

Editorial: the canonical and non- canonical endocannabinoid system as a target in ...

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Editorial on the Research Topic

The Canonical and Non-Canonical Endocannabinoid System as a Target in Cancer and Acute and Chronic Pain

The endocannabinoid system (ECS) comprises the canonical receptor subtypes CB1R and CB2R and endocannabinoids (anandamide, AEA and 2-arachidonoylglycerol, 2-AG), and a “ non-canonical” extended signaling network consisting of: (i) other fatty acid derivatives; (ii) the defined “ ionotropic cannabinoid receptors” (TRP channels); other GPCRs (GPR55, PPAR α); (iii) enzymes involved in the biosynthesis and degradation of endocannabinoids (FAAH and MAGL); and (iv) protein transporters (FABP family) ([Pisanti et al., 2013](#) ; [Iannotti et al., 2016](#)). The ECS is currently a hot topic due to its involvement in cancer and pain.

High CB1R expression correlates with poor prognosis in different type of cancers including prostate, pancreatic, colorectal, and ovarian cancer ([Michalski et al., 2008](#) ; [Cipriano et al., 2013](#) ; [Jung et al., 2013](#) ; [Messalli et al., 2014](#)); while high CB2R expression correlated to poor prognosis in HER2-positive breast cancer ([Blasco-Benito et al., 2019](#)). Endocannabinoids such as AEA and 2-AG were found upregulated in different tumors (colorectal carcinomas) compared to healthy subjects ([Pyszniak et al., 2016](#)). Despite these changes there have been variable mechanisms suggested for these endocannabinoids in terms of their antitumorigenic activity. The antiproliferative effect induced by AEA in prostate and breast cancers has been reported to be due to CB1R activation ([Grimaldi and Capasso, 2011](#)); while the apoptosis induced by R(+)-methanandamide in lymphoma cells is reported to be due to the activation of both CB1R and CB2R ([Gustafsson et al., 2016](#)).

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[al., 2008](#)). While its anticancer effect in cervical and lung tumors may be from other pathways ([Eichele et al., 2009](#)). The antiproliferative effect of 2-AG appears dependent on pathways involving CB1R-mediated p42/44 MAPK and AKT signaling. Recent studies have demonstrated a link between TRPV2 and CBD-induced autophagy in glioblastoma cells and CB2R-GRP55 heteromers as a cause of cancer cell proliferation have been found ([Moreno et al., 2014](#) ; [Nabissi et al., 2015](#)).

For pain, the ECS plays a role at different points in the nociception axis. AEA and 2-AG elicit long-term depression of both excitatory and inhibitory synapses increasing neural circuit output. Endocannabinoid/TRPV signaling induces the sensitization of the shortening reflex while CB1 and CB2 receptors are targeted in the treatment of pain.

The current Research Topic highlights various ways the ECS can impact cancer and pain.

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