Roles of regulator of chromosome condensation 2 in cancer: Beyond its regulatory function in cell cycle

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Abstract

Regulator of chromosome condensation 2 (RCC2) is an essential protein in order for mitosis to proceed properly. It localizes in the centrosome of chromosomes where is involved in chromosome segregation and cytokinesis. Furthermore, RCC2 associates with integrin networks at the plasma membrane where participates in the control of cell movement. Because of its known role in cell cycle, RCC2 has been linked with cancer progression. Several reports show that RCC2 induces cancer hallmarks, but the mechanisms explaining how RCC2 exerts these roles are widely unknown. Here, we aim to summarize the main findings explaining the roles and mechanisms of RCC2 in cancer promotion. RCC2 is overexpressed in different cancers, including glioblastoma, lung, ovarian, and esophageal which is related to proliferation, migration, invasion promotion in vitro and tumor progression and metastasis in vivo. Besides, RCC2 overexpression induces epithelial-mesenchymal transition and causes poorer prognosis in cancer patients. RCC2 overexpression has also been linked with resistance development to chemotherapy and radiotherapy by inhibiting apoptosis and activating cancer-promoting transcription factors. Unfortunately, not RCC2 inhibitors are currently available for further pre-clinical and clinical assays. Therefore, these findings emphasize the potential use of RCC2 as a targetable biomarker in cancer and highlight the importance for designing RCC2 chemical inhibitors to evaluate its efficacy in animal studies and clinical trials.

Introduction

Regulator of chromosome condensation (RCC2) is a nuclear protein that was first discovered as a protein localizing at the chromosomal centromeres essential for cell division.1 Later, RCC2 became known as a molecule belonging to the passenger protein family because of its similar cell location with this group of proteins and its essential role for both proper chromosome segregation and completion of mitosis.2 These passenger proteins are a group of proteins located in the cell nucleus that move from centromeres to the spindle midzone during mitosis.3,4 They are situated in chromosomes during early mitosis, before transferring to the spindle midzone during late mitosis. These passenger proteins control several mitotic events, including chromosome segregation and cytokinesis.3 During these processes, RCC2 promotes a suitable cell division by binding with a group of these passenger proteins belonging to the chromosomal passenger complex (CPC) and ensuring cell division proceed accurately. The CPC comprises Aurora B kinase and the regulatory components inner centromere protein (INCENP) and survivin.4-6 The CPC controls several activities involved in cell division, such as chromosome condensation, kinetochore-microtubule attachment, completion of cytokinesis, and spindle checkpoint signaling.3 Borealin, another nuclear protein, was then identified as another component of the CPC bound to Aurora B fundamental for mitosis since its depletion by RNA silencing delays mitotic progression and results in kinetochore-spindle misattachments, severely disrupting the partitioning of chromosomes in anaphase.7 In the other hand, cortactin, a protein regulating actin polymerization during the formation of membranous protrusions known as lamellipodia and invadopodia in migrating cells, was also identified as an interacting protein of RCC2. Cortactin co-localizes in the juncture of the dividing cells, suggesting a functional role of the cortactin/RCC2 complex in cells undergoing mitosis.8 However, whether cortactin is directly associated with the CPC is unknown.

Several reports discussed below have shown evidence linking RCC2 with tumor invasion and progression in in vitro and in vivo studies. For example, RCC2 was overexpressed in several kinds of cancer and this upregulation was related with higher proliferation, migration, and oncogene expression in cancer cell lines and mice.
Furthermore, RCC2 overexpression has been also associated with poorer survival in cancer patients. However, these studies were limited to fully understand the mechanisms trough RCC2 promotes tumor development, as well as its possible use as an antitumoral target. It is greatly because the unavailability of RCC2 chemical inhibitors for preclinical studies. In this paper, we aim to discuss the available evidence regarding to the tumor growth supporting mechanisms reported for RCC2 as well as the in vivo and in vitro cancer hallmarks promoted by the dysregulation of RCC2.

Methods of research

Articles were selected using the databases Pubmed and Science direct. Articles published between 1990 and 2020 were selected. The following keywords were used as search criteria: RCC2; cancer, metastasis, cell division, TD-60. Reports regarding to the function of RCC2 and its effects in cancer were included. For the graphical abstract and figures we used the software Science X. The graphs showing the survival data in cancer patients was downloaded from The Human Protein atlas, Pathology Atlas (Website: https://www.proteinatlas.org/ENSG00000179051-RCC2/pathology).

