A STUDY OF CELL-CYCLE SURVIVAL WITH REGULATORS IN DUAL FUNCTIONS OF LUNGS CANCER

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ABSTRACT

Lung cancer is the leading cause of cancer death worldwide. Histologically, 80% of lung cancers are classified as non-small cell lung cancer (NSCLC), and the remaining 20% as small-cell lung cancer (SCLC). Lung carcinoma is the result of molecular changes in the cell, resulting in the deregulation of pathways controlling normal cellular growth, differentiation, and apoptosis. This review summarizes some of the most recent findings about the role of cell-cycle proteins in lung cancer pathogenesis and progression. The mammalian cell cycle is important in controlling normal cell proliferation and the development of various diseases. Cell cycle checkpoints are well regulated by both activators and inhibitors to avoid cell growth disorder and cancerogenesis. Cyclin dependent kinase 20 (CDK20) and p21Cip1/Waf1 are widely recognized as key regulators of cell cycle checkpoints controlling cell proliferation/growth and involving in developing multiple cancers. Emerging evidence demonstrates that these two cell cycle regulators also play an essential role in promoting cell survival independent of the cell cycle, particularly in those cells with a limited capability of proliferation, such as cardiomyocytes. These findings bring new insights into understanding cytoprotection in these tissues. Here, we summarize the new progress of the studies on these two molecules in regulating cell cycle/growth, and their new roles in cell survival by inhibiting various cell death mechanisms. We also outline their potential implications in cancerogenesis and protection in heart diseases. This information renews the knowledge in molecular natures and cellular functions of these regulators, leading to a better understanding of the pathogenesis of the associated diseases and the discovery of new therapeutic strategies.

KEYWORDS: Cell cycle; CDK20; p21Cip1/Waf1; cancer; cardiovascular disease.

INTRODUCTION

Lung cancer remains a worldwide major health challenge. Despite improvements in staging and the integrated application of surgery, radiotherapy, and chemotherapy, the 5-year survival rate for individuals with lung cancer is only about 15%. Histologically, 80% of lung cancers are diagnosed as non-small-cell lung cancer (NSCLC), whereas the remaining 20% of cases are diagnosed as small-cell lung cancer (SCLC). On the basis of cell morphology, adenocarcinoma, and squamous cell carcinoma are the most common types of NSCLC. The current staging system for NSCLC is based upon the size and location of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M). The standard treatment of patients with stage I NSCLC (T1- 2, N0, M0) is resection of the primary tumor alone (no adjuvant therapy). Survival for patients with stage I disease ranges between 40% and 70%, and the failure of treatment is due to distant recurrences. This suggests that a significant number of patients with stage I NSCLC may actually be under-staged. Therefore, if correctly identified, these patients may benefit from adjuvant therapy in addition to resection, with a predictable improvement in the survival rates. Indeed, to identify patients with stage I NSCLC who might benefit from adjuvant therapy, investigators have attempted to identify factors predicting poor prognosis. These studies included analysis of performance status, histological subtype, size of the primary tumor, the degree of tumor differentiation, mitotic rate, and evidence of lymphatic or vascular invasion. However, all of these factors have failed, to date, to precisely identify a group of stage I patients who would benefit from adjuvant therapy. Cigarette smoking remains the main risk factor for lung cancer, accounting for about 90% of the cases in men and 70% of the cases in women. Over the past few years, our research group has investigated the possible involvement of several molecular mechanisms, such as cell-cycle and apoptosis regulators, oncogenes and tumor suppressor genes, cell adhesion molecules in the pathogenesis, and progression of lung cancer. The goal of this review is to summarize some of the most recent findings about the role of cell-cycle proteins in lung cancer pathogenesis and progression.

THE CELL-CYCLE MACHINERY AND LUNG CANCER

In the last decade, several studies have focused on the role of cell-cycle control in lung carcinogenesis. A precise regulation of the cell-cycle is a fundamental requirement for the homeostasis of a eukaryotic cell. The cell cycle machinery is comprised of five sequential stages: G0, G1, S, G2, and M. Non-replicating cells reside in the quiescent state G0. A complicated balance of different signals, such as those produced by growth factors and growth factor inhibitor pathways, determines if the cell enters into the G1 phase of the cell-cycle. During the last decade, scientists successfully delved into the molecular machinery devoted to the fine regulation of the cell-cycle phases, identifying and characterizing several genes and gene products involved. A key role is played by cell-cycle kinases (cdks), relatively small proteins with an apparent molecular mass between 33 and 43 kDa whose activity is regulated by their arrangement in a multimeric

complex with larger proteins, called ‘‘cyclins,’’ after their cyclical expression and degradation during the cell-cycle. Different cdkcyclin complexes, formed with clear-cut timing throughout the cell-cycle, together with their phosphorylation/ dephosphorylation, efficiently regulate the activity of the multimeric holoenzyme.

