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Review

Long noncoding RNA OIP5-AS1 in cancer

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ABSTRACT

Long noncoding RNAs (lncRNAs) can be over two hundred nucleotides in length and lack an obvious open reading frame (ORF). Interestingly, these RNAs form a group of nucleic acids involved in a variety of diverse cellular mechanisms involving proliferation, differentiation, apoptosis,and senescence. Given these characteristics, it is not unexpected that the aberrant expression of certain lncRNAs is strongly linked to oncogenesis and tumor advancement. OIP5-AS1, a prominent tumor-associated lncRNA, contributes to intricate cellular mechanisms during the evolution of malignant tumors. For example, it not only represses cyclin G-associated kinase (GAK) expression thus impacting mitosis, but also regulates cell proliferation and apoptosis in many cancers, including lung adenocarcinoma, breast, glioma and hepatoblastoma. In this paper, we review our current understanding of OIP5-AS1 in carcinogenesis and its potential application as a clinical biomarker or therapeutic target in malignancy.

1. Introduction

Complete genome sequencing of eukaryotes indicates that although approximately 70% of the human genome is transcribed into RNAs, < 2% has protein-coding functions [1]. Such noncoding RNAs (ncRNAs) were initially regarded as transcriptional noise with no specific biological function [2]. With the advance of biotechnology, however, some ncRNAs were found to be involved in cellular processes important for normal development and physiology [3] and were classified into novel categories such as small nucleolar RNAs (snoRNAs), circular RNAs (circRNAs), microRNAs (miRNAs), and long noncoding RNAs (lncRNAs) [4–7]. LncRNAs are largely transcribed by RNA polymerase II and defined by a length > 200 nucleotides with no functional open reading frame (ORF) [8,9]. In the past few years, more studies have shown lncRNAs could serve as biological modifiers of gene expression, and their misregulation is closely related to many diseases, including cancers. Therefore, studying these transcripts provides a broad prospect of identifying novel diagnostic and therapeutic targets.

The OPA-interacting protein 5 antisense transcript 1 (*OIP5-AS1*) is a newly identified and promising lncRNA that is located on chromosome 15q15.1 [10]. It was first recognized by Ulitsky et al. as *Cyrano*, which is expressed in the nervous system and notochord in zebrafish embryos and is required for the neurogenesis during embryonic development [11]. Zebrafish embryos with repressed *Cyrano* expression had developmental deficits, including small heads and eyes, short tails, and defects in the neural tube opening, which could be partly rescued by the injection of mature *Cyrano* with a conserved fragment of 67 nt that is homologous to human and mouse *Cyrano* genes [11]. *OIP5-AS1* can suppress the proliferation of HeLa cervical cancer cells by sponging HuR, an RNA-binding protein, to sponge it from binding target mRNAs of proliferation-associated genes such as *CCNA2*, *CCND1* and *SIRT1* [12]. Thus, when the level of *OIP5-AS1* decreases, the quantity of these proliferation-related proteins is higher and leads to cell proliferation. In addition, *OIP5-AS1* can also control mitosis in HeLa cells by repressing GAK protein expression [13].

OIP5-AS1 has been shown to play various roles in multiple other tumors; *OIP5-AS1* is strongly up-regulated in tumor samples as well as breast cancer cell lines, where it acts as an oncogene by modulating

Abbreviations: OIP5-AS1, OPA-interacting protein 5 antisense transcript 1; lncRNA, long noncoding RNA; ncRNA, non-coding RNA; ceRNA, competing endogenous RNA; miRNA, microRNA; GAK, cyclin G-associated kinase; NSCLC, non-small cell lung cancer; BRCA, breast cancer; CC, cervical cancer; BLBC, basal-like breast cancer; OS, osteosarcoma; HB, hepatoblastoma; CRC, radio-resistant colorectal cancer; MM, multiple myeloma; CDK4, cell cycle dependent kinase 4; CDK6, cell cycle dependent kinase 6; *SOX2*, sex-determining region Y-box 2; *Bcl-2*, B-cell lymphoma 2; *ZEB1*, zinc finger *E*-box binding homeobox 1; *FN1*, fibronectin-1; GLS, glutaminase; *ITGA6*, integrin alpha6; *DYRK1A*, dual-specificity tyrosine phosphorylation-regulated kinase-1A; EMT, the epithelial-mesenchymal transition; *CCNA2*, mRNA encoding cyclins A2; *CCND1*, mRNA encoding cyclins D1; *SIRT1*, mRNA encoding sirtuin 1; *KLF10*, transforming growth factor-beta inducible early gene 1

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Table 1
Expression and functional characterization of *OIP5-AS1* in cancers.