Functions of regulator of chromosome condensation 2 in the cell

Functions of regulator of chromosome condensation 2 in cell division

Instead of the importance of RCC2 in cell division, not many papers in the literature have deeply studied the whole functions of RCC2 in this cell process. However, RCC2 has been closely related to cell cycle progression. RCC2 was first reported as a mitosis-specific human autoantigen in HeLa cells that arises at the centromeres of prophase chromosomes, but ultimately participates in formation of an organelle that bisects the cell at late anaphase and during telophase. Later reports about RCC2 stabilized that downregulation of RCC2 expression disturbs the process of cell division. For example, silencing of RCC2 inhibits overall spindle assembly, activates the spindle assembly checkpoint, and blocks cells in prometaphase, indefinitely stopping HeLa cells in mitosis and showing condensed chromosomes. Furthermore, RCC2 depletion causes spindle abnormalities in prometaphase that are associated with abnormal centromeric accumulation of CPC components in human cells. Because these evidences, RCC2 was shown as an important protein in global spindle assembly and it may be specifically required to integrate kinetochores into the mitotic spindle. RCC2, similar to its partner RCC1, showed guanine exchange factor (GEF) activity for several proteins such as Ralα and Ral1 in 293T and HeLa cells. Precisely, through its GEF activity, RCC2 promotes RalA activation, which is fundamental for the correct localization of the CPC components at centromeres. Moreover, RCC2 depletion causes a deregulation of kinetochore-microtubule interactions in early mitosis, which is associated with decreased Aurora B kinase activity in human cells. Aurora B kinase is the catalytic subunit of the CPC, and its activation in vitro requires RCC2 and microtubules. RCC2 is critical in the localization of Aurora B kinase to centromeres in Xenopus oocyte cystostatic factor extracts, and thus regulates its centromeric kinase activity. All these findings strongly suggest a role for RCC2 in the mitotic spindle assembly and its participation in cell cleavage by regulating the recruitment and activity of passenger proteins at centromeres.

Moreover, RCC2 was also shown to be an essential regulator of cell cycle progression during interphase. Suppression of RCC2 with siRNA blocks progression of G1/S phase and G2 phase into mitosis in HeLa cells, significantly decreasing the percentage of mitotic cells and the proliferation rate. Besides, suppression of RCC2 expression alters the microtubule organization in nucleus, rapidly ceasing the cell proliferation after RCC2 silencing. The fact that RCC2 downregulation freezes cell cycle progression at multiple stages highlights its functionally important role throughout the entire cell cycle and not just in mitosis.

Regarding to these evidences, it is clear that RCC2 controls the cell division at several levels beyond just cell cleavage, including location of passenger proteins to centromeres, regulating kinase activity of Aurora B, spindle assembly and regulation of GTPases like RalA (Figure 1). However, recent studies report different roles for RCC2 beyond its function in mitosis and cell division. These roles include directional cell migration, integrin signaling, regulation of transcription factor activity, metastasis, and promotion of cancer. For the remainder of this review, we summarize and discuss what is known about each of the lesser-known roles for RCC2, focusing on its functions in cancer.

Roles of regulator of chromosome condensation 2 in directional cell migration

Directional cell migration plays important roles in the embryonic development, wound healing, and maintenance of tissue homeostasis. This migration requires a correct orientation of the cell and the formation of membrane protrusions, which is the key-stone of directional migration and results in a different molecular ensemble at the front of the cell compared to that at the back. These protrusions are structures formed by changes in membrane organization which require reorganization of the actin and microtubule cytoskeleton. These structures are called lamellipodia, filopodia, and invadopodia. The formation of these membrane protrusions is controlled mostly by protrusive signals that rely on activation of GTPases, like Rho and Rac1. Beyond its known functions in the regulation of cell cycle, RCC2 has been shown to participate in the control of these protrusive signals.

