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Cannabinoid Cancer Biology and Prevention

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Abstract

Abstract Plant-based, synthetic, and endogenous cannabinoids have been shown to control a diverse array of biological processes, including regulation of cell fate across cancers. Their promise as broad-based antitumor agents in preclinical models has led to the initiation of pilot clinical trials. Session 5 of the National Cancer Institute's Cannabis, Cannabinoids and Cancer Research Symposium provides an overview of this research topic. Overall, the presentations highlight cannabinoid signal transduction and specific molecular mechanisms underlying cannabinoid antitumor activity. They also demonstrate the broad-based antitumor activity of the plant-based, synthetic, and endogenous cannabinoid compounds. Importantly, evidence is presented demonstrating when cannabinoids may be contraindicated as a treatment for cancer, as in the case of human papilloma virus–meditated oropharynx cancer or potentially other p38 MAPK pathway–driven cancers. Finally, it is discussed that a key to advancing cannabinoids into the clinic is to conduct well-designed, large-scale clinical trials to determine whether cannabinoids are effective antitumor agents in cancer patients.

Cannabinoid Signaling and Biology

The endocannabinoid system consists of receptors, endogenous ligands, and synthetic and degradative enzymes (1). The CB_1 cannabinoid receptor was discovered (2) and subsequently cloned (3) on the basis of its responsiveness to (-)-Δ^9-tetrahydrocannabinol (THC). THC is the primary psychoactive constituent in cannabis, hence the name *cannabinoid* receptor. CB_1 is a member of the G-protein coupled receptor (GPCR) family. An arachidonic acid metabolite, N-arachidonylethanolamide, was shown to activate CB_1, and named *anandamide* from the Sanskrit word for "bliss" (4), and this was followed by the identification of a second metabolite 2-arachidonoylglycerol (2-AG) (5,6). A second cannabinoid receptor (CB_2) was isolated from differentiated myeloid cells. The CB_2 receptor shares 44% amino acid homology with CB_1 and a distinct yet similar binding profile, thus representing a receptor subtype.

The CB_1 and CB_2 receptors are GPCRs coupled to the Gi/o α proteins that inhibit adenylyl cyclase thereby reducing cellular cAMP levels (7). In addition to Gi/o-mediated signaling, CB_1 and CB_2 stimulate extracellular signal-regulated kinase 1 and 2.

A range of pharmacological and genetic tools have been developed and used to delineate cannabinoid receptor-mediated activity. Five structurally distinct classes of cannabinoid compounds have been identified: 1) the classical cannabinoids (eg, THC, Δ^8-THC-dimethylheptyl [HU-210]); 2) bicyclic cannabinoids (eg, CP-55 940), indole-derived cannabinoids (eg, WIN-55 212-2), eicosanoids (eg, the endogenous ligands anandamide, 2-AG), and antagonist and/or inverse agonists (eg, SR141716A for CB_1, SR145528 for CB_2) (8).

The CB_1 receptor is one of the most abundant GPCRs in the brain; it is highly expressed in the basal ganglia nuclei, hippocampus, cortex, and cerebellum (9). The distribution of this

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receptor within the central nervous system correlates with its role in the control of motor function, cognition and memory, and analgesia. CB_1 receptors are primarily localized to the terminals of central and peripheral neurons, where they mediate inhibition of neurotransmitter release. The CB_1 receptor is also expressed throughout the periphery, albeit at much lower levels than in the central nervous system (CNS).

The CB_2 receptor is abundantly expressed in peripheral organs with immune function, including macrophages, spleen, tonsils, thymus, and leukocytes as well as the lung and testes. CB_2 receptor expression has been reported in the CNS, although its presence in adult native brain tissue remains somewhat controversial (10).

The wide range of therapeutic potential for cannabinoids includes treatment of nausea due to chemotherapy, for which THC and nabilone are approved. In addition, Sativex (ie, nabiximols, a plant-derived THC: cannabidiol [CBD] formulation) is approved in several countries for the treatment of pain and spasticity in patients with multiple sclerosis. CB_1 antagonists were explored for obesity and weight loss but were withdrawn from the market because of CNS side effects. Recently, Epidiolex, a plant-derived CBD formulation, has received US Food and Drug Administration approval for the treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome, or tuberous sclerosis complex and intractable forms of childhood epilepsy.