Cancer types	Expression	Role	Function	Reference
Breast cancer	Up/down	Oncogenic/suppressor	Proliferation, invasion, migration, anti-apoptosis	[14,24]
Glioma	Up	Oncogenic	Proliferation, invasion, migration, cell cycle arrest, anti-apoptosis	[15,20,21]
Lung cancer	Up/down	Oncogenic	Proliferation, invasion, migration, Ki67 protein expression, EMT	[17–19]
Hepatoblastoma	Up	Oncogenic	Proliferation, invasion, migration, EMT	[16]
Osteosarcoma	Up	Oncogenic	Proliferation, anti-apoptosis, cell cycle arrest, chemo-resistance	[25,26]
Cervical cancer	Up	Oncogenic/ suppressor	Proliferation, invasion, migration	[12,13,22,23]
Multiple myeloma	Down	Suppressor	Proliferation, cell cycle progression, apoptosis	[29]
Malignant melanoma	Up	Oncogenic	Proliferation	[27]
Bladder cancer	Up	Oncogenic	Tumor cell viability, apoptosis rate, cell cycle arrest	[40]
Undifferentiated oral tumor	Up	Oncogenic	Cancer cell stemness	[30]
Radio-resistant colorectal cancer	Down	Suppressor	radiosensitivity	[28]

Table 2
Related genes and clinical significance of *OIP5-AS1* in cancers.

Cancer types	Related genes	Clinical significance	Reference
Breast cancer	miR-129-5p, *SOX2*	tumor size, lymph node metastasis, pathological grading, TNM stage	[14]
Glioma	miR-410, Wnt-7b, *YAP*, Notch pathway	pathological grading, tumor WHO grade	[15,20]
Lung cancer	miR-378a-3p, CDK4, CDK6, miR-448, *Bcl-2*	tumor size, Ki67 expression rate, overall survival, prognosis,independent prognostic factor	[17,18]
Hepatoblastoma	miR-186a-5p, *ZEB1*	overall survival, vascular invasion, Edmindson grade, prognostic factor	[16]
Osteosarcoma	miR-223, CDK14, miR-200b-3p, *FN1*	prognosis, overall survival	[25,26]
Cervical cancer	miR-143-3p, *SMAD3*, miR-143-3p, *ITGA6*, GAK	FIGO stage, lymph node metastasis, overall survival	[12,13,22,23]
Multiple myeloma	miR-410, *KLF10*, PTEN/PI3K/AKT pathway	–	[29]
Malignant melanoma	miR-217, GLS	prognosis, clinical stage, overall survival	[27]
Bladder cancer	*OIP5*	Tumor staging, muscularis invasion, tumor size, overall survival time	[40]
Undifferentiated oral tumor	stemness-associated transcription factors	undifferentiated pathology status, tumor pluripotency, prognosis	[30]
Radio-resistant colorectal cancer	miR-369-3p, *DYRK1A*	overall survival	[28]

SOX2 through miR-129-5p [14]. It also encouraged malignant behavior in glioma, hepatoblastoma, lung adenocarcinoma both *in vitro* and *in vivo* experiments [15–17]. In the present review, we summarize the latest progress in our understanding of the *OIP5-AS1* mechanism and the role of this cancer-implicated lncRNA in the occurrence and development of various malignant tumors (Tables 1 and 2).