The directional migration through a fibrillar extracellular matrix requires that cells localizes these protrusive signals to the leading edge of the membrane in order to perform the cell migration accurately. At this point, the GTPase Rac1 plays a key role by redistributing its activity from off-axial positions (non-protrusive membranes out from the leading edge) to the leading edge in the membrane after contact of the tip of the protrusion with fibronectin. Here, RCC2 exerts control of these protrusive signals by inhibiting Rac1 activation outside the protrusive tip of the membrane by binding Rac1 switch regions and competitively inhibiting GEF access, preventing Rac1 activation in off-axial positions. Coronin-1C, another protein binding to the RCC2/Rac1 complex, mediates the release and relocation of Rac1 from non-protrusive membrane regions to the protrusive tip. The fact that RCC2 can control Rac1 activation has also been observed in cancer, where RCC2 overexpression attenuates Rac1 activity in lung and ovarian tumors. Disrupting the RCC2/Coronin-1C/Rac1 interactions or the downregulation of RCC2 cause an overactivation of Rac1 in off-axial protrusions leading to loss of unidirectional migration and cell polarity, resulting in shunting migration and delays of the arrival of neural crest derivatives at the correct location in developing zebrafish, demonstrating the role of RCC2 in migration guidance in vivo. Furthermore, another study showed
that deregulation of Rac1 function by RCC2 knockdown effectively abolished persistent migration along fibronectin fibers, resulting in an accelerated cell spreading and confirming that RCC2 limits the signaling required for membrane protrusions formation.\textsuperscript{16-18}

In addition, RCC2 has been detected in fibronectin-signaling networks associated with fibronectin binding integrins \( \beta3 \) and \( \alpha5\beta1 \) where it mediates microtubule stability.\textsuperscript{18,19} Integrins are cell-surface adhesion receptors that mediate the interactions cell-cell and cell extracellular matrix (ECM), which control cell movement and tissue integrity. The association of RCC2 with both \( \alpha5\beta1 \) integrin and Rac1 is particularly interesting because \( \alpha5\beta1 \) integrin has been linked to Rac1-dependent activation of cell cycle progression, indicating that the GTPase Rac1 is essential in propagating proliferative \( \beta1 \)-integrin signals,\textsuperscript{20} where RCC2 could be playing an important role.

In conclusion, these findings indicate that RCC2 limits the signaling required for membrane protrusion by acting like a brake in the activation of GTPases like Rac1, which supports directional cell migration by preventing random extension of membrane protrusions outside of leading edge.\textsuperscript{11,18} Thus, these reports highlight new important roles of RCC2 in supporting cellular movement, which are beyond its known roles in cell cycle progression. Because of these findings, asking whether RCC2 could be involved in the control of migration and invasion, proliferation, and oncogenic potential in cancer cells is worthwhile. Next, we will discuss the findings regarding the roles of RCC2 in cancer and what is known about the function of this protein in promotion of tumor progression.

**Functions of regulator of chromosome condensation 2 in cancer**

**Upregulation of regulator of chromosome condensation 2 promotes cancer development and poorer prognosis**

Because of its role in cell division, an association between RCC2 and cancer has been explored. Several reports have indicated an oncogenic role for RCC2 in different types of cancer. These insights rely on the finding that RCC2 is overexpressed in various types of tumor tissues compared to normal tissues. This increase in RCC2 expression is associated with higher malignancy, resistance to chemotherapy and radiotherapy, and shorter patient survival time.\textsuperscript{10,21-26} Furthermore, mutation status in the 5'UTR of RCC2 can identify high risk patients with microsatellite instable (MSI) tumors in colon cancer.\textsuperscript{27} Importantly, increased levels of RCC2 are significantly associated with higher size and extension of primary tumor (T status), lymph node metastasis, and advanced clinical stage in lung adenocarcinoma patients. Patients with higher expression of RCC2 also have shorter overall survival (Figure 2) and poorer prognosis.\textsuperscript{24} Based on this evidence, RCC2 seems to play a clinically important role in the development of tumors. Hence, further clarification of these findings and the mechanisms by which RCC2 promotes oncogenesis requires attention.

In support of the hypothesis that RCC2 acts as an oncogene, both in vitro and in vivo studies show that forced expression of RCC2 promotes hallmarks of malignancy, including uncontrolled cell growth, invasion, and angiogenesis. Moreover, RCC2 expression is correlated with poor prognosis and shorter survival in various cancers, such as breast, lung, and colorectal cancer. Therefore, understanding the mechanisms by which RCC2 promotes cancer development is crucial for the development of targeted therapies.

