

Cannabigerol binds TGF- β I receptor activating autophagic pathway.

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The plant *Cannabis sativa* produces over 421 chemical molecules, including about 80 terpeno-phenolic compounds named phytocannabinoids. Phytocannabinoids include psychotropic and many other non-psychotropic compounds of therapeutic interest, such as cannabigerol (CBG). Cannabigerol binds with high affinity α 2-adrenergic agonist receptors and with low affinity CB1 and CB2 receptors. Recently it has been shown that CBG and its derivatives have anti-inflammatory, neuroprotective properties and acts like antioxidant agents in cells such as macrophages (David W. Pate et al., 1994, Christelle M. Andre et al., 2016). Several research has shown that CBG inhibits cell proliferation in a panel of tumor cells.

Previous studies conducted in our laboratory on murine cell lines (NIH 3T3 wt and NIH 3T3 K-Ras) shown that cell proliferation rate decreases after CBG treatment. Furthermore cells detached and suspended in the medium, deriving from 72-hours of treatment with different CBG concentrations, are able to re-adhere to plates and growth in absence of this cannabinoid. This behavior is also observed in different human cancer cell lines (UM-UC-3, 5637, MDA-MB 231).

The aim of this study was to define the molecular mechanisms of action of CBG by clarifying how it acts on tumor cell lines and which pathways it regulates. In particular, we used the triple negative MDA-MB-231 breast cancer cell line.

In order to define at which concentrations CBG is able to inhibit proliferation, growth kinetic was conducted. These experiments showed that CBG has effects at low concentrations (5 μ M) in serum deprivation medium (0,5 % FBS), whereas in complete medium (10 % FBS) the effect is observed at higher concentrations (20 μ M); so the serum influences the action of cannabigerol.

It is well known that when cells stop to grow they can activate the apoptotic or autophagic pathways. In order to evaluate if one of these two pathways is active, Western Blot analyses were performed. Data shown that treatment with CBG induces autophagy.

Autophagy represents a normal response of cancer cells to stress. In particular, it is known that transforming growth factor- β (TGF- β) induces activation of autophagy by binding to TGF- β receptors (T β RI and T β RII) in breast and liver cancer. This process is involved in tumor and metastasis progression (Kunihiko Kyono et al., 2009). We evaluate if CBG is able to activate autophagy due to interaction with TGF- β receptors in this regard. Therefore, we have pre-treated MDA-MB-231 cells with two different inhibitors of T β RI. Results suggest the hypothesis that CBG could bind the T β RI. Furthermore docking experiments show the presence of two hydrophobic pockets on the T β RI, one of which appears to be responsible for CBG binding. All these data will give new insight in CBG action.