2. Dysregulation and biology of lncRNA *OIP5-AS1* in cancers

2.1. Lung cancer

OIP5-AS1 expression was significantly enhanced in lung adenocarcinoma and squamous cell cancer compared to adjacent tumor-free tissues ($P < .01$), which was positively related with larger tumor size ($P = .012$) and Ki67 protein expression rate ($P = .045$), but not with lymph node metastasis [18]. The patients with highly up-regulated *OIP5-AS1* had poorer overall survival than those with low expression levels ($P = .021$). Functionally, *OIP5-AS1* overexpression significantly promoted tumor cell viability ($P < .05$) *in vitro* and tumor growth *in vivo* ($P = .005$), while the contrary outcome was observed when *OIP5-AS1* was silenced [18]. Deng et al. similarly revealed that *OIP5-AS1* was significantly over-expressed in tumor tissues ($P < .01$) and the H1975 and HCC827 lung adenocarcinoma cell lines ($P < .01$) [17]. Increased *OIP5-AS1* expression was closely related with a worse prognosis for patients with lung adenocarcinoma ($P < .01$) and as a result, *OIP5-AS1* expression is an independent prognostic factor in lung adenocarcinoma ($P = .01$) [17]. However, the opposite was also observed for *OIP5-AS1* expression measured in 32 patients with NSCLC, which was significantly lower in tumor tissues than neighboring non-cancerous cell samples ($P < .0001$) [19]. This discrepancy in the effect of *OIP5-AS1* expression might be due to sample heterogeneity or varying pathogenesis from discrepancies in geographical environment or hazard exposure [19]. These results show that the lncRNA *OIP5-AS1* is a potential indicator of cancer development and could be used in at least some populations with lung cancer when its underlying mechanisms are fully clarified.

2.2. Glioma

Sun et al. reported that *OIP5-AS1* expression increased in glioma in comparison with tumor-free tissue ($P < .05$); with more expression in high-grade glioma than low-grade tissues ($P < .05$), which suggests *OIP5-AS1* levels are related with the pathological grading of glioma [15]. Silencing *OIP5-AS1* reduced proliferation ($P < .05$) and weakened invasion and migration abilities (all $P < .05$) of U87 human glioma cells, as well as caused G0/G1 stasis of cell cycle ($P < .05$) and tumor cell apoptosis ($P < .05$). *In vivo*, *OIP5-AS1* knockdown significantly reduced tumor volume and weight (all $P < .05$) [15], which was similar to a report that *OIP5-AS1* had an oncogenic role when it was overexpressed in 111 glioma cases (66.5%) compared with normal samples [20]. Moreover, its expression level was positively related to the tumor WHO grade ($P < .01$). Knockdown of *OIP5-AS1* not only inhibited proliferation ($P < .05$) and migration ($P < .05$) in T98G and A172 glioma cells, but also significantly reduced tumor growth ($P < .01$) *in vivo* in nude mice [20]. Besides, Liu et al. also confirmed that *OIP5-AS1* was overexpressed in glioma tissues as well as U87 and U251 glioma cell strains ($P = .0014$, $P = .0026$, respectively) [21]. Taken together, these studies confirmed the correlation between abnormal expression of *OIP5-AS1* and the malignant characteristics of glioma, providing a direction for future, large sample clinical research.

2.3. Cervical cancer (CC)

OIP5-AS1 levels were strongly promoted in 16 cervical cancer samples ($P < .001$) and the three cervical cancer (CC) cell lines Caski, HeLa, SiLa ($P < .01$, $P < .001$, $P < .001$, respectively) in comparison

with nontumor tissues or normal cervical epithelial cells, respectively [22]. Moreover, silencing *OIP5-AS1* effectively suppressed tumor cell viability ($P < .01$), invasion and migration ability ($P < .001$) [22]. Another study similarly reported increased *OIP5-AS1* levels in 57 CC samples compared to adjacent nontumor tissues ($P < .05$), which was similar to results reported in five tumor cell lines (C33A, SiHa, HeLa, CaSki, ME-180) ($P < .05$) [23]. *In vivo*, silencing *OIP5-AS1* not only hindered tumor growth in nude mice ($P < .05$), but also distinctly lowered Ki-67 protein expression ($P < .05$) [23]. Clinically, correlation analysis demonstrated elevated *OIP5-AS1* was linked to advanced International Federation of Gynecology and Obstetrics (FIGO) stage ($P = .02$), as well as lymph node metastasis in patients with CC ($P = .006$). Survival analysis confirmed the patients with enhanced *OIP5-AS1* in cervical cancer had shorter overall survival than those with low *OIP5-AS1* expression ($P < .05$) [23]. In summary, the lncRNA *OIP5-AS1* is a CC pro-tumor factor that is likely to be prognostic factor and a potential therapeutic target for cervical cancer.

