

SUN2: A potential therapeutic target in cancer (Review)

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Abstract. The incidence of cancer is increasing at an alarming rate despite recent advances in prevention strategies, diagnostics and therapeutics for various types of cancer. The identification of novel biomarkers to aid in prognosis and treatment for cancer is urgently required. Uncontrolled proliferation and dysregulated apoptosis are characteristics exhibited by cancer cells in the initiation of various types of cancer. Notably, aberrant expression of crucial oncogenes or cancer suppressors is a defining event in cancer occurrence. Research has demonstrated that SAD1/UNC84 domain protein-2 (SUN2) serves a suppressive role in breast cancer, atypical teratoid/rhabdoid tumors and lung cancer progression. Furthermore, SUN2 inhibits cancer cell proliferation, migration and promotes apoptosis. Recent reports have also shown that SUN2 serves prominent roles in resistance to the excessive DNA damage that destabilizes the genome and promotes cancer development, and these functions of SUN2 are critical for evading

initiation of cancer. Additionally, increasing evidence has demonstrated that SUN2 is involved in maintaining cell nuclear structure and appears to be a central component for organizing the natural nuclear architecture in cancer cells. The focus of the present review is to provide an overview on the pharmacological functions of SUN2 in cancers. These findings suggest that SUN2 may serve as a promising therapeutic target and novel predictive marker in various types of cancer.

Contents

1. Introduction
2. Structure of SUN2
3. The role of SUN2 in different cancers
4. SUN2 and DNA damage
5. Overview of SUN2 signaling pathways in cancer
6. Conclusion and prospective

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Abbreviations: SUN2, SAD1/UNC84 domain protein-2; LINC, linker of nucleoskeleton and cytoskeleton; MEFs, mouse embryonic fibroblasts; KASH, klarsicht/ANC-1/syne-1 homology; AT/RT, atypical teratoid/rhabdoid tumor; OS, overall survival; DDR, DNA damage response; ATM, ataxia telangiectasia mutated; HU, hydroxyurea; 3'UTR, 3'-untranslated region; INM, inner nuclear membrane; ONM, outer nuclear membrane; MB, medulloblastoma; CDS, complete coding sequence; SIRT5, silent information regulator-5; HDAC, histone deacetylase; NSCLC, non-small cell lung cancer; GLUT1, glucose transporter-1; LDHA, lactate dehydrogenase A; PARP, poly (ADP-ribose) polymerase; JAK, janus protein tyrosine kinase; PTEN, phosphatase and tensin homology deleted on chromosome; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; DNA-PKcs, DNA-dependent protein kinase catalytic subunit

Key words: SUN2, cancer, proliferation, apoptosis, DNA damage

1. Introduction

Cancers originate from normal cells that gain the ability to aberrantly proliferate and eventually turn malignant. These cancerous cells then grow clonally into tumors and eventually acquire the potential to metastasize (1). Alteration of cellular processes is a central component in cancer development, including changes in cancer cell growth, apoptosis, migration and invasion (2-6). Inhibition of the abnormal growth of cancer cells and the promotion of cancer cell apoptosis are widely recognized as crucial goals for intervention of cancer progression. In addition, dysregulations of oncogenes and cancer suppressors tightly correlate with cancer occurrence (7-9). However, the lack of useful cancer biomarkers and targets is a major contributor to the high mortality rate and prevalence of cancer.

SAD1/UNC84 domain protein-2 (SUN2), a member of the SUN domain protein family, is a key component of linker of nucleoskeleton and cytoskeleton (LINC) complex. The nuclear architecture functionally provides a framework for organizing and regulating diverse processes within cells. Notably, cancer cells generally exhibit variety of features indicative of atypical nuclei (10), although the molecular mechanism of these phenomena remains to be elucidated. A number of studies

have shown that loss of LINC complexes reduces nuclear and cellular rigidity, increasing tissue fluidity, promoting invasive activity, and inducing cancer progression (10-12). Interestingly, studies have uncovered a fundamental role of SUN2 in nuclear structure determination function (13). Therefore, we hypothesize that the effects of SUN2 on regulating nuclear architecture may affect biological function in cancer cells. Indeed, abnormal expression of SUN2 and LINC complexes is associated with the occurrence of many human diseases, especially cancers (10).

