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CDK4-INHIBITION INDUCES TUMOR REGRESSION OF BLADDER CANCER INDEPENDENTLY OF RB1 GENE STATUS

Carolina Rubio[1] , Mónica Martínez-Fernández[3] , Cristina Segovia[2] , Iris Lodewijk[1] , Ester Munera-Maravilla[2] , Cristian Suarez-Cabrera[1] , Alejandra Bernardini[3] , Marta Dueñas[2] , Daniel Castellano[1] , Jesus Paramio[2]

1) Biomedical Research Institute. Univ. Hosp. “12 de Octubre”, Ave. Córdoba s/n, E-28041 Madrid (Spain) 2) Molecular Oncology Unit, CIEMAT, Ave Complutense 40, E-28040 Madrid (Spain) 3) CIBERONC, Centro de Investigación Biomédica en Red de Cáncer (Spain)

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1 Biomedical Research Institute. Univ. Hosp. “12 de Octubre”, Ave. Córdoba s/n, E-28041 Madrid

2 Molecular Oncology Unit, CIEMAT, Ave Complutense 40, E-28040 Madrid (Spain)

3 CIBERONC, Centro de Investigación Biomédica en Red de Cáncer (Spain)

## Introduction

Bladder cancer (BC) is the most common malignancy of the urinary tract. At diagnoses, two major classes of BC are distinguished. Approximately 80% of patients present a non-muscle invasive disease (NMIBC), the rest of the patients shows muscle-invasive BC (MIBC). NMIBC is considered a relatively indolent tumor and is treated by transurethral resection. The current therapeutic options of MIBC include radical cystectomy and cisplatin-based chemotherapy. However, in a high proportion of the cases, the disease progresses showing metastatic spreading, accounting for extremely low survival rates. Another difficulty is the presence of other pathological conditions in an important fraction of MIBC patients, which precludes the use of conventional therapies. These so-called “unfit” patients have few or no therapeutic options.

The RB pathway is a predominant alteration observed in BC. The inactivation of *RB1* gene itself only accounts for a small percentage, being the rest of the alterations due to mutation or amplification of different genes whose products mediate the functional inactivation of the pRb protein. Therefore, inhibitors targeting these gene products are attractive therapeutic tools. Among them, CDK4/6 inhibitors are being tested for a large number of solid malignancies characterized by the presence of wt *RB1* alleles and/or cyclin D or *CDK4/6* amplification, and have been approved for treating hormone receptor-positive breast tumors in combination with compounds targeting ER-dependent signaling.

## Objectives

Prior consideration of palbociclib, a Cdk4/6 specific inhibitor in clinical use, as a therapeutic option in BC management, we performed a detailed preclinical study using *in vitro* and *in vivo* systems.

## Methods

A series of BC cell lines of known genomic characteristics and differences in their RB1 status were tested for their sensitivity to Palbociclib *in vitro* and in vivo using xenografts. Various overexpression and knock down experiments were performed to delineate the mechanism of palbociclib in BC cell. A metastatic BC mouse model based on the specific ablation of *Trp53, Pten, p107 and Rb1* tumor suppressor genes in urothelial cells was developed and used to test its *in vivo* activity.

Results

All cell lines tested *in vitro* and in xenograft *in vivo* were sensitive to CDK4/6 inhibition, independent of RB1 gene status. However, differences were found in biochemical and cell cycle effects among RB1 wild type and RB1 mutant BC cell lines. Integrated transcriptome analyses of *RB1* wild type and mutant BC cell lines revealed a major role for FoxM1 in this response. CDK4/6 inhibition resulted in reduced FOXM1 phosphorylation *in vitro* and *in vivo,* and showed synergy with CDDP (the chemotherapeutic agent most active in advanced BC patients) allowing a significant tumor regression. Using a transgenic mouse model of metastatic bladder cancer, we confirm the antitumoral and anti-metastatic roles of palbociclib when combined with reduced CDDP doses.

Conclusions

Our results present a novel therapeutic approach for the management of advanced BC patients, including cisplatin unfit patients, in which the use of CDK4/6 inhibitor may allow significantly reduced doses of cisplatin with the concomitant reduction in side off effects.

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