2.4. Breast cancer (BRCA)

Zeng et al. reported *OIP5-AS1* levels were elevated in 70 breast cancer samples ($P < .05$), and a high *OIP5-AS1* level was correlated with tumor size ($P = .033$), metastatic status of lymph nodes ($P = .032$), pathological grading ($P = .016$) and TNM stage ($P = .042$) [14]. Functionally, when *OIP5-AS1* expression level declined, the proliferation, colony formation ability, invasion and migration of breast cancer cells were dramatically weakened ($P < .01$); however, apoptosis was promoted ($P < .01$) [14]. The decline of *OIP5-AS1* reduced tumor growth ($P < .01$) and weight *in vivo* by subcutaneous xenotransplantation in nude mice ($P < .01$) [14]. Another research group, however, reported the level of *OIP5-AS1* significantly decreased in basal-like breast cancer (BLBC), and that cell growth could be upregulated by siRNA-mediated *OIP5-AS1* silence in the cell line MDA-MB-231 ($P < 8.1E-10$) [24]. These results suggest that the lncRNA *OIP5-AS1* acts as a tumor-suppressor in BLBC. Although the results of these two studies are inconsistent, they nevertheless show the value of further study of *OIP5-AS1* in different subtypes of breast cancer.

2.5. Osteosarcoma (OS)

Dai et al. reported *OIP5-AS1* expression levels were increased in 48 osteosarcoma tissues samples compared to non-cancer tissue samples ($P < .01$), and analogous outcomes were observed in four OS cell lines (MG-63, U2OS, 143B, and Saos-2) ($P < .01$). Patients with osteosarcoma that expressed high levels of *OIP5-AS1* had a worse prognosis than the control cohort ($P < .01$) [25]. As for biological function, knocking down *OIP5-AS1* inhibited the proliferation of tumor cells ($P < .01$), induced cell cycle stasis at G0/G1 phase ($P < .01$), and upregulated the apoptotic rate ($P < .01$). An *in vivo* assay in nude mice illustrated that *OIP5-AS1* knockdown significantly repressed tumor growth ($P < .01$) [25]. Subsequently, another study also confirmed lncRNA *OIP5-AS1* expression was enhanced in chemotherapy-resistant OS patients ($P < .01$), and the higher *OIP5-AS1* levels were, the worse overall patient survival rate was ($P < .01$) [26]. Chemotherapy resistance in doxorubicin-resistant osteosarcoma cells was weakened by silencing of *OIP5-AS1* ($P < .05$), and strengthened when *OIP5-AS1* was upregulated ($P < .05$) [26]. In conclusion, these findings confirmed the misregulation of *OIP5-AS1* in osteosarcoma and forecast its potential value in future clinical application.

2.6. Hepatoblastoma (HB)

OIP5-AS1 expression was significantly induced in 80 tumor tissues from patients with hepatoblastoma compared with corresponding adjacent normal liver area ($P < .01$), had a higher level of expression in metastatic samples than those with no tumor metastasis ($P < .01$), and was similar to that identified in three HB cell lines ($P < .01$) [16]. Correlation analysis indicated that upregulated *OIP5-AS1* was strongly linked to shorter overall survival ($P < .01$), blood vessel invasion ($P < .003$), and Edmindson grade ($P < .025$); and could be used as prognostic factor in HB ($P = .028$) [16]. Knocking down *OIP5-AS1* inhibited tumor cell proliferation, migration, invasion (all $P < .01$), and epithelial-mesenchymal transition (EMT) progress by reversing the protein level of EMT-related proteins. HB patients with high *OIP5-AS1* levels had a worse prognosis compared to those with low *OIP5-AS1* levels ($P = .028$) [16]. Thus, *OIP5-AS1* could serve as a potential biomarker for hepatoblastoma and have good therapeutic target characteristics.