Several studies have also linked SUN2 function with various cancers. SUN2 plays a cancer suppressor role in miR-221/222-mediated malignant embryonal tumors of the central nervous system (14). Another study confirmed that expression of SUN2 was reduced in breast cancer (10). Moreover, SUN2 exhibited suppression of lung cancer cell proliferation and migration and promotion of lung cancer cell apoptosis; SUN2 also enhanced the chemotherapy sensitivity of lung cancer cells exposed to cisplatin, and higher SUN2 level predicts a better overall survival in lung cancer progression (12). Together these studies indicate that dysregulation of SUN2 may be involved in cancer development.

Failure to detect and repair DNA damage leads to genomic instability, which is one of the hallmarks that drive cancer occurrence (15). Recent reports also suggest that SUN2 exhibits resistance to DNA damage and maintaining the genome integrity (16). Lei *et al* confirmed that SUN2 is required for attenuating excessive DNA damage in mouse embryonic fibroblasts (MEFs) from SUN1^{-/-}SUN2^{-/-} double knockout mice (16). Whether SUN2 participates in maintaining genomic stability in other types of cancer needed further validation.

Following recent advances, this review presents recent information regarding the functions of SUN2 in the progression of cancer and discusses the emerging signal pathways regulated by SUN2 in cancer.

2. Structure of SUN2

The LINC complex is a nuclear envelope protein complex that mainly consists of SUN and nesprin proteins, connecting nuclear lamina and cytoskeletal filaments (10). LINC complex characteristics of architecture framework helps to regulate the size and shape of the cell nucleus. Several SUN proteins have been identified in several organisms, including *Schizosaccharomyces pombe* Sad1, *Caenorhabditis elegans* UNC-84 and SUN1, and five human SUN proteins (17). Human SUN proteins can be grouped into two subfamilies based on their intracellular localization: SUN1 and SUN2 are integral membrane components of the inner nuclear membrane (INM) (18-20); SUN3 and the sperm-associated antigen 4 localize to endoplasmic reticulum and outer nuclear membrane (ONM) (21,22).

SUN proteins are conserved among all eukaryotes and characterized by a C-terminal 200 amino acid SUN domain (18,19,23-25). SUN proteins form a trimer through the SUN domain and exhibits a perfect three-fold symmetry, resembling a cloverleaf (65 Å diameter) sitting on a short stem (30 Å of length) (26). As shown in Fig. 1, SUN2 extends into the perinuclear space by its C-terminal SUN domain and interacts with nuclear lamina via its nucleoplasmic N-terminal

domain (11,27,28). Additionally, SUN2 connects with klar-sicht/ANC-1/syne-1 homology (KASH) domain, providing mechanical transduction between the cytoskeleton and nuclear interior, directly (19,22,28-30). Recent reports indicate that the SUN domain is at the center of a nucleocytoplasmic bridge that is essential for nuclear motility in cells (31). These observations suggest that the structural characteristics of SUN2 are crucial for nuclear anchoring, migration, and positioning (19,22,29,30,32,33), centromere localization (34) and regulating the tethering of meiotic telomere (26). Thus, SUN2 may possess anti-cancer by regulating atypical nuclei structures in cancer cells.

3. The role of SUN2 in different cancers

Atypical teratoid/rhabdoid tumors (AT/RTs). AT/RT frequently occur in children. However, the pathogenesis of AT/RT remains to be uncovered. Several studies have indicated that the miR-221/222 gene cluster serves as an oncogenic miRNA in several types of human cancer (35,36). Recently, miRNome and transcriptome traits in AT/RT were evaluated using small RNA sequencing and gene expression microarray analyses. Hsieh *et al* showed that miR-221/222-encoded miRNAs are abundantly expressed in AT/RT and substantially contribute to the malignancy of embryonal tumors (10). In AT/RT cells, overexpression of miR-221/222 leads to faster cell growth, and this observation is supported by previous reports that miR-221/222 promotes AT/RT malignancy and tumor growth in nude mice (14). AT/RT tissue microarray demonstrated that SUN2 is markedly decreased in AT/RT specimens. miRNAs generally execute their cellular functions through regulating target gene expression. Notably, miR-221/222 promotes cancer cell proliferation and tumor malignancy by targeting SUN2 mRNA in AT/RT, directly. Adherent cell growth of human medulloblastoma Daoy and human ATRT CHLA-02-ATRT cells was significantly increased upon transfection of SUN2 short hairpin-producing plasmids, parallelly, while overexpression of SUN2 reduced the proliferation rate (14). Together these studies show that SUN2 plays a critical role in miR-221/222-mediated AT/RT malignancy, indicating that SUN2 may be a promising target of AT/RT. For the first time, SUN2 was demonstrated closely relate to cancer initiation and progression.

