Review Article

Could cell division cycle protein 42 be a target for lung cancer treatment?

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Abstract: Cell division cycle protein 42 (Cdc42), a member of the Rho GTPase family, which is part of the Ras superfamily, plays important roles in multiple fundamental cellular processes. Deregulation of Cdc42 may cause cellular defects that are responsible for the activation of signaling pathways, and such deregulation is related to cancer formation. Lung cancer is one of the most devastating diseases worldwide. Cdc42 is overexpressed in human lung cancer samples, which suggests that this protein is associated with lung carcinogenesis. Herein, we review the functions of Cdc42 in lung cancer and discuss potential pharmacological approaches that target Cdc42 in cancer cells.

Keywords: Cell division cycle protein 42 (Cdc42); lung cancer; Rho GTPase; cancer therapy; target

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Introduction

Rho GTPases, which are important members of the Ras superfamily, participate in a variety of cellular biochemical processes, such as proliferation, migration, and transformation, in different types of cells, including endothelial cells, immune cells, and tumor cells (1-4). Cell division cycle protein 42 (Cdc42) is a classic member of the Rho GTPase family, which includes RhoA and Rac1. As a member of the Rho family, Cdc42 was first reported to regulate the actin cytoskeleton as a key gene product in *Saccharomyces cerevisiae* (5,6). Then, Cdc42 was demonstrated to establish and maintain cell polarity in yeast (7). Subsequently, Cdc42 was implicated in the regulation of signaling pathways required for a variety of biological activities, including cell cycle progression, the maintenance of cell polarity and morphology, intracellular trafficking and transformation (5,8-11).

Cdc42 is a molecular switch that cycles between an active GTP-bound form and an inactive GDP-bound form (12). The switching of Cdc42 between these two states is controlled by three main regulatory proteins: GTPase-activating proteins (GAPs), guanine-nucleotide exchange factors (GEFs), and guanine-nucleotide dissociation inhibitors (GDIs). GEFs act as positive regulators to activate Cdc42 by causing the conversion of GDP to GTP, while GAPs act as negative regulators by accelerating the activation of GTPase, which is responsible for converting GTP to GDP and decreasing the activity of Cdc42 (13). GDIs bind to the inactive GDP-bound state of the protein and sequester the release of Cdc42 away from the cellular membrane to inhibit GTPase (14). In its GTP-bound state, Cdc42 induces conformational changes and activates a large number of effectors that initiate signaling cascades that control diverse cellular functions, such as proliferation, migration and transportation (15). However, aberrant activation of Cdc42GTPase has been linked to oncogenic phenotypes in some of human cancers, which suggests that targeting these proteins may be useful for the treatment of tumors.

With advances in gene-specific knockout techniques, recent results obtained from studies of conditional gene deletion of Cdc42 in specific tissues revealed that Cdc42 plays a significant role in the development of multiple organs, including the liver, lungs and kidneys (16-18). These results provide useful genetic information concerning the physiological roles of Cdc42 in states that mimic human diseases, such as acute respiratory distress syndrome (ARDS), polycystic kidney disease, and deficient B cell maturation, among others (19-21). Considering its varied cellular functions, many studies have concentrated on Cdc42 activity in cancer progression. Cdc42 has been shown to regulate diverse cell behaviors in several types of cancer (22,23). In addition, increasing knowledge about Cdc42 has revealed its important roles in cancer diagnosis, treatment and prognosis.

In this review, we focus on the role of Cdc42 in lung cancer and discuss potential therapeutic strategies that target the Cdc42 signaling pathway.

Cdc42 signaling and lung cancer

The Cdc42 gene has not been reported to be mutated or deleted in lung cancer (24), which suggests that Cdc42 is not a tumor suppressor. This differs from the role of RhoA in gastric cancer. However, Cdc42 and its effectors or regulators have been implicated in lung cancer. Increasing numbers of investigations have focused on the mechanisms by which Cdc42 could be activated. These mechanisms include altered expression of Cdc42 GTPases, increased GEF activity and decreased GAP activity.

Cdc42 GTPases in lung cancer

The overexpression of Cdc42 has been detected in several types of human cancer (25,26). It has been reported that Cdc42 is highly expressed in lung adenocarcinoma patients and that overexpression of Cdc42 is significantly associated with lymph node metastasis and TNM stage (27,28). Compared with that in human bronchial epithelial cells, the expression of Cdc42 in lung cancer cell lines, such as A549 cells, is much stronger. In another study, it was found that Cdc42 represents a candidate 'lung tumor progression' gene because altered expression of Cdc42 may affect tumor progression in mice (29). These results suggest that the altered expression of Cdc42 is associated with lung tumorigenesis and may serve as a prognostic marker.