CB_1 and CB_2 receptor knockout mice have been constructed in several laboratories. The persistence of biochemical, electrophysiological, and behavioral responses to cannabinoids in these knockout animals suggests the presence of additional cannabinoid receptor subtypes. One candidate receptor is the orphan receptor GPR55, which recognizes certain cannabinoid ligands (8). Whether GPR55 responds to the eCB ligands anandamide and 2-AG, phytocannabinoids, THC, and cannabidiol is cell-type and tissue dependent. In addition, lysophosphatidyl inositol is an endogenous ligand for GPR55, but lysophosphatidyl inositol has actions at sites other than GPR55 as well. Whereas several studies indicate that GPR55 activation is pro-carcinogenic, others report anticarcinogenic activity (11).

The class A orphan GPCR GPR18 was first cloned in 1997 (12). GPR18 shares low sequence homology with the CB_1 and CB_2 receptors (ie, approximately 13% and 8%, respectively) and moderate identity with the putative cannabinoid receptor GPR55 (ie, 21%). It was identified as a receptor for the anandamide metabolite *N*-arachidonylglycine in 2006 (13). Furthermore, a range of endogenous, phytogenic, and synthetic cannabinoids has been shown to modulate GPR18 (8).

In summary, cannabinoid receptors were first identified as GPCRs responsible for the effects of THC. Subsequently, an endogenous cannabinoid system (eCB system) consisting of lipid ligands and GPCRs has been elucidated. CB_1 and CB_2 are established cannabinoid receptors. GPR55 and GPR18 are candidate cannabinoid receptors.

Mechanism of THC Anti-Tumor Activity

The first report of the preclinical antitumor activity of THC dates to 1975. In that seminal *Journal of the National Cancer Institute*, Munson and colleagues (14) showed that the oral administration of THC and other phytocannabinoids to mice inhibits the growth of Lewis lung adenocarcinoma cells and increases the survival of the animals. Although these findings seemed promising, further investigations on this effect were essentially not performed until the late 1990s. Since then, a large body of evidence has accumulated supporting that different natural and synthetic cannabinoids exert antitumor effects in a wide variety of preclinical models of cancer, ranging from cancer cells in culture to genetically engineered mice (15). Many of those studies have focused essentially on using 1) THC as the main cannabinoid receptor agonist present in cannabis as well as some other pharmacodynamically related synthetic compounds (eg, the CB_1/CB_2-mixed agonists WIN-55 212-2 and HU-210 and the CB_2-selective agonist JWH-133), 2) mouse and rat as species for modeling cancer in the laboratory, and 3) malignant brain tumors (specifically, glioblastoma [World Health Organization grade IV astrocytoma]) as type of cancer. Thus, THC was initially found to induce apoptosis of glioblastoma cells in vitro (16,17) and inhibit the growth of glioblastoma cell-based xenografts in mice and rats in vivo (17,18) through the activation of CB_1 and CB_2 receptors located on the cancer cell surface. Currently, we know the mechanism of cannabinoid receptor-evoked antitumor activity in experimental glioblastoma models is very complex and involves an inhibition of not only cancer cell survival and proliferation, but also invasiveness, angiogenesis, and the stem cell-like properties of cancer cells, thereby exerting profound impact on the complex tumor microenvironment (15,19-21).

To date, the best-established antitumor effect of THC on glioblastoma cells is the induction of apoptosis. Thus, THC and other cannabinoids trigger the apoptotic death of glioblastoma cells by a CB_1 and CB_2 receptor-dependent stimulation of the biosynthesis of the pro-apoptotic sphingolipid ceramide (16,17). This event occurs in a specific cell organelle, the endoplasmic reticulum, and activates the so-called endoplasmic reticulum stress response (22), involving the sequential upregulation of the stress-regulated protein p8 and its downstream targets, the transcription factors ATF4 and CHOP, (23,24). Then, ATF4 and CHOP action converges in the expression of TRIB3, a pseudokinase that binds to and inhibits the key prosurvival protein kinase Akt. Consequently, the Akt substrate mammalian target of rapamycin complex 1 is inhibited, thereby leading to the stimulation of autophagy and, in turn, of a mitochondrial damage mediated pro-apoptotic response (24) (Figure 1). This process of glioblastoma cell death may be accompanied by other CB_1 and CB_2 receptor-evoked cell growth-inhibiting mechanisms such as the induction of oxidative stress and the blockade of the G1/S cell-cycle transition (19-21).