![Figure 1. Known function for regulator of chromosome condensation 2 (RCC2) in cell cycle. Functional RCC2 binds with proteins belonging to CPC and contributes with the correct location of this complex in the centromere of chromosomes. Here, RCC2 also seems to regulate the kinetochore-microtubule interactions during cell division. RCC2 promotes the progression from prophase to telophase during mitosis and also seems to contribute to cell cleavage. Furthermore, RCC2 also promotes the activation of Aurora B kinase and GTPases as RalA which play a role in the correct location of chromosomal passenger complex (CPC) to centromeres for completion of mitosis. When RCC2 is depleted by siRNA, CPC proteins are abnormally accumulated in centromeres and cells stop in prometaphase and inhibiting cell division. Figure was done using Canvas X software.](image-url)
proliferation, transformation, increased migration capacity, and tumor progression in human cell lines and mice.\textsuperscript{10,21,24-26} Moreover, forced expression of RCC2 promotes intrapulmonary metastasis \textit{in vivo} and markedly enhances lung adenocarcinoma cell migration, invasion, and proliferation \textit{in vitro} by activating the epithelial-mesenchymal transition (EMT).\textsuperscript{24} Similarly, another study showed that RCC2 is overexpressed in primary lung and ovarian cancers and the high expression was more substantial in higher grade tumors. These findings have been reported in other cancers as well, where the overexpression or downregulation of RCC2 increases and decreases proliferation of tumor cells, respectively.\textsuperscript{10,25,26,28} In breast cancer, the overexpression of RCC2 significantly enhances cell proliferation and migration abilities of cancer cells both \textit{in vitro} and \textit{in vivo} through the activation of the Wnt signaling pathway.\textsuperscript{26} In gastric carcinoma cells, RCC2-knockdown decreases both cell viability and BrdU incorporation, a marker of DNA replication.\textsuperscript{21} Collectively, these data clearly show an oncogenic effect for RCC2, indicating that the overexpression of this protein could be a marker of poor prognosis and higher tumor grade in cancer patients. Hence, more research is needed to address more deeply how RCC2 induces tumor progression and whether it could be used as a biomarker in cancer.

**Regulator of chromosome condensation 2 activates cancer-promoting transcription factors**

The mechanisms by which RCC2 promotes tumor progression remain mostly unknown. Nevertheless, some studies have shown various insights regarding how RCC2 could promote these oncogenic effects. A few reports established RCC2 as a partial mediator of cancer-promoting transcription factors. For example, RCC2 can activate the JNKs signaling pathway, which is known to activate the transcription factor c-Jun, and this promotes hallmarks of oncogenesis, such as increased proliferation and migration of lung adenocarcinoma cancer cells.\textsuperscript{24} In breast cancer, RCC2 promotes tumor progression by activating the Wnt pathway and upregulating β-catenin transcriptional activity.\textsuperscript{26} Similarly, RCC2 promotes tumorigenic effects in glioblastoma by regulating DNA methyltransferase 1 (DNMT1) expression in a p-STAT3 transcription factor-dependent manner.\textsuperscript{25} Our own results confirm this hypothesis because we found that RCC2 promotes esophageal cancer \textit{in vivo} and \textit{in vitro} through the stimulation of the transcriptional activity of Sox2,\textsuperscript{29} a transcription factor known for its oncogenic effects. On the other hand, RCC2 is associated with an important role for microtubule stability.\textsuperscript{19} Obviously, failures in cytoskeletal architecture can affect proliferation rate; and disturbs in the mechanisms...
related to preserve the cell cytoskeleton could lead to cell arrest. However, whether RCC2 mediates tumor progression by its direct effects on microtubules is unknown.

Thus, the role most relevant for RCC2 in cancer seems to be its influence on different transcription factors associated with tumor progression. Therefore, more research is needed that focuses on the role of RCC2 as an oncoprotein and the mechanisms by which it facilitates tumor progression, for example, regulating gene expression. Additionally, the development of RCC2 inhibitors to evaluate its antitumor activity in pre-clinical and clinical settings is also essential.

