

Pharmacological cyclin dependent kinase inhibitors: Implications for colorectal cancer

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Abstract

Colorectal cancer accounts for a significant proportion

of cancer deaths worldwide. The need to develop more chemotherapeutic agents to combat this disease is critical. Cyclin dependent kinases (CDKs), along with its binding partner cyclins, serve to control the growth of cells through the cell cycle. A new class of drugs, termed CDK inhibitors, has been studied in preclinical and now clinical trials. These inhibitors are believed to act as an anti-cancer drug by blocking CDKs to block the uncontrolled cellular proliferation that is hallmark of cancers like colorectal cancer. CDK article provides overview of the emerging drug class of CDK inhibitors and provides a list of ones that are currently in clinical trials.

Key words: Colorectal cancer; Cyclin; Cyclin dependent kinase inhibitor

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Core tip: This article provides a brief overview of an emerging drug class, cyclin-dependent kinases inhibitors and their potential implications in colorectal cancer treatment.

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INTRODUCTION

In the United States, colorectal cancer (CRC) is among the three most common causes of death and accounts for approximately 8.4% of all cancer related deaths^[1]. Colorectal cancer is primarily asymptomatic in earlier stages and therefore, often not diagnosed until the later stages of the disease. Currently, surgical

intervention with chemotherapy is the primary treatment for patient^[2]. In metastatic disease, systemic chemotherapy is coupled with surgical resection of metastases, which are commonly seen in the liver^[3,4]. A deeper understanding of the intricate molecular biology that mediates the pathogenesis of this disease may be beneficial in identifying new drug targets with the ultimate goal of improving survival time.

GOALS AND LIMITATIONS OF CURRENT THERAPEUTICS

Current therapeutic agents against cancerous cells aim to disrupt the rapid proliferation of cancerous cells; this is achieved either through directly targeting and killing cancerous cells or indirectly by slowing down cell growth. These drugs can be given systemically *via* oral medication or in a more targeted manner by direct injection into the blood^[5]. Using drugs in combination has been proven to increase survival time and can prevent some drugs from developing resistance. Molecular pathways that mediate the processes of apoptosis, angiogenesis, invasion and the cell cycle are main targets of chemotherapy^[6]. By understanding how molecular mechanisms regulate essential cellular processes, chemotherapeutic agents can be developed to combat the cancerous cells. The mammalian cell cycle, for example, is precisely regulated during periods of development and growth. This regulation is essential for proper cell differentiation and proliferation. Any loss of control over the events of the cell cycle can lead to unregulated growth and is associated with cancer development^[7].

There have been several chemotherapeutic drugs that are FDA approved and are currently used in cancer treatment. Development of resistance to chemotherapeutic agents, difficulties in controlling metastatic disease and devastating side effects to drugs are only some of the limitations of the current arsenal of drugs^[8,9]. The various limitations to the current drugs available that make the need to discover new drugs even greater. In this article, the authors aim to provide an update of search of cyclin-dependent kinases (CDK) inhibitors as an anti-cancer drug and provide information on new areas for therapy.

OVERVIEW OF CYCLINS AND CYCLIN DEPENDENT KINASES

Disruptions of the cell cycle have been well documented to be involved in the genesis and propagation of a variety of cancers, including colorectal cancer. The cell cycle is divided into two broad stages: mitosis and interphase. Mitosis is characterized as a period of division, whereas interphase is a period of metabolic growth^[10]. The cell cycle itself is closely regulated by cyclins, a protein that activates CDK, a group of serine/threonine proteases. Cyclins serve as the

regulatory unit that is vital for CDK activity; it is the interaction of cyclins with CDKs that helps mediate normal development and proliferation of mammalian cells^[11]. Alterations in the function of any of the cell cycle regulator proteins such as cyclins and CDK are a hallmark of cancer development^[12].

There have been numerous families of cyclins identified that are associated with specific stages of the cell cycle. Although different families of cyclins differ in primary amino acid sequence, they all share a common 100 amino acids sequence termed the cyclin box. This structure is responsible for binding to cyclin dependent kinases^[13]. When a cyclin binding partner binds to its respective CDKs, it is now in the active form and can serve as a modulating signal that allows for progression through the cell cycle. Typically, these kinases are serine or threonine kinases that belong to a larger family of kinases that includes mitogen-activated kinases and glycogen synthase kinases^[14]. There currently have been over nine CDK's identified, with five of them being directly implicated with regulation of specific checkpoints in the cell cycle. Activated CDK's serve a regulatory role in the cell cycle and in transcription^[15].

CDK INHIBITORS

It has been established in previous literature that deregulation in the function or mutation of the structure of CDK can result in disease processes^[16,17]. Any changes in the levels of CDK interacting proteins can impact the phosphorylation of CDK^[18]. For example, the loss of Cables, a CDK interacting protein, is linked to development of cancers including colon cancer^[19]. The intricate and complex binding between cyclins and CDKs is difficult to mimic *in vitro* and success to fully elucidate the binding pattern has been limited^[20]. In recent years, studies have been done to understand more about the roles of CDK inhibitors and if they can regulate uncontrolled cellular proliferation.

