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Editorial

Targeting Abnormal Cell Cycle in Cancer: A Preface to the Special Issue

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The accelerated cell cycle progression is one of the hallmarks of human cancer [1]. Chemotherapeutic drugs typically screw up nucleotide metabolism, DNA replication or mitotic machinery that assure rapid and accurate tumor cell division. Many molecular targeted drugs have been designed to inhibit oncogenic kinases upstream of D-type cyclins. However, therapeutic approaches aiming to directly suppress cell cycle motor functions have for long time been hampered by insufficient efficacy exhibited by inhibition or genetic deletion of individual cyclin-dependent kinase (CDK). Moreover, simultaneous deletion of several key CDKs did not present lethality [2]. The emergence of compounds that can dually inhibit CDK4 and CDK6 activity started to draw attention to this category of drugs from researchers and clinicians. Currently, palbociclib, abemaciclib and ribociclib have an indication in advanced breast cancers with recommendation of combination with endocrine therapy. The current recipes succeeded in extending the progression-free survival of patients [3]. Later, one of the mechanisms, whereby breast cancer cells resist CDK4/6 inhibitors, appeared to include activation of cyclin E-CDK2 complex [4]. Inhibition of CDK4/6 results in prevention of RB1 mono-phosphorylation, allowing the persistent presentation of unphosphorylated RB1, which subsequently causes cellular senescence, cell death and increased immunogenicity [4]. However, leaked-out mono-phosphorylated RB1 are quickly hyper-phosphorylated first by cyclin E-CDK2 complex and subsequently by other cyclin-CDK complexes when cells cross the restriction point. Therefore, simultaneous inhibition of cyclin E-CDK2 activity may help us prevent therapy resistance. Recently, the development of a compound that simultaneously inhibits CDK2, CDK4 and CDK6 has been reported [5]. This compound, named PF-06803600, was generated by altering chemical modifications on the backbone of palbociclib (PD-0332991) and designed so as not to inhibit CDK1 activity, as genetic deletion of this kinase gene has been proven to be toxic to mouse [5]. Thus, to date, PF-06803600 could be a drug that provides the most ideal target specificity. Inhibitors to CDKs that do not phosphorylate RB1 also attract attention. These include CDK9 which promotes cell cycle by enhancing RNA polymerase II-directed transcription as a component of TAK/P-TEFb complex [2]. FoxM1 is one of critical substrates of CDK4/6, thus inhibitors to this molecule may yield clinical benefits even against RB1 mutated or deleted cancers [6]. Besides inhibitors to cyclin-CDK axis, inhibitors to molecules involved in spindle assembly checkpoints such as Aurora A, B or WEE1 have long been debated regarding their superiority over conventional chemotherapeutic agents [7]. This Special Issue will aim to provide readers with new insights on the possible therapeutic approaches to treat cancers by targeting abnormally controlled cell cycle progression in them. We welcome the submission of original research papers or review articles on such aspects.

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