extracellular signal-regulated kinase (ERK) pathways have been reported to be associated with EMT in tumors^[53,54]. Liu *et al*^[8] also found that GINS2 could enhance the proliferation, migration, invasion and EMT of NSCLC cells *in vivo* and *in vitro* and further demonstrated that GINS2 could regulate the PI3K/Akt and MEK/ERK signaling pathways. In conclusion, GINS2 may be a therapeutic target for NSCLC.

Pancreatic cancer

Due to the adverse survival prognosis of pancreatic cancer, the number of deaths is almost as high as the number of patients, and morbidity and mortality rates have

remained stable or increased slightly in many countries^[55]. It is therefore of interest to identify new targets for the diagnosis and treatment of pancreatic cancer. ERKs belong to the MAPK family and function in signaling cascades that transmit extracellular signals to cells. MAPK cascades are key signaling elements that regulate key processes such as cell proliferation, differentiation, and stress responses^[56-58]. The ERK cascade is a tightly controlled cascade responsible for fundamental cellular processes. Excessive activation of proteins and kinases in the ERK pathway has been shown to contribute to a variety of diseases, including cancer, inflammation, developmental disorders, and neurological disorders^[59,60]. Huang *et al*^[10] found that overexpression of GINS2 in pancreatic cancer could stimulate EMT *in vitro*. In MiaPaCa-2 and PANC-1 cells with high GINS2 expression, GINS2 colocalized and coprecipitated with ERK, suggesting that GINS2 interacts closely with the MAPK/ERK pathway. Zhang *et al*^[18] used small interfering RNA to reduce GINS2 expression and explored its mechanism of action in pancreatic cancer. Their results showed that GINS2 interference inhibited pancreatic cancer cell viability through the MAPK/ERK pathway, induced cell cycle arrest and promoted apoptosis in pancreatic cancer cell lines. The above findings suggest that GINS2 may play a negative role in pancreatic cancer and has a guiding role in treating pancreatic cancer.

TC

Since the 1980s, the incidence of TC has increased rapidly in most parts of the world. However, the aetiology of TC is not well understood, and the study of its development is particularly critical in its prevention and treatment^[55]. Cbp/p300-interacting transcription factor 2 (CITED2) has a Glu/asp-rich carboxy-terminal domain and is a non-DNA-binding transcriptional coregulator. CITED2 can directly bind to host transcription factors and coactivators, interacting with them to activate gene transcription and affect their function^[61]. Several studies have demonstrated that interference with CITED2 can induce apoptosis^[62]. Lysine oxidase class 2 (LOXL2) is a member of the lysine oxidase (LOX) family, and some researchers have found that

overexpression of LOXL2 activates cell growth in BC. In addition, LOXL2 can directly bind to substrate-like 1 of myristoylation alanine-rich kinase (MARCKSL1), activate the FAK/Akt/mTOR signaling pathway, and inhibit MARCKSL1-induced apoptosis^[63]. Ye *et al*^[12] found that GINS2 plays a role in TC cell proliferation and apoptosis by regulating the expression of CITED2 and LOXL2 in TC cells. He *et al*^[13] reported that GINS2 plays a vital role in the survival, migration and invasion of TC cells and regulates the MAPK signaling pathway. GINS2 may be a potential biomarker for TC diagnosis or prognosis and a drug target for treatment.

CONCLUSION

Most studies have shown that GINS2 expression is upregulated in tumor tissues such as CC, gastric adenocarcinoma, glioma, pancreatic cancer and OC compared to adjacent normal tissues, while GINS2 expression levels correlate with various clinicopathological parameters such as tumor size and TNM stage. These findings suggest that GINS2 can promote tumor progression by regulating tumor cell proliferation, apoptosis, migration, the cell cycle and EMT. In addition, at the cellular level, GINS2 affects the function of several pro- or oncogenic molecules through several signaling pathways, leading to poor patient prognosis. These results imply that GINS2 may be a new target in the diagnosis and treatment of certain tumors.

Currently, there are few publications on interfering with GINS2 in tumor therapy, and no corresponding inhibitors have been reported. In contrast, GINS2 expression is increased in the vast majority of tumors compared to normal tissues, which may make it possible to interfere with GINS2 expression and inhibit GINS2 protein function as an effective way to control tumor development. In future research, potent agents can be explored through molecular docking based on the GINS2 structure, for example.

In conclusion, ² a better understanding of the role of GINS2 in clinicopathological features and mechanisms of tumor development may help improve diagnostic and therapeutic outcomes. Further studies on GINS2 and its regulatory mechanisms may

help improve prevention and treatment based on patient biological and pathological characteristics.

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