There are two families of CDK-inhibitors: INK4 and CIP/KIP class^[21]. These two families differ in the particular cyclin families that they interact with. The inhibitor of CDK4 family, or INK4 consists of four individual proteins that selectively inhibit the D family of cyclins. The kinase inhibitor protein family or CIP/KIP is composed of three proteins that act to interact with other cyclin families. The inhibitor of CDK4 family, or INK4 consists of four individual proteins that selectively inhibit the D family of cyclins. The kinase inhibitor protein family or CIP/KIP is composed of three proteins that act to interact with other cyclin families^[22]. From a mechanistic standpoint, it has been theorized that CDK-inhibitors can be used as an anti-cancer drug by blocking CDK's and therefore halting the uncontrolled cellular proliferation seen in cancer. Flavopiridol was the first CDK inhibitor ever tested in human clinical trials. This drug showed promise in preclinical cellular studies and was initially tested in patients with a

variety of carcinomas, including colon^[23]. This drug was the first of its kind to be tested in a clinical trial and set the stage for more investigation and further study of CDK inhibitors. Unfortunately, flavopiridol has had limited success individually and in combination with other medications as an anti-cancer drug. Since the testing of the first CDK inhibitor, flavopiridol, several other CDK inhibitors have been developed and tested. Inhibitors have been developed that target various stages of the cell cycle based on the specific cyclin-CDK blocked.

PHARMACOLOGICAL CDK INHIBITORS

There is great variability in the range of action of CDK inhibitors - some target specific points in the cell cycle while others are pan-CDK inhibitors that act much more broadly. This cell cycle attenuating effect documented in the literature of cellular CDK inhibitors implicate the use of pharmacological CDK inhibitors as an anti-cancer drug. There are several that have entered clinical testing. Here is a selected list of CDK-inhibitors that have entered or are in various stages of clinical trials^[24].

CDK-INHIBITORS AND COLORECTAL CANCER

Based on preclinical research on colorectal cancers, there have been a few CDK alterations that have been strongly linked to the progression of the cancer. Understanding these cellular changes can serve as a potential indicator of prognosis and help scientists focus on the areas needed in drug development. The overexpression of CDK1 has been associated with increased risk of metastasis^[4]. CDK2 overexpression has been seen in roughly 86% carcinomas^[25]. Lastly, CDK4 overexpression is linked to a poor prognosis in colorectal cancer^[26].

From the list of inhibitors currently in clinical trials, found in Table 1^[23,27-41], there have been a few that have been studied more specifically in colorectal cancer. One that has shown particular promise is PD-0332991, from Pfizer, New York, NY. This is an inhibitor of CDK4 and CDK6. Studies done in human carcinoma cells have shown inhibited growth^[42]. Additional studies done in mice with human colon carcinoma, Colo-205, have shown significant tumor regression^[43]. This drug has shown promise as a clinically useful CDK-inhibitor that can potentially be used in colorectal cancers. Phase I clinical studies have been conducted that have shown positive results in patients with colorectal cancers^[44,45].

LIMITATIONS TO CDK-INHIBITORS

A major difficulty in identifying CDK-inhibitors is finding one that has the potential to target a specific

cyclin; a majority that have entered clinical trials either directly impact multiple cyclins/CDKs or have off target effects^[46]. The poor selectivity between different CDKs results in a higher dose of CDK-inhibitor being used^[47]. Lower doses of CDK-inhibitors used in trials have proved to be inefficient; yet, the proper management of dosage is critical to avoid reaching toxic doses. The challenges in finding a highly selective CDK-inhibitor has resulted in higher dosage that renders the side effects seen from CDK inhibitors in clinical trials become a limiting factor for their use. For example, flavopiridol has a dose-limiting toxicity of secretory diarrhea^[48]. This inhibitor is a pan-CDK inhibitor and therefore requires a higher dose to elicit a cytotoxic effect. The high degree of homology amongst the group of CDKs, particularly in the ATP-binding site, has made it quite challenging to identify selective targets against particular CDKs^[49]. Further work must be done to identify more selective molecular signatures of individual CDKs in preclinical studies to develop more targeted CDK-inhibitors.

Despite the promise that CDK-inhibitors hold, it is important to be cautious of any potential limitations. These compounds were identified over a decade ago and have been studied ever since. Although a few CDK-inhibitors have entered clinical trials, none have yet to show the promise of being a potent anti-cancer drug. CDK-inhibitors are a type of kinase inhibitor. A major concern that has been noted with the use of kinase inhibitors is the possibility of acquired drug resistance over the treatment regimen. For example, Imatinib, a well-established tyrosine kinase inhibitor, is known to cause an acquired resistance during the treatment course^[50]. This resistance can be conferred through point mutations in the oncogene that result in the drug becoming less effective during the treatment regimen^[51]. Currently, there have not been any reported incidents of CDK-inhibitors resulting in acquired resistance in the literature. However, it is important to note that there are highly conserved side chains present in CDKs that are specific targets of CDK-inhibitors^[52]. Any point mutation or alteration of the unique molecular signature that CDK-inhibitors target can potentially confer resistance to the drug.