Initiation of the cell-cycle via extracellular signals induces the transcription of several proteins including cyclin D, complexed with cdk4 (and cdk6), and leads to phosphorylation of the tumor suppressor protein pRb in the pRb–E2F complex. The phosphorylated form pRb is unable to bind to the E2F transcription complex, permitting the E2F-dependent transcription proteins to continue proliferation. The progression through G1 is also influenced by negative regulators of the cdk–cyclin complexes. These proteins belong to two different families: the INK4 family of proteins, and the kinase inhibitory protein (CIP/KIP) family. The INK4 family of proteins, which inhibit cdk4 and cdk6, includes the p15, p16, p18, and p19 proteins, while the KIP family includes p21, p27, and p57 and is regulated by the tumor suppressor gene p53. Normal progression through the S phase into the premitotic G2 phase, and through the G2/M checkpoint, is also regulated by specific cdk–cyclin complexes, such as the cdk2–cyclinA and cdk2–cyclinB dimers. The p53 protein has been termed the guardian of the genome due to its role in initiating growth arrest or apoptosis during cellular proliferation by responding to the presence of damaged DNA within the cell. The p53 tumor suppressor gene is involved in cell-cycle checkpoints by virtue of its action as a transcription factor for several cell-cycle regulatory proteins, including the p21 gene. On the other hand, proliferating cell nuclear antigen (PCNA) is involved in activation of DNA polymerase d, a function required for DNA replication and repair (Bravo et al., 1987; Prelich et al., 1987). Moreover, the p53 to p21 pathway also inhibits DNA replication through p21’s interaction with PCNA, without affecting PCNA’s DNA repair abilities (Li et al., 1994; Waga et al., 1994). The tumor suppressor protein p53 also regulates progression through the G1 checkpoint of the cell-cycle. In particular, p53 is activated in response to DNA damage and serves to arrest cell-cycle progression in G1 and hence allow time for DNA repair. It is recognized that p53 is a point of convergence of a complex network of signaling pathways that regulate its level in the cell. In turn, p53 binds to specific DNA sequences and transactivates a group of target genes (including the cell-cycle inhibitor p21Waf1/Cip1), thereby inhibiting cell proliferation and promoting apoptosis.

Cell Cycle Regulators as Targets for Lung Cancer Therapy

Aberrations in cell cycle control are a hallmark of lung tumors. Therefore, modulation of cell cycle regulators may have an important use for the treatment of these cancers. In this last part, we discuss the strategies that are currently developped to target the cell cycle machinery in lung tumors (Table 1).

Table 1 Selected inhibitors of cell cycle regulators used in clinical trials for lung cancer therapy

Inhibitor	Main targets	Clinical trials
	Inhibitors of cyclin-dependent kinases	
Flavopiridol also known as alvocidib	CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9	Phase I: NSCLC in combination with paclitaxel and carboplatin
Aminothiazole SNS-032 also known as BMS-387032 (Sunesis)	CDK2, CDK7 and CDK9 (CDK1 and CDK4)	Phase I: NSCLC Sensitized radioresistant NSCLC cells to ionizing radiations
R-roscovitine also known as CYC202 and seliciclib (Cyclacel)	CDK1, CDK2, CDK5, CDK7 and CDK9	Phase I–II: NSCLC
Indisulam, also known as E7070	Not Assigned	Phase I: lung cancer in combination with irinotecan
SCH 727965	CDK1, CDK2, CDK3 and CDK9	Phase II: NSCLC
	Inhibitors of mitotic checkpoint kinases	
VX-680, also known as MK-0457	Pan-aurora	Phase I–II: NSCLC Trials discontinued owing to QT prolongation
	Inhibitors of DNA Damage Checkpoint kinases	
7-hydroxy-staurosporine, also known as UCN-01	CHK1 and MARK3 (PKC, PDK1, GSK3β, CDK1, CDK2 and CHK2)	Phase II: SCLC (with topotecan)

Inhibitors of cyclin-dependent kinases.