2.7. Malignant melanoma

Luan et al. observed that the levels of *OIP5-AS1* were increased in 30 melanoma samples ($P < .0001$) and three cell strains (A375, SK-MEL-1, SK-MEL-5; $P < .001$, $P < .001$, $P < .01$, respectively) compared to adjacent normal tissues or human epidermal melanocytes (HEMa-LP and HEMn-LP), respectively [27]. The elevated *OIP5-AS1* expression was also related to poor prognosis ($P < .05$) and advanced clinical stage ($P = .01$), which indicated that patients with high *OIP5-AS1* levels had shorter overall survival than those with low *OIP5-AS1* expression ($P < .05$) [27]. Moreover, *OIP5-AS1* silencing not only suppressed the proliferation ability of tumor cells *in vitro* ($P < .05$), but also shrunk tumor size including tumor weight ($P < .01$) and volume ($P < .01$) *in vivo* [27]. In summary, *OIP5-AS1* overexpression is positively linked to poor prognosis, clinical stage progression and overall survival of melanoma, and could be clinically used as a tumor diagnostic indictor or promising therapy target in the future.

2.8. Radio-resistant colorectal cancer (CRC)

Zou et al. revealed that CRC cells exposed to a 2 Gy dose of X-rays expressed a lower level of *OIP5-AS1* compared with those with no radiation exposure [28]. Similarly, *OIP5-AS1* levels were decreased in radio-resistant tumor cells than in maternal cells ($P < .01$) [28]. The patients with lower *OIP5-AS1* expression had a poorer survival than those with higher expression of *OIP5-AS1* ($P = .0006$). Silencing *OIP5-AS1* improved CRC cell viability when a 24-h dose of 6 Gy X-ray irradiation compared to unirradiated cells ($P < .001$), while overexpressed *OIP5-AS1* reduced the survival rate of radioresistant CRC cells ($P < .001$) [28]. *OIP5-AS1* could enhance radiation sensitivity in colorectal cancer cells and therefore, has potential as a gene therapy for radio-resistant colorectal cancer patients.

2.9. Bladder cancer

Wang et al. found that *OIP5-AS1* expression was significantly upregulated in bladder cancer tissues ($P < .001$) as well as in four cancer cell strains (SW780, J82, T24, and RT4; $P < .001$). Higher expression levels of *OIP5-AS1* were more common in patients with advanced tumors ($P < .001$), muscularis invasion ($P < .001$) or large tumor size ($P < .001$), indicating a shorter overall survival than patients with lower *OIP5-AS1* expression ($P < .001$) [40]. In *in vitro* studies, when *OIP5-AS1* was down-regulated, tumor cell (J82 and RT4) viability decreased ($P < .01$) and had an elevated apoptosis rate ($P < .01$), meanwhile, the proportion of cells in the G2/M phase remarkably elevated and those in G0/G1 phase declined ($P < .01$), which indicated a G2/M to G0/G1-phase arrest in J82 and RT4 cells [40]. In short, *OIP5-AS1* could effectively predict malignant characteristics in patients and be a sign of developing malignant behaviors of bladder cancer tumor cells.

2.10. Multiple myeloma (MM) and undifferentiated oral tumors

Yang et al. reported *OIP5-AS1* levels in multiple myeloma(MM) patients were generally lower than those in healthy donors ($P < .05$). Overexpression of *OIP5-AS1* inhibited cell proliferation, cell cycle progression and accelerated cell apoptosis ($P < .05$), and had an opposite effect on these factors when down-regulated [29]. In oral tumors, Arunkumar et al. observed that overexpression of *OIP5-AS1* was closely correlated with undifferentiated pathology status ($P < .01$). In other words, high-grade undifferentiated carcinoma had significant upregulation of *OIP5-AS1* compared to those with a differentiated cellular pathology ($P = .0038$) [30]. In addition, high *OIP5-AS1* expression levels may be related to enhanced tumor pluripotency and poor clinical prognosis in undifferentiated oral tumors [30]. Taken together, whether in multiple myeloma or oral cancer, *OIP5-AS1* deserves further study due to its potential as a therapeutic target and functional index for clinicians.