Breast cancer. Several studies have provided evidence that abnormalities of the LINC are associated with complex alteration of biological processes and cancer occurrence. Reduced expression of lamin A/C was detected in colon cancer (37), small cell lung cancer (38), leukemias and lymphomas (39,40). However, lamin A/C is overexpressed in colorectal cancer (41), prostate cancer (42), and skin cancer (43,44). Therefore, the precise relationship between LINC complex components and the clinical significance of cancer still has not yet been well elucidated. In the present study, evaluation of four LINC complex and nuclear lamina components, SUN1, SUN2, nesprin-2, and lamin A/C, in breast cancer was performed. Matsumoto *et al* collected 73 breast cancer samples and found lower expression levels of LINC components in tumor regions compared with cancer-associated noncancerous regions (11). Furthermore, decreased expression of SUN2 was detected in

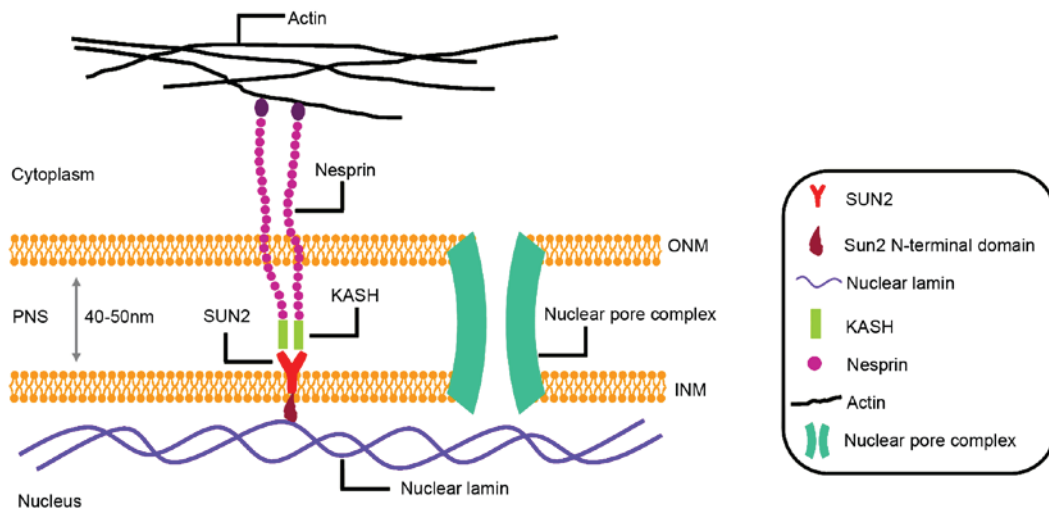


Figure 1. Schematic representation of SUN2 at the nuclear envelope. In the nuclear envelope, SUN2 exhibits a three-fold symmetry with its C-terminal extending into the perinuclear space and its nucleoplasmic N-terminal interacting with nuclear lamina. SUN2 connects with actin binding domain through binding to the KASH domain of Nesprin in cytoplasmic. The structure of SUN2 is functions as a bridge between the nuclear membrane and cytoplasm. SUN2, SAD1/UNC84 domain protein-2; KASH, klarsicht/ANC-1/syne-1 homology; PNS, perinuclear space; INM, inner nuclear membrane; ONM, outer nuclear membrane.

several breast cancer cell lines compared with noncancerous mammary gland cells *in vitro*. Together this demonstrates that the expression of SUN2 is attenuated in human breast cancer clinical specimens, indicating that SUN2 may have fundamental pathological functions in human breast cancer progression.

