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Editorial

Synthetic Inhibitors of CDK4/6 Activities and Tumor Suppression: A Preface to the Special Issue

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The status of RB1 in cancer may help us determine the optimal therapeutic approach to patients. In cancers harboring deletions or mutations in the RB1 gene allele (RB1-negative cancers), many molecules, including CHK1, PLK, Aurora-A and B, SKP2, Ras and IL6, CCL2-CCR2 axis and associating genetic deletion of *SUCLA2* gene, have been proposed to be the therapeutic targets [1–4], whereas, for cancers retaining the intact *RB1* gene (RB1-positive cancers), synthetic inhibitors of CDK4/6 are theoretically applicable. Synthetic CDK4/6 inhibitors exert their anti-tumor effects by keeping RB1 in an unphosphorylated state for an extended time, causing not only cell cycle arrest in the G1 phase but also cellular senescence, apoptosis and enhanced immunogenicity [5]. Currently, palbociclib, abemaciclib and ribociclib have an indication in advanced breast cancers in combination with endocrine therapy, which was shown to double the disease-free survival of patients [6]. In addition to breast cancer, synthetic CDK4/6 inhibitors are in clinical trials for many other solid tumors. However, single administration of a synthetic CDK4/6 inhibitor often ended in sub-optimal results [7]. As in the case of breast cancer therapy, we are now in need of developing combination therapy using a CDK4/6 inhibitor together with a compound that would enhance the efficacy of this agent. To this aim, we further need to investigate the intrinsic or acquired resistant mechanisms to CDK4/6 inhibitors in various RB1-positive cancers, as has been investigated in breast cancers. The mechanism whereby breast cancer cells resist CDK4/6 inhibitors to date has been proposed to include loss of RB1, estrogen receptor (ER) or progression receptor (PR); overexpression of $p16^{INK4A}$, CDKs, cyclin E, E2Fs, WEE1 or MDM2; activation of FGFR, PI3K/AKT/mTOR, interferon (IFN) or IL6-STAT3 pathway; activating mutation in PI3KCA or loss-of-function mutation in FAT1; and epithelial-mesenchymal transition (EMT) [8]. More information from basic, translational and clinical studies may promote trials of CDK4/6 inhibitors in a wider variety of cancers.

This Special Issue will provide readers with new insights on possible intrinsic and acquired mechanisms whereby cancer cells become resistant to synthetic CDK4/6 inhibitors, and also valuable information on novel mechanisms whereby synthetic CDK4/6 inhibitors may exhibit their efficacy. We welcome the submission of original research papers or review articles on various aspects of synthetic CDK4/6 inhibitors and their roles in tumor suppression.

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