POTENTIAL ALTERNATIVES BESIDES CDK-INHIBITORS

There is a clear association between the role of cyclins and cyclin dependent kinases in regulation of the cell cycle. The research and studies of CDK-inhibitors have proved that much more work must be done. Instead of focusing on CDK-inhibitors, it would be wise to investigate other potential aspects of cyclins and CDKs that can be harnessed to develop therapeutics. We have chosen to discuss two other methods of potentially interrupting the cell cycle to create an anti-cancer drug: Cyclin-groove inhibitors and the

Table 1 Cyclin dependent kinases-inhibitors that have entered clinical trials

Drug name	Cyclin/CDK targeted	Manufacturer	Potential implications
Flavopiridol	Cyclin D and CDK-4/6 Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin A and CDK-1	Sanofi-Aventis, Bridgewater, NJ, United States	Renal cancer, Prostate cancer, colon cancer, non-Hodgkin's Lymphoma ^[23]
PD-00332991	Cyclin D and CDK-4/6	Pfizer, New York, NY, United States	Breast cancer ^[25] Gastrointestinal tumors ^[26]
P276-00	Cyclin D and CDK-4/6 Cyclin E and CDK-2 Cyclin A and CDK-2	Piramal Life Sciences Limited, Mumbai, India	Mantle Cell Lymphoma ^[27]
PHA-848125	Cyclin D and CDK-4/6 Cyclin E and CDK-2 Cyclin A and CDK-2	Nerviano Medical Sciences, Nerviano, Italy	Metastatic solid tumors ^[27,28]
LY2835219	Cyclin D and CDK-4/6	Eli Lilly, Indianapolis, IN, United States	Lung cancers ^[29]
LEE011	Cyclin D and CDK-4/6	Novartis, Basel, Switzerland	Gastrointestinal cancers ^[30] Breast Cancer ^[31]
AZD5438	Cyclin D and CDK-4/6 Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin A and CDK-1	Astra Zeneca, London, England	Solid malignancies ^[32]
BAY 1000394	Cyclin D and CDK-4/6 Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin B and CDK-1	Bayer, Barmen, Germany	Small cell lung cancer ^[33]
P1446A-05	Cyclin D and CDK-4/6	Piramal Life Sciences Limited, Mumbai, India	Advanced malignancies ^[34]
SNS-032	Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin B and CDK-1	Sunesis Pharmaceutical, South San Francisco, CA, United States	Multiple myeloma, chronic lymphocytic leukemia ^[35]
Bryostatins-1	Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin B and CDK-1	Ellisville, MO, United States	Metastatic renal cell carcinoma, soft tissue sarcoma ^[36]
Roscovitine	Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin B and CDK-1	Cyclacel Pharmaceuticals, Short Hills, NJ, United States	Advanced malignancies ^[37]
Dinaciclib	Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin B and CDK-1	Merck, Whitehouse Station, NJ, United States	Breast Cancer ^[38]
UCN-01	Cyclin E and CDK-2 Cyclin A and CDK-2 Cyclin B and CDK-1	Sigma-Aldrich, St. Louis, MO, United States	Breast Cancer ^[39]

CDK: Cyclin dependent kinase.

disruption of the cyclin-CDK interaction through peptides.

The cyclin binding groove is utilized in substrate recruitment. Theoretically, being able to place a cyclin groove inhibitor (CGI) peptide in this pocket would prevent cyclin from binding to CDKs^[53]. The CGI peptide could potentially be used as an anti-cancer drug that acts by stopping the characteristic uncontrolled proliferation seen in cancer. Preclinical studies using cell permeable CGI peptides have been done in cellular models and *in vivo* using a mouse tumor model. These studies have shown promising results of blocking CDK activity^[54]. The process of identifying and understanding the intricate protein structure and binding has been a hurdle in discovery of a CGI peptide suitable for clinical trial^[55]. However, this is an avenue of research that should be investigated further and actively pursued.

An essential and critical step required for CDK control over the cell cycle is the disruption of the cyclin-CDK interaction. Studies have identified a peptide termed NBI1 that acts as a non-competitive inhibitor

with certain cyclins^[56]. Other preclinical studies in cell models have garnered more information about this novel peptide^[57]. Further studies must be done in order to fully understand the capabilities of this peptide and see if there is a potential for clinical application. There are still many aspects of cyclin-CDK interactions that are not fully understood, so there may be other ways besides the use of CDK-inhibitors to disrupt uncontrolled cellular proliferation.

CONCLUSION

The discovery of cyclins and their enzyme effectors, the cyclin dependent kinases, has been monumental to deepening the understanding of the intricate and complex regulatory mechanisms of cell cycle. The mission to develop CDK inhibitors as a potent anti-cancer drug has been excellent in theory but limited in clinical results. Combination therapies with CDK-inhibitors and other cancer drug types have yielded better results but continued work must be done to increase the specificity and effectiveness of these

treatments. Further work must be done in both preclinical studies and clinical studies to identify and understand the complex molecular mechanisms that regulate the cell cycle.

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