Lung cancer. Previous studies have demonstrated that SUN2 exhibits anti-cancer functions in lung cancer progression. Higher SUN2 expression predicts a better overall survival (OS) in lung cancer (12). Lv *et al* confirmed that expression level of SUN2 was significantly reduced in lung cancer tissues compared with paired normal tissues using Oncomine Database (12). According to the Protein Atlas Database, the expression of SUN2 is reduced in 75% (9 out of 12) of lung cancer tissue samples (12). Furthermore, in a previous study evaluating the relationship between SUN2 and lung cancer, lung cancer samples were subdivided into two groups and OS was analyzed. Individuals with lower SUN2 expression levels exhibited shorter OS than those with high SUN2 expression level (12). Together this indicates that down-regulation of SUN2 in lung cancer progression and higher expression of SUN2 may predict a good outcome in human lung cancer occurrence. Additionally, ectopic expression of SUN2 inhibited lung cancer cell proliferation and colony formation abilities, and chemotherapy sensitivity to cisplatin treatment was increased when SUN2 was overexpressed in lung cancer cells. Further, knockdown of SUN2 promoted lung cancer cell proliferation and migration (12). Together these observations suggest that SUN2 is a key player in lung cancer development.

4. SUN2 and DNA damage

Cancers research remains a challenge to researchers, as genomic instability causes a constantly changing genetic profile of cancer occurrence (45). Failure of the DNA damage response (DDR) leads to genomic instability,

which is one of enabling hallmarks that drive cancer occurrence (46). Phosphorylation of ataxia telangiectasia mutated (ATM) and H2A.X are among the earliest events in response to DNA damage (47-49). Recent studies showed that the expression level of γ -H2A.X is significantly reduced in MEFs isolated from SUN1^{-/-}SUN2^{-/-} double knockout mice compared with wild-type mice. Although ATM is activated by 0.1 mM of hydroxyurea (HU) in wild-type MEFs, ATM is not activated by HU in SUN1^{-/-}SUN2^{-/-} MEFs (16). There was no significant difference in tail moment between wild-type and SUN1^{-/-}SUN2^{-/-} MEFs in the absence of methyl methane-sulfonate (16), which induces DNA damage (50). Interestingly, after treatment of SUN1^{-/-}SUN2^{-/-} MEFs with methyl methane-sulfonate, a substantial increase occurred in the number of cells with prominent comet tails, indicative of DNA fragmentation (16). These observations reveal that DNA damage may accumulate rapidly in SUN1^{-/-}SUN2^{-/-} MEFs.

Phosphorylated checkpoint kinase-1 (Chk1), a cell-cycle checkpoint factor downstream of the DDR pathway, is reduced in SUN1^{-/-}SUN2^{-/-} MEFs compared with wild-type mice (16). In addition, perinuclear heterochromatin is decreased in SUN1^{-/-}SUN2^{-/-} MEFs, indicating that SUN1 and SUN2 participate in maintaining genomic stability, possibly by affecting DDR or DNA repair. Furthermore, MEFs from SUN1^{-/-}SUN2^{-/-} mice exhibit a premature proliferative arrest at the S phase of cell cycle and increase in cell apoptosis (16,51,52), leading to the death of SUN1^{-/-}SUN2^{-/-} mice shortly after birth. These reports suggest that SUN2 may have crucial effects on evading cancer occurrence by its involvement in the DDR, and eliminating DNA lesions, maintaining genome stability and integrity.

SUN2 also interacts with DNA-PKcs that are potentially involved in the DDR, especially in DNA repair (16). Of note, cancer cells exhibit a high rate of proliferation and metabolic activities and DNA-PKcs plays an active part in regulation of cell proliferation (53). Of further interest, a previous study demonstrated that SUN2 exhibits suppression of cancer cell

proliferation activity. In summary, uncovering the function of DNA-PKcs/SUN2 in regulation of cancer cells may offer potential avenues for cancers treatment.