3. Molecular mechanisms related to *OIP5-AS1*

3.1. OIP5-AS1 and microRNAs

The competing endogenous RNA (ceRNA) is a heterogeneous class of transcripts able to regulate the expression of mRNAs by competitively binding microRNAs [31]. This functional behavior was shown to be extensively involved in the regulation of malignant phenotypes of tumor cells [32]. As one of the ceRNAs, *OIP5-AS1* exerts an oncogenic role in glioma by promoting the expression of *Wnt-7b*, which activates the Wnt-β-catenin pathway by outcompeting miR-410 [15]. In NSCLC cells, the proliferation-related proteins CDK4 and CDK6 could decrease when miR-378a-3p is up-regulated, thus inhibiting cell proliferation. *OIP5-AS1* plays a role as tumor promoter by repressing miR-378a-3p function [18]. *OIP5-AS1* not only acts as a miR-129-5p sponge in BRCA, resulting in elevated expression of the *SOX2* transcription factor [14], but also upregulates *Bcl-2* by targeting miR-448 in lung adenocarcinoma [17].

Similar modalities exist in a variety of tumors; in hepatoblastoma, *OIP5-AS1* elevates *ZEB1* expression by competitively binding to miR-186a-5p [16], and down-regulates miR-223 to boost CDK14 expression in osteosarcoma [25], which is similar to mechanism in cervical cancer that *OIP5-AS1* accelerates *SMAD3* and *ITGA6* expression by sponging miR-143-3p [22,23]. *OIP5-AS1* also promotes doxorubicin resistance in osteosarcoma by directly binding miR-200b-3p and modulating *FN1* expression [26]. In addition, *OIP5-AS1* targets miR-217 to up-regulate GLS expression in malignant melanoma, thus promoting glutamine catabolism and melanoma growth [27], and enhance the radio-sensitivity of colorectal cancer cells through the modulation of *DYRK1A* expression by miR-369-3p [28]. *OIP5-AS1* interacts with stemness-associated transcription factors and downstream miRNAs to maintain the stemness properties of undifferentiated oral tumors [30]. It is worth noting that *OIP5-AS1* could also sponge the RNA-binding protein HuR away from its target mRNAs, *CCNA2*, *CCND1* and *SIRT1* [12] (Fig. 1).

3.2. OIP5-AS1 and cancer-related signaling pathways

The role of *OIP5-AS1* in regulation of cancer-related signaling pathways has been investigated in some cancer types. The Wnt-7b signaling pathway regulates distinct glioma-vascular interactions and tumor microenvironments [33]. Silencing *OIP5-AS1* inhibits the Wnt-7b/β-catenin pathway, as well as its target genes *cyclin D1* and *c-Myc* by up-regulating miR-410, which can lead to cell cycle arrest in glioma [15]. Hu et al. show that silencing *OIP5-AS1* effects the behavior of glioma cells partly through the inhibition of *YAP* and Notch signaling pathway activity [20]. *KLF10*, which was originally called TGF-β inducible gene 1 (*TIEG1*), can modulate the PTEN/AKT signaling pathway [34,35]. Reduced *OIP5-AS1* induces miR-410 accumulation and promotes tumor cell proliferation by activating *KLF10*-regulated PTEN/AKT signaling in multiple myeloma [29]. Finally, *OIP5-AS1* induces the LPAATbeta/PI3K/AKT/mTOR signaling pathway through binding miR-340-5p, resulting in cisplatin resistance in osteosarcoma [36] (Fig. 1).

3.3. OIP5-AS1 and EMT progress

The epithelial-mesenchymal transition (EMT) is a crucial event in the acquisition of mesenchymal properties during epithelial cell development, and plays a vital role in malignant transformation and tumor progression by supporting metastatic potential [37]. Accumulating scientific evidence confirms that *OIP5-AS1* is involved in the regulation of the EMT progress [37]. *OIP5-AS1* down-regulation inhibits EMT by elevating the level of the protein E-cadherin, while reducing N-cadherin in lung adenocarcinoma, which results reduced metastasis [17]. Similar results were also observed in hepatoblastoma with knocked-down *OIP5-AS1*, which resulted in an inhibition of EMT progress [16] (Fig. 1).

