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MEETING ABSTRACT

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CDK4 and CDK6 cooperate in counteracting the INK4 family of inhibitors during murine leukemogenesis

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Background: Cyclin-dependent kinase (CDK) 4 and 6 are key players mediating G_1 progression of the cell cycle. When bound to D-type cyclins they become active and phosphorylate their substrates, most importantly the retinoblastoma protein (Rb). High CDK6 levels are frequently observed in human malignancies and CDK4/6 inhibitors show promising efficacy against different types of tumors in clinical trials. INK4 proteins negatively regulate CDK4/6 activity and are frequently inactivated upon transformation.

Methods: We used knock-in mice that express a CDK6 (CDK6-R31C) or CDK4 (CDK4-R24C) mutant insensitive to INK4-mediated inhibition. Spontaneous tumor formation was analyzed over a period of two years and leukemic cell lines were generated by transducing freshly isolated bone marrow cells with BCR-ABLp185. These leukemic cell lines harboring different genotypes were compared in transplantation experiments using NSG mice, investigated biochemically and studied in microarray analysis.

Results: Mice harboring both mutant alleles (CDK6-R31C and CDK4-R24C) developed predominantly spontaneous hematopoietic and endocrine tumors and showed a drastic reduction in life span compared to the individual single mutants. Using BCR-ABL-transformed cells as model system we found that CDK6-R31C causes increased binding of p16INK4a to the remaining wild-type CDK4. In the presence of both INK4-insensitive kinases we observed accelerated disease onset that can be explained by hyper-phosphorylated Rb and significant alterations in the transcriptional profile.

Discussion: The importance of CDK4/6 for tumor formation is reflected by the emerging success of CDK inhibitors, such as palbociclib, which has been shown to significantly prolong progression-free survival of breast-cancer patients and hence has been designated as a breakthrough therapy of the year 2013 by the FDA. Our observations reveal that CDK4 and CDK6 cooperate in hematopoietic tumor development. In the presence of at least one functional INK4 protein, the concomitant overexpression of both CDK4 and CDK6 may be required to overcome the limited phosphorylation of Rb that is inflicted by increased binding of the inhibitor to the remaining wild-type CDK. Our study underlines the importance of simultaneous targeting of CDK4 and CDK6 in hematopoietic tumors in which INK4 proteins are inactivated.

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