5. Overview of SUN2 signaling pathways in cancer

MiR-221/222. miRNAs mainly function by regulating the expression of target genes at the post-transcriptional level. Up-regulation of miR-221/222 is associated with initiation and progression of breast cancer (54-59), liver cancer (60-63), pancreatic cancer (64-68), gastric cancer (69-73), colorectal cancer (74-78), glioma (79-85), multiple myeloma (86-89), and malignant melanoma (90,91). TargetScan indicated a potentially favorable interaction between miR-221-3p/miR-222-3p and an 8-mer site at the position 255-262 in the SUN2 3'-untranslated region (3'UTR). Luciferase assays demonstrated that both miR-221-3p and miR-222-3p directly bind to the recognition element and reduce activity of Luc fused to full-length 3'UTR of SUN2 (14). Moreover, correlation coefficients (Pearson's *r*) between SUN2 and miR-221-3p as well as SUN2 and miR-222-3p are -0.777 and -0.802, respectively, indicating negative correlation between SUN2 and miR-221/222 in AT/RT and medulloblastoma (MB) (14). A previous report also showed that the transcript and protein level of SUN2 was reduced after ectopic expression of miR-221/222, further supporting SUN2 as a direct target of miR-221/222. Increasing numbers of studies illustrate that expression of miR-221/222 induces cancer cell proliferation and invasion by inhibiting cancer suppressors and apoptotic genes (92). Over-expression of miR-221/222 significantly increases cell proliferation, while over-expression of both miR-221/222 and the complete coding sequence (CDS) of SUN2, which possesses no miR-221/222 recognition elements, counteracted the pro-proliferative effects (14). Together this suggests that one of the crucial pathways of miR-221/222 increasing cancer cell proliferation may occur by down-regulating SUN2 expression (Fig. 2).

SIRT5. Silent information regulator-5 (SIRT5) is a key component of the sirtuin family. SIRT5 expression has been associated with cancer prognosis and survival (93) via stimulating cancer cell proliferation and tumor growth, attenuating the tumor-type metabolism (94). Of note, the expression of SIRT5 is decreased in squamous cell carcinoma (95) and endometrial carcinoma (96). Thus, inhibition of SIRT5 may become a potential strategy to suppress the progression of cancers (97). Nevertheless, SIRT5 has also been found to have negative implications in certain types of malignancies (98). For instance, SIRT5 is highly expressed in human non-small cell lung cancer (NSCLC) and facilitates tumor growth and drug resistance (99). SIRT5 is also downregulated with histone deacetylase (HDACs) inhibitor treatment (100), while SUN2 expression dramatically increased in response to nicotinamide, an inhibitors of HDAC (101,102), indicating that SUN2 may be regulated by SIRT5. Additionally, ectopic expression of SIRT5 significantly reduced SUN2 expression, while knockdown of SIRT5 dramatically increased SUN2 expression. Expression of SIRT5 inversely correlates with SUN2, indicating that SIRT5 acts as a negative regulator of SUN2, at least in part (12). The precise role

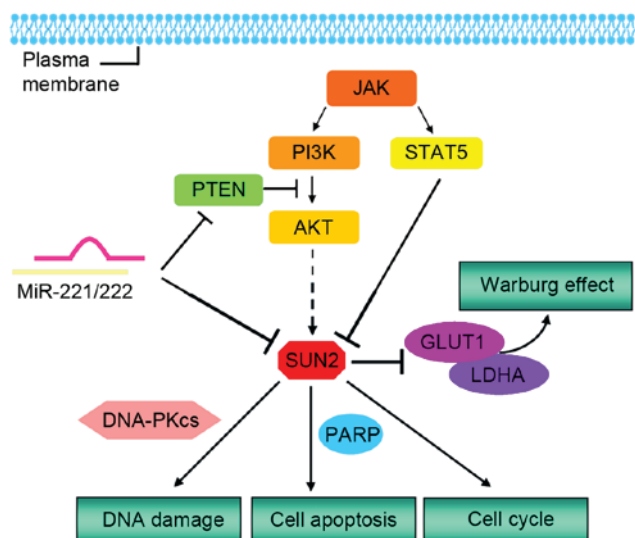


Figure 2. The potential target genes of SUN2 and SUN2-mediated effects implicated in cancer. The JAK signaling pathway-related PI3K/AKT and STAT pathways participate in the occurrence of cancers. Among the members of these pathways, STAT5 plays a role in the inhibition of SUN2. Ectopic expression of miR-221/222 reduces the expression of SUN2. Notably, SUN2 exhibits crucial functions in the cancer cell cycle, and SUN2 may exert effects on cancer cell apoptosis by regulating the cleavage of PARP. Besides, SUN2 influences cancers progression by contacting GLUT1 and LDHA to attenuate the Warburg effect. During DNA damage response, SUN2 interacts with DNA-PKcs, which are involved in DNA repair and proliferation in cancer cells. JAK, janus protein tyrosine kinase; PTEN, phosphatase and tensin homology deleted on chromosome; PI3K; phosphatidylinositol 3-kinase; AKT, protein kinase B; SIRT5, silent information regulator-5; GLUT1, glucose transporter-1; LDHA, lactate dehydrogenase A; PARP, poly (ADP-ribose) polymerase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit.

of SIRT5/SUN2 as a novel axis in the regulation of different types of cancers is currently unclear, and the relationship between SUN2 with cancer occurrence related to SIRT5 requires further exploration.

