Chemical Cyclin-Dependent Kinase Inhibitors

Therapeutic Implications

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1. INTRODUCTION

As reviewed in other chapters of this book, the regulation of the eukaryotic cell cycle machinery is closely controlled by proteins whose levels of expression vary (cyclins) and that serve as activators of a unique family of protein kinases, by catalytic subunits (cyclin-dependent kinases [CDKs]), by endogenous CDK inhibitors (CKI), and by posttranslational modifications of these complexes (1–3). An abnormality in any component of this machinery could lead to deregulation in proper cell cycle progression, abnormal cell proliferation, and ultimately disease (3).

Several disease entities are known to be associated with aberrations in cell cycle regulation. Theoretically, the use of cyclin-dependent kinase modulators in these diseases could potentially have a therapeutic role. Examples of non-neoplastic diseases entities that fit this description include angiogenic processes, such as diabetic retinopathy and coronary atherosclerosis/restenosis after coronary angioplasty (4,5), and neurodegenerative diseases such as Alzheimer’s disease, where brain tissues recovered from afflicted patients demonstrate abnormality in expression of cell cycle-related proteins (6,7). Moreover, in in vitro models, the use of inhibitors of CDKs was able to prevent neuronal cell apoptosis secondary to growth factor deprivation (8). Abnormal cellular proliferation and expression of cyclins or CDKs have also been observed in experimental models of glomerulopathies and renal tubule regeneration (9,10). Again, inhibitors of CDK1 and CDK2 prevented the development of experimental proliferative glomerulonephritis (11), substantiating a potentially therapeutic role for CDKs in these diseases. Other disease entities in which aberrant cell proliferation and abnormal expression of cell cycle-related proteins are observed are inflammatory disorders, psoriasis, degenerative muscle disorders, and pulmonary fibrosis, among others (12–15).

Neoplastic diseases represent the most readily recognized and numerically significant category of disorders with alteration on cell-cycle control (3,16–18). It has been known for decades that neoplastic cells have intrinsic derangements in the progression of the normal cell cycle (16,19). In contrast to normal cells, tumor cells are unable to stop

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at predetermined points of the cell cycle, so-called checkpoints. These delays or pauses in the cell cycle are necessary to verify the integrity of the genome before cells advance to the next phase (20,21). With the discovery of the function of oncogenes and tumor suppressor genes, it was evident that tumor cells frequently acquire either mutations or deletions in those genes important to tumorigenesis. Some of these regulatory genes are necessary to regulate these checkpoints. Specifically, most, if not all, tumor types have an abnormality in some component of the retinoblastoma gene product (Rb) pathway, including CDK4 or CDK6, cyclin D1, D2, D3, and Rb (3,22). As a consequence of these cell cycle alterations, tumor cells are able to transverse the S phase of the cell cycle, in a way that ignores growth factor signals, because of a lack of G1 checkpoints (3). Certainly, specific inhibitors of the Rb pathway, including CDK4 or CDK6, could prevent cells from entering S phase, inducing cell cycle arrest with consequent beneficial antiproliferative effect (23,24). In cells that have bypassed the necessity for these G1 kinases (25), the development of CDK2 inhibitors could alternatively act efficiently to prevent S phase progression (26,27). Another strategy to develop antiproliferative drugs with altered potential CDK regulation as targets would be to abrogate the remaining intact cell cycle checkpoints with small molecules (28). Thus, the abrogation of intact checkpoints could induce the inappropriate acceleration of certain phases of the cell cycle, including premature mitosis, in the case of G2 checkpoint abrogation, with consequent apoptosis. The last strategy is of particular interest in sensitizing cells to agents that would normally cause pause or arrest in G2. In either case, modulators of the cyclin-dependent kinases are unique novel targets for cancer chemotherapy.

We can classify the available chemical CDK inhibitors into two groups. The first are the classic direct chemical inhibitors that directly interact with the CDK holoenzyme. Examples include flavopiridol congeners, polysulfates, butyrolactone I, 9-hydroxyellipticine, toyocamycin derivatives, and purine derivatives. This chapter focuses on this group. The second group is composed of agents that indirectly downregulate the activity of the CDKs by interacting with upstream pathways necessary for CDK activation or interaction with proteins/cofactors necessary for the catalytic activity of these enzymes. There is a long list of agents with these properties, including vitamin D3 and its analogs, rapamycin and lovastatin, among others (29–31). Moreover, we could include in this latter group the endogenous CDK inhibitors (CKIs) such as p21, p16, and p27 that interact with components of the CDK complex resulting in CDK inhibition (17). Intense efforts are being undertaken to introduce these CKIs into tumor tissues to induce local cell cycle arrest and apoptosis (32). The results of these efforts are still too premature to draw any conclusions.

2. BIOCHEMICAL PROPERTIES OF CDK INHIBITORS

Chemical (small molecule) CDK inhibitors (CDKI) can be subdivided into seven families (Fig. 1): (1) purine derivatives (isopentenyladenine, 6-dimethyl aminopurine, olomucine, roscovitine, and CVT-313), (2) butyrolactone I, (3) flavopiridols (flavopiridol and deschloroflavopiridol), (4) staurosporines (staurosporine and UCN-01), (5) toyocamycin, (6) 9-hydroxyellipticine, and (7) polysulfates (suramin). Not all CDKI are specific to CDKs; staurosporine, UCN-01, suramin, 6-dimethylaminopurine, and