

TARGETING THE p73 PATHWAY FOR TREATMENT OF REFRACTORY BREAST CANCERS

Kai Hung Tiong¹, Heng Lungh Choo¹, Boon Shing Tan¹, Rozita Rosli², Soon-Keng Cheong³, Leif W. Ellisen⁴ and Chee-Onn Leong^{1,4}

¹ School of Pharmacy and Health Sciences, International Medical University, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

² Medical Genetics Laboratory, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.

³ Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Bandar Sungai Long, Selangor, Malaysia.

⁴ Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA 02114, USA

INTRODUCTION

We have recently identified a novel p53-independent cell death pathway involving the pro-apoptotic p53 family member, p73. We found that p73 is selectively upregulated in the basal-like (triple-negative) subtype of human breast cancers, but its activity is repressed in tumor cells through co-expression of the related p53 family member, p63. As a result, either inhibition of p63 or activation of p73 induced apoptosis selectively in this tumor subset. The specificity of the p63/p73 pathway implies that regulatory molecules identified might be attractive therapeutic targets for these tumors.

OBJECTIVE

This project seeks to identify novel regulatory mechanisms for the p63/p73 pathway present in refractory triple-negative breast tumors.

METHODS

To screen for p73 activation, we developed a luciferase-based reporter assay using the promoter for *PUMA*, a pro-apoptotic BCL-2 family member that is a direct transcriptional target of p73. The screening was conducted using the Dharmacon SMARTpool siRNA library targeting the whole human genome (219,956 genes) to identify novel p73 regulators and druggable targets that show therapeutic potential for the treatment of basal-like breast cancers.

RESULTS

A total of 57 positive regulators and 352 negative regulators were identified through the primary screen. Out of the 409 hits, 27 were kinases/phosphatases, 32 were G protein-

coupled receptor (GPCR), 155 drugable targets and 195 from the remaining genome. Further analysis using an isogenic cell line that has been depleted for p73 identified 234 of these hits are direct regulator of p73. Extensive study of candidate genes identified through this screen is currently being carried out.

CONCLUSION

Using a genome-wide RNAi screening approach, we have identified several target genes that play a critical role in the regulation of p73-dependent apoptosis in a tumor-specific manner. As such, these molecules may prove to be attractive therapeutic targets for this refractory breast cancer subtype.