Warburg effect. Compared with normal cells, cancer cells exhibit a unique metabolism (103) to promote cell growth, survival, proliferation and long-term maintenance and fulfill the energetic demands of activities required for cancer cells (104). Studies have shown that the majority of cancer cells preferentially use aerobic glycolysis instead of oxidative phosphorylation to meet their increased energetic and biosynthetic demands (105,106). This shifted metabolic patterning is known as the Warburg effect and is associated with cancer development (106,107). Glucose transporter-1 (GLUT1) and lactate dehydrogenase A (LDHA), two key genes closely related to the Warburg effect, are needed for glucose uptake and conversion of pyruvate to lactate in cancer development (108). Recently, Recent studies demonstrated inverse correlations between SUN2 and GLUT1 as well as between SUN2 and LDHA. Ectopic expression SUN2 markedly decreased GLUT1 and LDHA expression levels, while knockdown of SUN2 increased expression of GLUT1 and LDHA (12). These results indicate that SUN2 may suppress cancer progression via attenuating the Warburg effect, at least in part. Though majority of cancer cells preferentially use aerobic glycolysis instead of oxidative phosphorylation to meet

their increased energetic and biosynthetic demands (105,106). Prostate cancer does not exhibit Warburg effect, an increase in glucose uptake (109). Herein, we cannot conclude that SUN2 exerts its anti-cancer effects in all types of cancers by inhibiting the Warburg effect.

PARP. Poly (ADP-ribose) polymerase (PARP) is verified as tightly correlated with cellular functions, such as DNA repair and transcriptional and posttranscriptional modulation of oncogenic gene expression, ultimately modulating carcinogenesis (110). Several studies suggested that PARP interacts with breast cancer (111), ovarian cancer (112), prostate cancer, lung cancer, gastric cancer and hepatocellular carcinoma (113,114). Cleavage of PARP is a well-known marker of cell apoptosis, and interestingly, higher expression level of SUN2 increases PARP cleavage events (12). Together this suggests that SUN2 expression may inhibit cancer progression by regulating PARP-mediated cell apoptosis.

6. Conclusion and prospective

Overall, the complete underlying molecular mechanisms of cancers are still poorly elucidated. Many studies have established that dysregulations of oncogenes and cancer suppressor genes distinctly correlate with the initiation and progression of cancers. As outlined in this review, we discussed recent insights into the function of SUN2 in cancer progression. SUN2, as an anti-cancer member, participates in AT/RT, breast cancer and lung cancer by regulating biological processes in cancer cells, including cell cycle, apoptosis and migration. In addition, deficiency of SUN2 distinctly induces DNA damage, which is critically involved in cancer initiation.

Of note, SUN2 is widely expressed in different organs and tissues, such as the heart, brain, spleen, lung, liver, skeletal muscle, testis and embryos (17). Previous studies have shown an involvement of SUN2 in human cancers, such as cervical carcinoma, colorectal cancer, esophageal carcinoma and oral cavity squamous cell carcinoma. Furthermore, recent findings in fission yeast suggest that SUN2 may serve as a predictor and prognostic biomarkers in cancer. Therefore, we hypothesize that SUN2 may act as a potential biomarker in multiple cancer cell types. However, current findings suggest that SUN2 may present different functions in various cancers, and thus, we cannot definitively conclude that SUN2 solely functions as a cancer suppressor in all types of cancers. Undoubtedly, the precise functions and potential signaling pathways of SUN2 in cancer progression remain to be elucidated, and further studies and validations are urgently needed.

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Availability of data and materials

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Authors' contributions

In this review, study concept and design: JL, XC, YC. Draft of the manuscript: XC, YC. Analysis of data: HMM, HDL, CH, XMM. Critical revision of the manuscript for important intellectual content: FTB, XYP, YY, WXL, XFL. All authors agreed the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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