As discussed above, CDKs are often overactive in lung cancer resulting in loss of checkpoint integrity and uncontrolled proliferation. Therefore, selective inhibitors of CDKs may limit the progression of a tumor cell through the cell cycle and facilitate the induction of apoptotic pathways. The therapeutic value of small molecules CDK inhibitors that modulate CDK by competing with ATP binding is the subject of intense work. First generation compounds to be evaluated in clinical trials included the pan-CDK inhibitor Flavopiridol which induced partial responses or stable disease in patients with NSCLC in a phase I study, when using in combination with the cytotoxic agents paclitaxel and carboplatin. A second-generation CDK inhibitor, the aminothiazole SNS-032 which was recently shown to sensitize radiotherapy-resistant NSCLC cells to ionizing radiation, is currently in phase I clinical trials as an intravenous agent. R-roscovitine (CYC202, seliciclib) is another pan-CDK inhibitor which has antitumor activity against a broad range of cancer cell lines and human cancer xenografts including NSCLC. This molecule is currently undergoing phase I-II trials in patients with NSCLC. Other inhibitors undergoing clinical trials in advanced cancers including NSCLC are indisulam (E7070) which is in phase I trial in combination with irinotecan and SCH727965 which is in phase II trial. Of note Indisulam is not a direct CDK inhibitor but it cause a depletion of cyclin E which reduces CDK2 activity.

Inhibitors of mitotic checkpoint kinases

Many patients with cancer receive antimitotic agents that act as microtubule toxins as first-line therapy. However, because of the side effects of these drugs, these last year's much work has focused on the identification of new mitotic targets that could block spindle assembly without affecting microtubules. In this respect, aurora kinases and PLKs have received particular attention and diverse arrays of inhibitors have been developed. Preliminary clinical data from phase I trials have largely been consistent with cytostatic effects, with disease stabilization as the best response achieved in solid tumors. As an example, the pan-aurora inhibitor MK-0457 (VX-680) blocks tumor xenograft growth and induces tumor regressions in preclinical models. In phase I-II trials, MK-0457 was given to patients with previously treated tumors and

disease stabilization was observed in one patient with lung tumor. However, owing to QT prolongation in 1 in 100 patients, trials have been discontinued. Numerous other compounds targeting Aurora and PLK kinases are currently in clinical development. Their use in lung tumors therapy has not been yet evaluated.

Inhibitors of DNA damage checkpoint kinases.

Two small molecules ATM inhibitors have been described (KU55933 and CP466722) that target ATM by blocking its ATP-binding site and display high specificity. Both compounds prevent phosphorylation of ATM effectors and sensitize cells to drugs that induce DNA double-strand breaks. They also specifically and reversibly disrupt ATM-dependent cell cycle checkpoint in response to DNA damage induced by ionizing radiation. Although this has to be fully investigated "in vivo," the "in vitro" effects of these novel lead chemotypes are promising. At present, no specific ATR inhibitors have been identified. However, several CHK1 and CHK2 inhibitors have been developped and are currently in clinical evaluation. One of them, 7-hydroxystaurosporine (UCN-01) is undergoing Phase II trials in SCLC patients in combination with topotecan cytotoxic agent. This compound efficiently abrogates DNA damage checkpoint in cancer cells that lack p53 and have been treated with DNA-damaging drugs, resulting in mitotic catastrophe.

CDK20 and p21Cip1/Waf1 in Cell Cycle and Cell Growth

1. CDK20 and p21Cip1/Waf1 Regulate Cell Cycle via CDK2

CDK20 is a newly identified small CAK protein that was first reported in HeLa cells by Kaldis and Solomon in 2000. They found that CDK20 contains all 11 conserved subdomains characteristic of Ser/Thr protein kinase and has sequence homology to both Cak1p and CDK7 groups of CAKs. CDK20 has a 43% sequence identity with CDK7, and is distinct in size from CDK7; the former peaks at 42 kDa, whereas the latter peaks at 140 kDa. It also has a substrate specificity that is different from CDK7, for example, in addition to being an activator of CDK2 as CDK7, CDK20 also favors MAK-related kinase/intestinal cell kinase (MRK/ICK) as the substrates in driving the progress of the cell cycle, which is not found in CDK7. Later on, Liu et al. further confirmed the CAK activity of CDK20 in regulating cell growth in HeLa cells. They showed that the RNAi-mediated ablation of CDK20 inhibited cell proliferation, through cell cycle G1 phase arrest by decreasing pCDK2 levels, and inhibiting CDK2 kinase activity [23]. Similar results were observed in human glioblastoma, LoVo, and DLD1 human colorectal cancer cell lines. Although the accurate regulatory mechanism of CDK20 in activating CDK2 remains incomplete, merging studies have indicated the direct role of this kinase as a catalyst for CDK2 activity. For example, it has been shown that excess CDK20 phosphorylates the CDK2 on Thr-160, subsequently promoting the transition from the G1 to S phase through the phosphorylation of key target proteins, including the pRb as well as the Rb family member's p130 and p107. It also releases transcription factors such as E2F that are complexed with pRb and activate the promoters of genes important in DNA synthesis [24]. Phosphorylation on CDK2 by CDK20 is stimulated by