3.4. OIP5-AS1 and mitoses

Cyclin G-associated kinase (GAK) is a ubiquitous protein in cells that regulates clathrin-mediated endocytosis and plays a vital role in normal cell cycle progression during M phase [38,39]. Knockdown of GAK causes an abnormality in the centrosome integrity and results in cell cycle arrest at metaphase [39]. Further studies show that *OIP5-AS1* knockdown in HeLa cells induces an increase in GAK level and triggers aberrant mitosis events with many aberrant monopolar, multipolar, misaligned mitotic spindles [13]. Simultaneous silencing of GAK and *OIP5-AS1* could partly rescue these abnormalities and return the mitotic characteristics close to normal, suggesting that *OIP5-AS1* controls mitosis at least in part by regulating GAK [13]. Similarly, when *OIP5-AS1* is down-regulated in bladder cancer, the proportion of cells in G2/M phase is increased and those in G0/G1 phase is reduced [40]. Other studies found that down-regulation of *OIP5-AS1* induces G0/G1 phase arrest and apoptosis in glioma tumor cells and osteosarcoma [15,25]. The detailed molecular mechanisms that support these observations are still unclear and require further studies (Fig. 1).

4. Conclusion and perspective

LncRNAs function through various and sophisticated molecular mechanisms; they act as a guide, scaffold, decoy or tether for other biomolecules [41,42]. Recently, considerable efforts were made to further detail their mechanisms of action, and there is increasing evidence that altered expression of lncRNA has important functions in tumor biology, such as oncogenesis, tumor advancement and metastasis, that results in uncontrolled tumor progression [43,44]. This evidence provides a new direction for further investigation of lncRNA. Defining the underlying mechanisms of lncRNA will help develop novel strategies for cancer diagnosis and treatment.

OIP5-AS1 is one novel lncRNA that has been confirmed as an oncogene or anti-oncogene in different cancer types [24]. The majority of current evidence suggests that *OIP5-AS1* is overexpressed in multiple carcinomas including breast cancer [14], lung cancer [17,18], glioma [15], hepatoblastoma [16], osteosarcoma [25,26,36], cervical cancer [22,23], malignant melanoma [27], undifferentiated oral cancer [30] and bladder cancer [40]. Overexpression of *OIP5-AS1* is correlated to later clinical cancer stages, larger tumor size, metastasis, and worse overall survival in these cancer types. Conversely, *OIP5-AS1* is poorly expressed in multiple myeloma and radioresistant colorectal cancer, where it plays an anti-tumor role [28,29]. Knockdown of *OIP5-AS1* could facilitate cell proliferation, inhibit apoptosis and contribute to a poor prognosis in these two cancer types. Moreover, *OIP5-AS1* also contributes to chemotherapy resistance in osteosarcoma [36]. In