Regulator chromosome condensation 2 overexpression is associated with radiotherapy and chemotherapy resistance

One of the primary challenges in the development of new cancer therapies is the occurrence of resistance to treatment in most patients. Hence, identifying new targets to overcome this issue is a critical concern in cancer research. Interestingly, RCC2 has been associated with the resistance development to chemotherapeutic drugs. Forced expression of RCC2 blocks chemotherapeutic drug-induced apoptosis in tumor cells by blocking Rac1 signaling, which is associated with increased proliferation in ovarian and lung cancer cells. Comparably, RCC2 is significantly enriched in glioblastoma compared to normal brain tissue, which is associated with a poorer prognosis and with promotion of radio-resistance through the activation of the p-STAT3 transcription factor and amplified transcription of DNMT1. Thus, the upregulation of RCC2 observed in several cancers might play a key role in the resistance of tumors to radiotherapy and chemotherapy clinically.

This idea is supported by the observation that RCC2 is upregulated in cisplatin-resistant ovarian cancer cells compared to sensitive cancer cells which has a positive role on cell proliferation, apoptosis resistance, and migration. These effects are mediated through RalA, a small GTPase known to be regulated by RCC2. Similarly, RCC2 overexpression is associated with bortezomib resistance, the first line drug for multiple myeloma treatment. Therefore, these findings indicate that RCC2 is an important regulator of resistance in several cancers, an effect beyond its known roles in mitosis. However, more research is needed to examine how RCC2 could promote development of resistance to different chemotherapeutic drugs and whether the chemical inhibition of RCC2 might help to overcome chemoresistance in cancer patients. In addition, determining the possible side effects of chemical inhibitors of RCC2 and to evaluate their selectivity level on tumor tissue in a clinical setting in cancer patients is highly important.

Regulator of chromosome condensation 2 and metastasis

Based on the roles of RCC2 regulating protrusive signals in cell membranes for directional migration, it is probable that this protein could be involved in migration and metastasis of cancer cells. However, studies have not been conducted to directly clarify the essential mechanisms by which RCC2 promotes metastasis. Below, we summarize the few available reports focusing on this topic.

RCC2 was associated with promotion of expression of EMT markers and metastasis in several cancers. In lung adenocarcinoma, RCC2 overexpression was found to be associated with metastasis in human patients and mice. This was based on the findings that forced expression of RCC2 increased cell invasion and migration through JNKs phosphorylation and the overexpression of metalloproteases, MMP-2 and MMP-9. Furthermore, in breast cancer cells, RCC2 induces migration and expression of EMT markers by activating the Wnt signaling pathway. Likewise, knocking down of RCC2 decreased metastatic ability and foci of breast cancer cells in liver and lungs from mice. RCC2 interacts with the RalA protein in ovarian cancer cells. RalA is a GTPase involved in cell migration and proliferation, leading to the activation of the RalA downstream effector, RalBP1, which stimulates migration in vitro and in vivo. Thus, RCC2 probably can influence the migration abilities of the cells by regulating the activity of GTPases like RalA.

In addition, 2 non-coding RNAs have been shown to downregulate RCC2 and alter migration capabilities of cancer cells. The microRNA miR-331-3p directly targets and down-regulates RCC2, leading to inhibition of migration and invasion in ovarian cancer cells. Similarly, the long non-coding RNA LCPAT1 binds and downregulates RCC2 in lung cancer cells and this downregulation inhibits cell migration, whereas RCC2 overexpression restores these phenotypes. Our own data revealed that RCC2 downregulation markedly decreases the migration ability of esophageal cancer cells. Thus, the preliminary evidence indicates a role for RCC2 in controlling cell migration and metastasis in several cancers both in vitro and in vivo. In contrast, only one study showed that RCC2 downregulation increased metastasis in colon cancer, questioning a role for RCC2 in cancer cell migration. Here, RCC2 overexpression inhibited cell migration by decreasing Rac1 signaling and filopodia formation on the cell surface of p53−/− cells. However, this is an artificial system, and we should consider that these p53 null cells could be associated with other changes that affect the normal role of RCC2 in migration. Therefore, more studies focusing on the role of RCC2 in metastasis and its mechanisms are critically needed.

