Role of WNT/β-Catenin Pathway in Endocannabinoid-Mediated Antitumoral Effects in Human CRC

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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 (FAP) forms of CRC, the inactivation of the APC tumor suppressor gene initiates tumor formation. APC negatively regulates the levels of β-catenin, a multifunctional protein that transduces Wnt signals, mediates cell-cell adherents junctions, and stimulates cell proliferation.

Moreover, WNT5A is frequently silenced in human CRC cell lines and in primary tumors due to its promoter methylation.

In this study we tested the hypothesis of a potential direct effect of cannabinoids on the WNT/β-catenin pathway in CRC.

We found that Met-F-AEA and SR141716 were able to modulate the expression of WNT5 protein in both DLD1 and SW620 cell lines through a cycling modulation of WNT5 expression.

Moreover, in both DLD1 and SW620 cell lines, transfected with a reporter construct containing the TRE for TCF/Lef, the treatment with Met-F-AEA or SR141716 increased the luciferase activity expressed under the control of TCF/LEF.

Finally, the cannabinoids significantly increased the luciferase activity controlled by the TRE for both Serum Response Element (SRE) and AP1.

In conclusion, our preliminary results support the hypothesis that cannabinoids could modulate the activation of the WNT signaling pathway mainly through a non canonical mechanism WNT5-mediated.

Acknowledgements: MCP was supported by a fellowship from FIRC (Italian Foundation for Cancer Research).