From a translational perspective, the use of combinational anticancer therapies has many theoretical advantages over single-agent strategies because they allow for the simultaneous targeting of tumor growth at various levels. Preclinical evidence supports that THC improves the therapeutic efficacy of conventional antineoplastic interventions in glioblastoma. Thus, the combined administration of THC with temozolomide, the benchmark chemotherapeutic drug for glioblastoma treatment (25), or with radiation therapy, the other standard first-line intervention in glioblastoma patients (26), acts synergistically to reduce tumor growth of glioblastoma cell-based xenografts in mice. Moreover, a desirable property of any antineoplastic therapy is its preferential targeting of malignant cells. In this regard, THC induces apoptosis of glioblastoma cells with no negative impact on the viability of normal, nonmalignant astroglial cells (27,28).

The major focus of anticancer-therapy design has progressively moved from nonspecific chemotherapies to “personalized” molecularly targeted drugs. In this context, as discussed above, engagement of an unambiguous molecular target (ie, CB_1 and CB_2

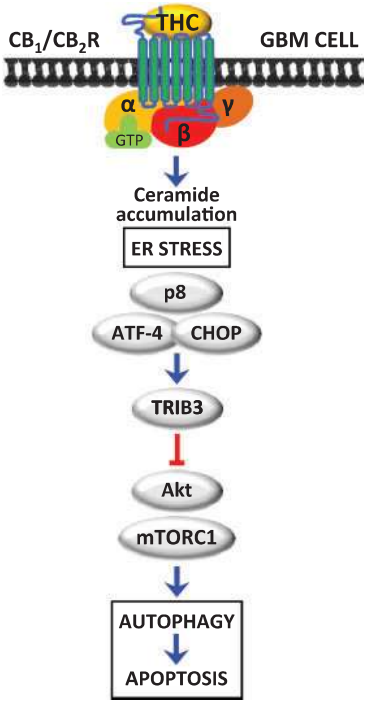

Figure 1. Scheme depicting the mechanism of Δ^9-tetrahydrocannabinol [THC]–induced apoptosis of glioblastoma cells. THC binds to cannabinoid CB_1 and CB_2 receptors on glioblastoma multiforme (GBM or glioblastoma) cells, thereby inducing ceramide accumulation and endoplasmic reticulum (ER) stress, which ultimately leads to the inhibition of the Akt-mTORC1 axis and the sequential activation of autophagy and apoptosis .

receptors) by a family of selective compounds (ie, THC and other cannabinoid receptor agonists) inhibits the growth of glioblastoma cells in animal (ie, mouse and rat) models through a well-established mode of antitumor action in a selective and safe manner (15,19,29) Moreover, THC sensitizes glioblastomas in mice to the standard of care (ie, chemoradiotherapy) currently used in patients with glioblastoma. All this accruing evidence may help optimize experimental THC-based therapies as well as the preliminary clinical testing currently underway (30,31). Undertaking the following issues may help address gaps in knowledge and set an agenda for future research: 1) increasing our understanding of the molecular mechanisms underlying THC antitumor activity; 2) identifying molecular biomarkers aimed to predict response to cannabinoid receptor agonist-based antineoplastic therapies; 3) designing the most appropriate cannabinoid-based combinational therapies in preclinical models of glioblastoma and other cancers; 4) defining the biological role of CB_1 and CB_2 receptors and other endocannabinoid system elements in tumor generation, growth, and progression; and 5) conducting controlled studies with THC and other cannabinoids as potential antitumor drugs in cancer patients.