the association of CDK2 with its relevant cyclin. On the other hand, p21Cip1/Waf1, also known as cyclin-dependent kinase inhibitor 1 or CDK-interacting protein 1, plays an opposite effect of CDK20 by inhibiting CDK2 activity, and thus functions as a negative regulator of cell cycle progression at G1 and S phase. P21Cip1/Waf1 belongs to a family of CDK interacting protein/Kinase inhibitory protein (CIP/KIP) inhibitor family with p27, p57. Those inhibitors share a homologous N-terminal domain, which contains a cyclin-binding motif 1(Cy1). This motif is indispensable for the inhibition property of p21Cip1/Waf1, which allows p21Cip1/Waf1 binding to CDK in a region that blocks its ability to complex with cyclins, and thus prevents CDK activation. Besides a direct interaction with the CDK2 complex, the Cy1 motif in p21Cip1/Waf1 mediates cell cycle arrest also through the completion with other cell cycle regulators. For example, cell division cycle 25A (cdc25A) is a phosphatase that activates the CDK2/cyclin E complex to go through the G1-S transition. Cdc25A and p21Cip1/Waf1 share a similar Cy1 motif and compete for interacting with the CDK2 complex, resulting in cell cycle arrest at the G1 phase.

2. The Role and Mechanisms of CDK20 and p21Cip1/Waf1 in Cell Growth

Studies have shown that both CDK20 and p21Cip1/Waf1 play important roles in cell growth, such as cell proliferation, division, and hypertrophy via variant mechanisms. CDK20 has been found expressed in various human tissues, predominantly in the brain and kidney, and to a lesser extent in the liver, heart, and placenta; it is also widely expressed in cell lines originating from a variety of tumor tissues. CDK20 has been indicated to play an important role in cell growth during normal tissue development. For example, it has been reported that CDK20 participates in the regulation of ciliogenesis, a process of outgrowth of cilia on the eukaryote cell surface, which is a crucial step in mammalian embryogenesis and neuron patterning by modulating the Hedgehog signaling pathway. A study in C. elegans also indicated the essential function of CDK20 in controlling microtubule dynamics in multiple sensory neuron types. In addition, CDK20 was found involved in the pathogenesis of diseases, particularly in cancers. In glioblastoma cells, knockdown CDK20 blocks cancer cell proliferation. These findings indicate that CDK20 is a key regulator of cell growth in various cell types. Despite the lack of full understanding of the functions and differences in cell lines, CDK20 is currently known to regulate cell growth in both a CAK and non-CAK manner in different cells, which have been reviewed previously. In addition to the direct effect in phosphorylating CDK2 on Thr-160 as mentioned above in the cell cycle, CDK20 may also bind and/or phosphorylate CDK7 (or other CDKs). Furthermore, other than the activation of CDK2, reports indicate that CDK20 promotes cell growth through activating MRK/ICK. CDK20 has also been found to regulate cell growth through other mechanisms such as regulating β-catenin-T-cell factor (TCF) signaling, Wingless-related integration site (Wnt) signaling pathway, phosphorylation of glycogen synthase kinase 3β (GSK3β) at Thr390, or inducing an expression of cyclin D1. However, these potential mechanisms still need further confirmation. P21Cip1/Waf1 is also found to be widely involved in cell growth through different mechanisms. One of the mechanisms is mediated by its inhibitory effect on CDKs. Although it is primarily associated with the