Cdc42 regulators in lung cancer

Some regulatory proteins, including GEFs and GAPs, lead to the activation of Cdc42 GTPase and promote cancer progression. For example, Vav1, which acts as a GEF for Cdc42, has been detected in primary human lung cancer samples, including adenocarcinoma and squamous cell carcinoma (30). It has also been shown that the risk of metastasis in lung cancer is associated with altered expression of Cdc42 and that of its upstream factor Vav1 (31). Ect2 is another regulator that can mediate guanine-nucleotide exchange on small GTP-binding proteins such as Cdc42. It has been reported that a high level of Ect2 expression leads to a poor prognosis of patients with non-small-cell lung cancer (NSCLC) (32,33).

As negative regulators of Cdc42, GAPs also mediate tumor progression in lung cancer. For instance, deleted in liver cancer-1 (DLC-1) is a multidomain protein that includes an internal RhoGTP domain through which DLC-1 functions as a GAP (34). In one study, it was demonstrated that DLC-1 exhibited strong GAP activity, with limited activity for Cdc42 in lung cancer cells (35). Another study showed that ARHGAP44 catalyzes GTP hydrolysis on Cdc42, which is responsible for the stimulation of cell spreading and migration by mutant p53 (36). Although RhoGDIs have been reported to correlate with some tumors such as colorectal and ovarian cancers (37,38), the involvement of a GDI in the regulation of Cdc42 in lung cancer has not yet been reported.

These results demonstrate that upstream regulators of Cdc42, such as GAPs and GEFs, play significant roles in controlling Cdc42 activity during lung cancer progression and are potential candidates for targeted therapy. However, more research on the expression of Cdc42 regulators during different stages of lung carcinogenesis is required.

Cdc42 effectors and signaling in lung cancer

Cdc42 GTPases regulate diverse cellular functions via downstream effectors (39). Well-known effector proteins of active Cdc42 include the proteins in the p21-associated kinase (PAK) family. Paks are a family of serine/threonine protein kinases that can be divided into group I (PAK1-3) and group II (PAK4-6) (40,41). Several members of the Paks family act as signal transducers in lung cancer. For example, Pak4 mediates the activation of LIMK1 for the regulation of migration and invasion in NSCLC (42). Pak4 is also correlated with NF-kB and β-catenin signaling in

A549 lung cancer cells (43). Mutations in another member of the Pak family, Pak5, have been reported to be associated with lung cancer (44). Another study showed that Cdc42 regulates the establishment of polarity in human bronchial epithelial cells via PAR6 (45), but this pathway has yet to be identified in lung cancer. Other effectors interact with Cdc42 to affect lung tumorigenesis. For instance, activated Cdc42-associated kinase 1 (ACK1), a common non-receptor tyrosine kinase, has been reported to be implicated in NSCLC and associated with the survival of NSCLC patients (46). ACK1 also regulates the growth, migration, and metastasis of NSCLC cells both *in vitro* and in vivo. Cdc42-interacting protein 4 (CIP4) is an adaptor protein that regulates EGFR trafficking in a variety of cancer cell models. It has been found that CIP4 promotes lung adenocarcinoma metastasis and is related to poor prognosis (47). These results indicate that Cdc42 effectors and signaling factors could be positive regulators and prognostic biomarkers of lung cancer.

Regulation of Cdc42 in lung carcinogenesis

Cdc42 participates in many cellular behaviors, such as motility and polarity, which can facilitate tumorigenesis and progression. The following sections demonstrate the function of Cdc42 in lung carcinogenesis and discuss the underlying mechanism by which Cdc42 is activated.

Cdc42 drives cancer cell metastasis

Metastasis is a multistep process in which tumor cells migrate out of their primary cancer site, invade the surrounding tissue and blood vessels, enter the blood or lymphatic system and induce tumor colonies in other organs (48,49). The invasive cells form invadopodia, which are actin-rich membrane protrusions that are associated with the degradation of the extracellular matrix (ECM) by matrix metalloproteinases (MMPs) (50,51). Invasive cells also contain filopodia, which are involved in the movement of cancer cells. The abundance of filopodia was thought to be correlated with the invasiveness phenotype (52,53). Cdc42 has been implicated in the suppression of both lung cancer invadopodium formation and ECM degradation via the N-WASP pathway (54). As the downstream effector of PI3K signaling, Cdc42 is activated, which promotes filopodium formation and cell migration during NSCLC progression (55). In addition, the LKB1-Cdc42-PAK pathway has been reported to impair the cell polarity required for cancer cell invasion into the surrounding environment (56). The evidence showed that maintenance of cell polarity may be one way in which Cdc42 affects cellular morphology and contributes to cancer progression. These studies suggest that Cdc42 plays a critical role in the cellular events that are responsible for lung cancer metastasis.

Cdc42 stimulates EMT

Cancer metastasis relies on cell migration and the ability of cancer cells to invade basement membranes and blood vessels (48). Cell migration involves a process termed epithelial-to-mesenchymal transition (EMT), in which tumor cells adopt a mesenchymal morphology to move through the ECM via the digestion of tumor cell-to-cell contacts (57-59). During EMT, epithelial cell surface proteins that regulate cellular adhesion, such as E-cadherin, are replaced by the mesenchymal proteins N-cadherin and vimentin.