Targeting Cancer with the Nonpsychoactive Cannabinoid CBD

Many people are familiar with the palliative effects of THC in patients undergoing cancer treatment (32), however, there is now ample preclinical evidence that shows direct inhibition of cancer progression by the cannabinoids THC and CBD (15,33). As opposed to THC, CBD does not interact efficiently with CB_1 and CB_2 receptors (34) and, as a result, CBD does not produce the psychoactive effects associated with THC.

Both THC and CBD have been shown to inhibit multiple processes involved in cancer progression (35) (eg, inhibition of cancer cell proliferation, invasion, metastasis, and angiogenesis). In addition, both cannabinoids induce apoptosis and inhibit cancer stem cell maintenance and self-renewal. THC and CBD have also been shown to enhance the activity of multiple first-line therapies across cancers.

In earlier work, CBD was shown to inhibit cancer cell proliferation in a rat glioma (36) and human glioblastoma cell lines (37). A pharmacological screen of plant-derived (eg, THC and CBD) and synthetic CB_1 and CB_2 agonists in human breast and glioblastoma cell lines found that CBD was the most potent cannabinoid tested at inhibiting cell proliferation (38). Currently, investigations across cancers show CBD targets many downstream genes involved in cancer, leading to inhibition of cancer cell proliferation, invasion, metastasis, and angiogenesis and induction of apoptosis as well as regulation of immune surveillance (35) (Table 1). Specific to each cancer, the impact of CBD treatment on these pathways leads in part to inhibition of cancer progression in multiple preclinical models of cancer.

As a specific example of CBD-dependent modulation of genes involved in cancer progression in breast and other cancers, CBD has been demonstrated to inhibit the expression of inhibitor of DNA-binding (ID) proteins (38). In breast cancer, ID1 is a master regulator of metastatic progression (50). Studies demonstrate that CBD-dependent downregulation of *ID1* gene expression is key to anti-invasive and antimetastatic activity of CBD (51); therefore, ID1 may represent a biomarker that predicts whether CBD may be effective at inhibiting tumor progression in a given cancer. In subsequent studies in breast, prostate, salivary gland, and head and neck cancers, CBD was found to be effective at inhibiting the expression of ID1 (52). Using inhibition of cell proliferation and ID1 as a marker of response to CBD, a series of structurally related analogs were tested for inhibitory activity in culture leading to the discovery of the more potent compound O-1663 (51). In a preclinical model of breast cancer, mice with advanced metastatic progression treated with O-1663 had a survival rate beyond that of those treated with CBD. This study demonstrates cannabinoid analogs more potent and efficacious than CBD can be developed to target cancer.

CBD does not interact efficiently with CB_1 and CB_2 receptors, and the initial site leading to antitumor activity across cancers is not defined. The search for a shared initial interaction site is complicated by the fact that when higher micromolar concentrations of CBD are used in cell culture models, as is the case in most investigations, CBD has been shown to act at multiple sites (Table 2). The most unifying downstream mechanism in culture is the initial CBD-dependent selective production of reactive oxygen species in tumor cells (33,42,43,47,56-58).

Recently, using microarray-based expression profiling, the full spectrum of genes regulated by CBD in breast cancer cells as well as in cancer cells from other origins was interrogated (52). The array analysis confirmed CBD downregulated ID proteins expression, specifically ID1 and ID3, and suggested a role for FOXM1, RAD51, AMPK, and TRIB3. Interestingly, the upregulation of AMPK, TRIB3, and corresponding autophagy-related pathways, is similar pathways targeted across cancers by the CB_1 and CB_2 receptor agonist THC (15). Studies in breast cancer models also showed that CBD-induced programmed cell death was the result of cross-talk between apoptosis and autophagy (42). This demonstrates that, although CBD and THC do not share the same initial interaction site(s), a portion of their

Table 1. Mechanisms involved in the antitumor activity of CBD

Mechanism	Reference
TRPV1	Bisogno et al. 2001 (39)
TIMP1	Ramer et al. 2010 (40)
PAI	Ramer et al. 2010 (41)
ID1	McAllister et al. 2007 (38)
PARP	Shrivastava et al. 2011 (42)
Caspases	Massi et al. 2006 (43)
ERK	Morelli et al. 2014 (44)
AKT/mTOR	Soroceanu et al. 2013 (45)
p21	Yang et al. 2020 (46)
PUMA	Petrocellis et al. 2013 (47)
CHOP	Petrocellis et al. 2013 (47)
PPARγ	Ramer et al. 2013 (48)
EGFR	Elbaz et al. 2015 (49)
NF-kB	Elbaz 2015 (49)
Autophagy	Shrivastava et al. 2011 (42)

