Tankyrase inhibition blocks Wnt/β-catenin pathway and reverts resistance to PI3K and AKT inhibitors in the treatment of colorectal cancer

O. Arqués[1], I. Chicote[1], I. Puig[1], S. Tenbaum[1], G. Argilés[2], R. Dienstmann[2,3], N. Fernández[2], G. Caratù[4], J. Matito[4], D. Silberschmidt[4], J. Rodon[5], S. Landolfi[6], A. Prat[7], E. Espín[8], R. Charco[9], P. Nuciforo[10], A. Vivancos[4], W. Shao[11], J. Tabernero[2], H. Palmer[1*]

[1]Vall d'Hebron Institut d´Oncologia (VHIO). Stem Cells and Cancer Laboratory. Barcelona, Spain. [2]Gastrointestinal and Endocrine Tumors Group, Vall d'Hebron Institute of Oncology (VHIO). [3]Sage Bionetworks (non-profit research organization), Fred Hutchinson Cancer Research Centre. Seattle, WA, USA. [4]Vall d'Hebron Institut d´Oncologia (VHIO). Genomics Cancer Group. Barcelona, Spain. [5]Early Clinical Drug Development Group, Vall d'Hebron Institute of Oncology (VHIO). Barcelona, Spain. [6]Department of Pathology, Hospital Universitari Vall d'Hebron. Barcelona, Spain. [7]Vall d'Hebron Institut d´Oncologia (VHIO). Translational Genomics Group. Barcelona, Spain. [8]General Surgery Service, Hospital Universitari Vall d'Hebron, Barcelona, Spain. [9]Department of HBP Surgery and Transplantation, Vall d'Hebron University Hospital. Barcelona, Spain. [10]Vall d'Hebron Institut d´Oncologia (VHIO). Molecular Oncology Group. Barcelona, Spain. [11]Novartis Institutes for Biomedical Research, Inc. Cambridge, MA, USA.

Presenting author: oarques@vhio.net

*Corresponding author: hgpalmer@vhio.net

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Abstract

Purpose

Oncogenic mutations in the KRAS/PI3K/AKT pathway are one of the most frequent alterations in cancer. Although PI3K or AKT inhibitors show promising results in clinical trials, drug-resistance frequently emerges. We previously revealed Wnt/β-catenin signaling hyper-activation as responsible for such resistance in colorectal cancer (CRC). Here we investigate Wnt-mediated resistance in patients treated with PI3K or AKT inhibitors in clinical trials and evaluate the efficacy of a new Wnt/tankyrase inhibitor, NVP-TNKS656, to overcome such resistance.

Experimental design

CRC patient-derived sphere cultures and mouse tumor xenografts were treated with NVP-TNKS656, in combination with PI3K or AKT inhibitors.

We analyzed progression-free survival of patients treated with different PI3K/AKT/mTOR inhibitors in correlation with Wnt/β-catenin pathway activation, oncogenic mutations, clinico-pathological traits and gene expression patterns in 40 CRC baseline tumors.

Results

Combination with NVP-TNKS656 promoted apoptosis in PI3K or AKT inhibitor-resistant cells with high nuclear β-catenin content. High FOXO3a activity conferred sensitivity to NVP-TNKS656 treatment. 13 out of 40 patients presented high nuclear β-catenin content and progressed earlier upon PI3K/AKT/mTOR inhibition. Nuclear β-catenin levels predicted drug-response whereas clinico-pathological traits, gene expression profiles or frequent mutations (KRAS, TP53 or PIK3CA) did not.

Conclusions

High nuclear β-catenin content independently predicts resistance to PI3K and AKT inhibitors. Combined treatment with a Wnt/tankyrase inhibitor reduces nuclear β-catenin, reverts such resistance and represses tumor growth. FOXO3a content and activity predicts response to Wnt/β-catenin inhibition and together with β-catenin may be predictive biomarkers of drug-response providing a rational to stratify CRC patients to be treated with PI3K/AKT/mTOR and Wnt/β-catenin inhbitors.