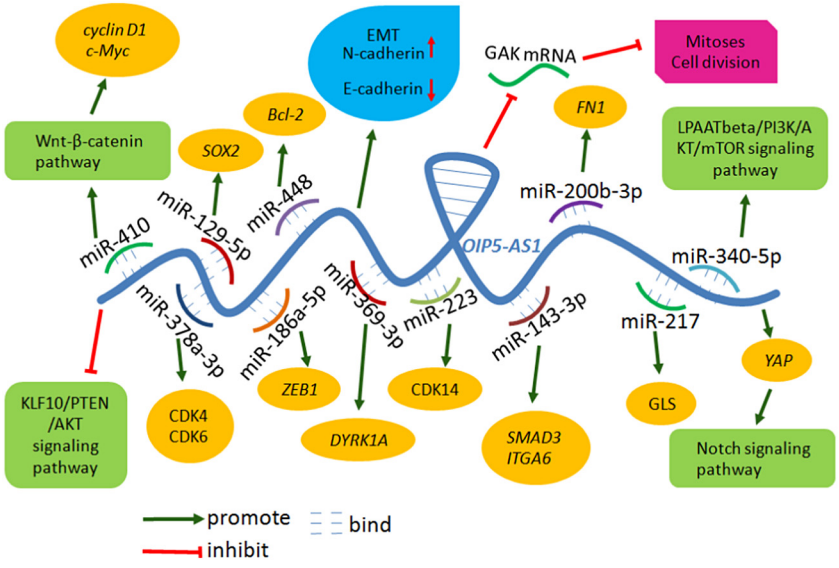

Fig. 1. Overview of the molecular mechanisms of *OIP5-AS1* involved in human cancers. *OIP5-AS1* exertes oncogenic roles through activating the Wnt-β-catenin pathway as well as downstream genes *cyclin D1* and *c-Myc* by binding miR-410. Besides, *OIP5-AS1* induces the LPAATbeta/PI3K/AKT/mTOR signaling pathway through binding miR-340-5p in cisplatin-resistant osteosarcoma. *OIP5-AS1* expression was significantly positive with YAP mRNAs which could activate Notch signaling pathway. Reduced *OIP5-AS1* induces miR-410 cumulation and promotes tumor cell proliferation by activating *KLF10*-regulated PTEN/AKT signaling pathway in multiple myeloma. The proliferation related proteins CDK4 and CDK6 are increased when *OIP5-AS1* suppresses miR-378a-3p. *OIP5-AS1* also regulates the expression of mRNAs by competitively binding microRNAs such as miR-448, miR-186a-5p, miR-223, miR-200b-3p, miR-143-3p, miR-217, miR-369-3p, miR-129-5p. Enhanced *OIP5-AS1* not only inhibits GAK mRNA expression and suppresses cell division, but also promotes EMT progress by means of largely elevating the level of protein N-cadherin, while cutting down E-cadherin resulting in a strengthening of metastasis.

conclusion, *OIP5-AS1* has clinical application value in cancer diagnosis, prognosis and therapy.

We also noticed that there were some conflicting data about the oncogenic role of *OIP5-AS1*. For example, *OIP5-AS1* was reported to be highly expressed in cervical cancer Hela cells as a carcinogen [10,22,23], while Kim et al. reported that *OIP5-AS1* suppressed Hela cell proliferation [12]. Naemura et al. indicated that this discrepancy in *OIP5-AS1* oncogenic function might result from different splice variants in the lncRNA that have distinct target genes or functions [10]. In lung cancer, *OIP5-AS1* was reported to be overexpressed [17,18], while Esfandi et al. detected down-regulation of the *OIP5-AS1* transcript in tumor specimens from lung cancer patients [19]. The authors seggest that the different pathogenesis due to different risk factor exposure may likely be responsible for the discrepancy in *OIP5-AS1* expression in this cancer. Moreover, this difference of *OIP5-AS1* expression also emerged in breast cancer studies. What actually promotes such differences in *OIP5-AS1* expression even in the same type of cancer? In our opinion, they may derive from tumor cell heterogeneity on account of genetic mutation, which is fertile molecular soil for further evolution during cell proliferation. Genome instability is a striking feature of cancer because it is a state of increased mutation that can change gene copy number and phenotypes within a cell [45,46]. These intracellular molecular instability may be partly responsible for the differences observed and reported in the *OIP5-AS1* expression research results summarized in this review. Supporting this, using single-cell analysis, Janiszewska et al. uncovered that the majority of the untreated HER2-positive breast cancer sample consisted of cells with wild-type *PIK3CA* and only a small number of *PIK3CA*-mutant cells, however, after neoadjuvant therapy the relative frequency of the *PIK3CA*-mutant cells increased significantly [47].

The amount and diversity in the molecular interactions involved even in the same cancer type forecast the intractability of malignant diseases. The lncRNA *OIP5-AS1*, which plays a significant role in neurodevelopment as *cyrano* in zebrafish embryos, is worthy of further study to better understand its role in oncogenesis, and promises to be a biomarker for diagnosis or a therapeutic target. Undoubtedly, with the advance of single-cell omics and sequencing technologies, more studies on *OIP5-AS1* will emerge, and further in-depth excavation in single-cell molecular level to detail the role of this transcript is a direction worthy of attention.

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Conflict of interest

The authors declare no conflict of interest.

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