Cdc42 has been implicated in mediating EMT, as indicated by the hallmarks of decreased E-cadherin levels and upregulated vimentin levels in lung cancer cells (60). The release of p120-catenin from adherens junctions (AJs) to the cytoplasm, which leads to E-cadherin degradation, has been associated with the activation of Cdc42 in human lung cancer (61). However, some results indicated that Cdc42 modulates smoke-induced airway cell migration through a p120-catenin-independent pathway during the early stages of lung carcinogenesis (62). Additional evidence suggests that E-cadherin can negatively mediate cell migration in NSCLC by reducing the level of active form of Cdc42 (63). Other reports have shown that during EMT, Cdc42 plays a key role as a downstream effector of the FAK/AKT pathway, through which Cdc42 is activated by the interaction between integrin αvβ3 on the cell and ECM ligands; this interaction in turn initiates the formation of filopodia in lung tumor cells (64). These studies suggest a critical role for Cdc42 in inducing EMT in lung cancer.

Cdc42 induces oncogenic transformation

Some studies have reported that Cdc42 is involved in Ras-mediated cellular transformation and tumorigenesis (65). For example, in the Cre-inducible conditioned knockout mouse model, Cdc42 deficiency in alveolar cells resulted in the inhibition of Kras-induced transformation and tumor formation, but Cdc42 loss in bronchial cells increased

bronchiole tumor formation (66). These results suggest that Cdc42 functions in a cell-specific manner in lung tumorigenesis.

In addition to Ras-related transformation, Cdc42 also affects oncogenic EGFR signaling. The activation of Cdc42 results in the inhibition of ubiquitin-mediated EGFR degradation, which leads to sustained EGFR signaling and cellular transformation (67). A contribution of Cdc42 to EGFR-mediated transformation has not yet been reported in lung cancer. Thus, future experiments will address this possibility and determine whether Cdc42-EGFR initiates lung cancer formation.

Targets of Cdc42

Since Cdc42 GTPase has proven to be difficult to target directly, significant efforts have been made to develop inhibitors based on the mechanisms of Cdc42 regulation and function and that target various aspects of Cdc42 signaling. In this section, we will discuss the potential strategies and inhibitors.

Curcumin inhibits lung cancer migration and downregulates Cdc42 (27). A natural compound, cycloartobiloxanthone, affects the migration and invasiveness of lung cancer cells (68). In addition, TAOCSB has been shown to inhibit the migration of A549 cells by suppressing Cdc42 (31). These results indicate that Cdc42 is a target of natural products with anticancer effects.

Other studies have identified small molecule inhibitors of Cdc42 activity that affect GEF function. For example, ML141 is a noncompetitive, nucleotide-binding inhibitor of Cdc42 that inhibits nucleotide re-association (69). Another small molecule inhibitor, CASIN, inhibits Cdc42 activation by preventing its binding to GEFs in a dose-dependent manner (70). However, these small molecule inhibitors have not yet shown clinical efficacy for lung cancer. In addition, emerging evidence has shown that microRNAs play important roles in lung carcinogenesis by affecting the expression or activation of Cdc42. The ectopic expression of miR-137 in lung cancer cells could downregulate Cdc42, which would lead to a decrease in cell proliferation (71). MiR-182 has been reported to suppress lung cancer metastasis (72). In addition, miR-25 has been implicated in patients with NSCLC and is associated with Cdc42 production in A549 cells (73). A recent result showed that long noncoding RNA 00707 is upregulated in LAD tissues compared with normal tissues and that its overexpression is related to an advanced TNM stage, as this miRNA regulates Cdc42 (74). These results indicate the importance of microRNAs as downstream effectors that target the Cdc42 gene.

Conclusions

Emerging evidence indicates that Cdc42 signaling plays an important role in the progression of lung cancer. However, additional studies are needed to determine the activity and expression patterns of Cdc42 and its signaling effectors during the stages of lung tumor initiation, progression and metastasis. The effectors and upstream regulators of Cdc42 have been implicated in the pathogenesis of lung tumorigenesis. Current efforts to block Cdc42 activity based on the regulatory mechanisms associated with Cdc42 signaling are in progress. However, there has been limited success in Cdc42 GTPase inhibitor development for lung cancer treatment. The small inhibitor ML141 was used to inhibit Cdc42 activity by binding to GEFs. In our previous study, we used an ML141 inhibitor during inflammatory lung injury and demonstrated that the inactivation of Cdc42 decreased endothelial cell proliferation and regeneration (21). Therefore, further studies are required to observe the effect of Cdc42 inhibitors on lung carcinogenesis. Recent results showed that microRNAs that target Cdc42 are associated with lung cancer. However, the regulatory mechanisms in these pathologic processes require further study. Overall, these data support a significant role for Cdc42 in lung tumorigenesis and reveal the protein as a novel candidate for therapeutic interventions, which warrants further investigation of Cdc42 signaling in lung cancer.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.01.13). The authors have no conflicts of interest to declare.

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