inhibition of CDK2, studies show that p21Cip1/Waf1 is capable of inhibiting almost all cyclin /CDK complexes. For example, the low concentration p21Cip1/Waf1 promotes proliferation through the assembly and activation of cyclin D/CDK4/6 complexes, and phospho-p21Cip1/Waf1 promotes cyclin B/CDK1 complexes activities. In addition, Insinga et al. showed that irradiation of hematopoietic stem cells results in the upregulation of p21Cip1/Waf1, causing p53 inhibition, ultimately leading to cell cycle entry and symmetric self-renewing divisions. Furthermore, p21Cip1/Waf1 can regulate cell proliferation by interacting with the PCNA, a DNA polymerase accessory factor, which plays a regulatory role in the S phase. PCNA is a regulator of DNA synthesis, and its expression is controlled by E2F (E2 factor) transcriptional factor containing complexes. Interaction between p21Cip1/Waf1 and PCNA ensures the progress of the cell cycle. p21Cip1/Waf1 displaces PCNA partners to control DNA replication in the S phase. In return, PCNA also controls the expression of p21Cip1/Waf1 in the S phase to prevent the upregulation of p21Cip1/Waf1, which arrests the cell cycle. Besides, DNA damage causes p21Cip1/Waf1 to bind CDK1 complexes, which inhibits the catalytic function of the complex, subsequently bringing about cell cycle arrest. Moreover, p21Cip1/Waf1 plays a dual role in the process of cell hypertrophy, a process by which a cell increases its size, either in physiological or maladaptive conditions. Studies have shown that the absence of p21Cip1/Waf1 did not affect transforming growth factor (TGF)-beta's action on proliferation, but did decrease TGF-beta-induced hypertrophy in p21Cip1/Waf1 knockout mesangial cells compared with the control. In the same study, it was discovered that the expression of p21Cip1/Waf1 was required for the initial phase of hypertrophy, and its absence caused a significant delay in hypertrophy. These results suggest that p21Cip1/Waf1 promotes hypertrophy. However, other studies have provided conflicting evidence of p21Cip1/Waf1 in cell hypertrophy. For example, upregulating p21Cip1/Waf1 was found to be associated with the inhibition of cardiomyocyte hypertrophy via a cardiac-restricted protein, called CHAMP (cardiac helicase activated by MEF2 protein) during prenatal and postnatal development of the heart, while a downregulation of p21Cip1/Waf1 was found in aortic constriction-induced cardiac hypertrophy in adult hearts, which was supported by a recent study showing that p21Cip1/Waf1 protects cardiac hypertrophy. Nevertheless, p21Cip1/Waf1 KO mice can grow normally despite exhibiting impaired G1 checkpoint control, indicating the complexity of its functions.

CONCLUSION

Taking into account the extensive functional network constituted by the cell-cycle regulator proteins, it appears evident that the knowledge of the expression levels of these factors, and their co-regulation, may be important in predicting patient clinical response to therapy. Nevertheless, targeting multiple checkpoint proteins may represent a good therapeutic strategy for the development of new molecular treatments for lung cancer. These data strongly suggest further studies to be performed in order to investigate the simultaneous expression of numerous cell-cycle regulators in lung cancer. Since cell cycle regulators have been extensively studied on proliferative cells and cancer cells, their cell survival roles and the underlying

mechanisms remain largely unknown. Future research could be focused on those cells with a limited capability of cell proliferation, such as cardiomyocytes and neural cells, since the regeneration of these cells is still a scientific challenge despite their importance. Understanding the effect of these cell cycle regulators inside these cells will bring new insights for discovering the therapeutic strategy for damaging these tissues and impaired function. Also, the role of CDK20 is different among the variants, so exploring the mechanism controlling the alternative splicing of CDK20 in other cells will help to understand the cell function and pathogenesis of various diseases. Furthermore, it has been shown that p21Cip1/Waf1 plays multiple roles in cell survival and cell growth that largely depend on the cell types and subcellular translocation. Understanding the mechanisms driving the translocations of p21Cip1/Waf1 in these cells will open a new avenue to control cellular function under disease conditions. Finally, since CDK20 and p21Cip1/Waf1 share many similar functions in multiple cells, further attention should be drawn to discover the links between p21Cip1/Waf1 and CDK20. There are a few potential common pathways between these two regulators: first, they regulate the cell cycle via acting on the CDK2. Second, it has been shown that CDK20 activates the ERK1/2 pathway, which subsequently induces p21Cip1/Waf1 expression [89]. Other links could involve the Wnt/beta-catenin pathway or even a direct link between CDK20 and p21Cip1/Waf1. CDK20 could also be possible as the upstream regulator for the translocalization of p21Cip1/Waf1 driving to an anti-apoptotic pathway. These studies would result in the discovery of an integrating mechanism in regulating cell growth and cell survival that could have a great application for treatment of various cell-cycle related diseases, including but not limited to cancer and heart disease, providing a significant clinical translational potential.

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