SR141716 exerts antitumor effect in colorectal cancer through WNT/β-Catenin-mediated pathway

M.C. Proto[1], D. Fiore[1], A.C. Pagano Zottola[1], S. Pisanti[2], E. Ciaglia[2], P. Picardi[1], A.M. Malfitano[2], C. Laezza[3], M. Bifulco[2], P. Gazzerro[1]

[1]Dept. of Pharmacy, University of Salerno, Fisciano (SA), Italy
[2]Dept. of Medicine and Surgery, University of Salerno, Baronissi (SA), Italy
[3]Institute of Endocrinology and Experimental Oncology, IEOS CNR, Naples, Italy

Colorectal cancer (CRC) arises through a multistep process involving a series of pathological alteration. Increasing evidence showed that the endocannabinoids control tumor growth and progression, both *in vitro* and *in vivo*, acting as antiproliferative, antiangiogenetic and antimetastatic compounds.
In a high percentage (≥ 85%) of both sporadic and familial adenomatous polyposis forms of CRC, the inactivation of the APC tumor suppressor gene initiates tumor formation and modulate the WNT/ β-catenin transduction pathways involved in the control of cell proliferation, adhesion and metastasis.
In this study we evaluated the potential direct effect of SR141716, a Cannabinoid Receptor 1 (CB1) antagonist/reverse agonist, on the WNT/β-catenin pathway in HCT116, a human CRC cell line.
In this model, SR141716 reduced the expression of WNT3, with inhibition of WNT/ β-catenin canonical pathway, and increased both β-catenin phosphorylation and APC protein levels. Moreover, SR141716 significantly reduced luciferase expression controlled by a TCF/LEF responsive element.
On the other hand, SR141716 was able to induce the activation of WNT/β-catenin non canonical pathway, through WNT5 induction and CaMKII activation.
Aimed to confirm the inactivation of WNT/β-catenin canonical pathway, we analyzed its target genes and we observed a significantly reduction of Cyclin D1, c-Myc, COX2 and SNAIL expression after treatment with SR141716.
Obtained data strongly suggested a direct effect of SR141716 in the regulation of both canonical and non-canonical β-catenin signaling in human CRC cellular model.