Targeting of regulator of chromosome condensation 2 by different non-coding RNA affects cancer progression

Micro-RNA (miRNAs) have been found to be frequently deregulated in human cancers and play both tumor-suppressive and oncogenic roles in cancer cells, depending on the specific type of miRNA. Interestingly, evidence shows that RCC2 expression is regulated directly by non-coding RNAs, such as micro-RNAs and long-RNAs, which affect tumor progression. For example, the microRNA-1247 works as a tumor suppressor in pancreatic cancer by inhibiting cell growth, proliferation, and migration. MiR-1247 has been shown to exert these tumor suppressor functions by targeting RCC2. Likewise, another micro-RNA, miR-29c, exhibits antitumor effects, which are mediated at least partially by targeting RCC2 in gastric cancer. In ovarian cancer, RCC2 is directly targeted and negatively regulated by the microRNA-331-3p, which inhibits cell proliferation. Furthermore, one long non-coding RNA, lung cancer progression-association transcript 1 (LCPAT1), exerts oncogenic effects and promotes lung cancer progression through RCC2. Thus, the oncogenic effects of RCC2 seem to be mediated at least partially by non-coding RNAs, suggesting that the tumorigenic function of RCC2 is also regulated at the epigenetic level for further control of cancer progression.

Concluding remarks and futures perspectives

It is intriguing that a protein like RCC2, whose main function was primarily focused on cell division, participates in a broad range of other cell processes, such as chromosome segregation, directional migration, and integrin signaling. Because of these diverse roles and the deregulation of RCC2 expression in tumor
tissue, studying whether RCC2 has important functions in cancer, such as tumor proliferation, metastasis, EMT marker expression, and oncogene activation, is highly interesting. Some studies have been conducted to address these issues. RCC2 is overexpressed in several cancers, including glioblastoma, lung, ovarian, and colon, which leads to an increased proliferation rate, apoptosis inhibition, migration, and invasion in vitro. In animal models, RCC2 accelerates tumor progression and promotes metastasis, increasing metastatic marker expression and foci both in vitro and in vivo. However, most of the mechanisms as to how RCC2 stimulates these oncogenic effects are not completely understood. The known findings in the literature that addressed this issue are summarized in Figure 3. Our primary observation is that the RCC2 overexpression appears to be associated with a higher tumor stage and metastatic nodule formation in cancer patients. Also, RCC2 was determined to be an independent prognostic factor for poorer outcome in cancer patients.

Furthermore, some studies showed that RCC2 is also involved in resistance to radiotherapy and chemotherapy and we suspect that these effects could be mediated by activating cancer-promoting transcription factors. RCC2 is able to mediate transcriptional activity and induce expression of the target genes of these cancer-promoting transcription factors such as STAT-3, c-Jun, Sox2, and β-catenin. In addition, some micro-RNAs, known for its tumor suppressor activity, targets RCC2 and decreases its expression, leading to the inhibition of its oncogenic effects. However, the identification of the main mechanisms of RCC2’s oncogenic functions is to be accomplished. Because of its effects on GTPases, we hypothesize that RCC2 likely could target some intermediate protein that ultimately would be responsible for activating transcription factors that promote cancer, metastasis, or drug resistance. Clearly, more studies should be conducted to clarify these issues. Here, the most important conclusion in this review is to realize that the oncogenic effects of RCC2 do not only depend on its roles in cell division but also on its functions beyond its known roles in cell cycle progression.

Figure 3. Oncogenic effects of regulator of chromosome condensation 2 (RCC2) and possible clinical benefits of its inhibition in patients. (A) Different tumor effects reported for RCC2 include increased cell proliferation, induction of chemotherapy resistance, activation of cancer-promoting transcription factors, metastasis, and poorer prognosis. (B) These effects could be inhibited at least partially with the design of chemical inhibitors or some micro-RNA to produce clinical benefits inducing better response to therapy, inhibition of highly proliferating cells, better prognosis, and metastasis inhibition. Figure was done using Canvas X software.
Unfortunately, no chemical inhibitors targeting specifically RCC2 are available. Hence, this impede studying the effects of inhibiting RCC2 in animal tumor models and cancer cell lines. Therefore, the development of inhibitors targeting RCC2 and its evaluation in pre-clinical models and clinical trials deserve attention, not only as a single therapy but in combination with current treatments in patients who have developed resistance to chemotherapy and radiotherapy. Furthermore, because the essential role of RCC2 in cell proliferation and directional migration, studying the possible side effects of these inhibitors in a clinical setting and evaluating their selectivity for cancer tissue is important.

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