

Gene Expression Signature-Based Chemical Genomic to Identify Potential Therapeutic Compounds for Colorectal Cancer

Authors : Yen-Hao Su, Wan-Chun Tang, Ya-Wen Cheng, Peik Sia, Chi-Chen Huang, Yi-Chao Lee, Hsin-Yi Jiang, Ming-Heng Wu, I-Lu Lai, Jun-Wei Lee, Kuen-Haur Lee

Abstract : There is a wide range of drugs and combinations under investigation and/or approved over the last decade to treat colorectal cancer (CRC), but the 5-year survival rate remains poor at stages II-IV. Therefore, new, more efficient drugs still need to be developed that will hopefully be included in first-line therapy or overcome resistance when it appears, as part of second- or third-line treatments in the near future. In this study, we revealed that heat shock protein 90 (Hsp90) inhibitors have high therapeutic potential in CRC according to combinative analysis of NCBI's Gene Expression Omnibus (GEO) repository and chemical genomic database of Connectivity Map (CMap). We found that second generation Hsp90 inhibitor, NVP-AUY922, significantly down regulated the activities of a broad spectrum of kinases involved in regulating cell growth arrest and death of NVP-AUY922-sensitive CRC cells. To overcome NVP-AUY922-induced upregulation of survivin expression which causes drug insensitivity, we found that combining berberine (BBR), a herbal medicine with potency in inhibiting survivin expression, with NVP-AUY922 resulted in synergistic antiproliferative effects for NVP-AUY922-sensitive and -insensitive CRC cells. Furthermore, we demonstrated that treatment of NVP-AUY922-insensitive CRC cells with the combination of NVP-AUY922 and BBR caused cell growth arrest through inhibiting CDK4 expression and induction of microRNA-296-5p (miR-296-5p)-mediated suppression of Pin1- β -catenin-cyclin D1 signaling pathway. Finally, we found that the expression level of Hsp90 in tumor tissues of CRC was positively correlated with CDK4 and Pin1 expression levels. Taken together, these results indicate that combination of NVP-AUY922 and BBR therapy can inhibit multiple oncogenic signaling pathways of CRC.

Keywords : berberine, colorectal cancer, connectivity map, heat shock protein 90 inhibitor

Conference Title : ICBPS 2016 : International Conference on Biomedicine and Pharmaceutical Sciences

Conference Location : Tokyo, Japan

Conference Dates : May 26-27, 2016