Table 2. CBD interaction sites

Interaction Site	Reference
TRPV1	Bisogno et al. 2001 (39)
TRPV2	Morelli et al. 2014 (44)
TRPM8	Petrocellis et al. 2012 (47)
PPRγ	Ramer et al. 2013 (48)
5HT1A	Ward et al. 2014 (53)
VDAC1	Rimmerman et al. 2013 (54)
Na/Ca^{2+} exchange	Ryan et al. 2009 (55)

downstream targets implicated in their antitumor activity is shared.

Important gaps in knowledge that require future research include understanding the initial interaction site(s) for CBD and the specific events leading to alterations in protein expression of shared pathways (eg, ID1, FOXM1) modulated across cancers. Also, determining whether potential beneficial interactions exist between CBD and standard first-line therapies will be important as new therapies that enter the clinic are often combined with standard of care. Additionally, little is known about the modulation of microenvironment and immune response in the context of cancer treatment with CBD. Finally, there is a significant need for well-developed clinical trials across cancers, which may be further enhanced by including potential biomarkers of response if they become available.

Cannabinoids and HPV-Mediated Oropharynx Cancer: Genes and Weed

Oropharynx cancer is increasing in incidence in the United States, and 70% of cases are attributed to human papilloma virus (HPV)–mediated oropharynx squamous cell carcinoma (HPVOPC), affecting 20 000 people in 2016 and a projected 30 000 in 2029, with HPV16 accounting for 95% of HPVOPC (59-61). The HPV E6 and E7 oncoproteins coded within the viral genome are able to disrupt the function of respective tumor suppressor genes Rb and p53, and HPVOPC is associated with *PI3K* mutations and other alterations in EGFR, HER2, PI3K/Akt and MAPK (62). HPVOPC has a 20% mortality at 3 years despite primary surgery or radiation therapy with adjuvant cytotoxic chemotherapy for locoregional disease as well as first-line PD-1 inhibitor therapy for recurrent/metastatic disease (63).

HPVOPC is not associated with tobacco and ethanol use but with lifetime exposure to sexual behaviors (ie, number of lifetime vaginal and oral sex partners) and cannabis exposure (64,65). Daily cannabis use is associated with HPV oral infection and development of HPVOPC. The independent association of daily cannabis use with HPVOPC (ie, $\geq$15 joint years, adjusted odds ratio = 6.4, 95% confidence interval = 1.6 to 26) is adjusted for tobacco, alcohol, sexual exposure, and exposure to HPV (65). Cannabis use has undergone dramatic expansion in the United States throughout the past few decades with increased frequency of daily use, higher concentration products, and diverse routes of administration and forms containing psychoactive THC and CBD (66,67). Therefore, the interacting risk factors for HPVOPC, sexual exposure, and cannabis are simultaneously increasing in at-risk populations.

Cannabinoids are GPCR ligands that classically signal through CB_1, CB_2, and other GPCRs (68). Prior studies provide conflicting data regarding modulation of the endocannabinoid system for tumor inhibition. However, reports of tumor inhibition via CB_1 and CB_2 agonists often use cannabinoid concentrations in the 5-20 μM range, whereas peak plasma and blood concentrations of THC rarely exceed the 1 μM level in marijuana smokers (69-71). CB_2 activation promotes colon cancer progression (72), and CB_1 and CB_2 activations are linked to adverse outcomes in colorectal carcinoma (73,74), hepatocellular carcinoma (75), glioblastoma and lung carcinoma (76), esophageal cancer (77), prostate cancer (78), pancreatic cancer (79), ovarian cancer (80), breast cancer (81), and others (82) through a variety of immunologic and tumor intrinsic pathways. CB_1 and CB_2 receptors have been defined as primarily activating the oncogenic MAPK pathway initially (83). In fact, CB_1, CB_2, and other noncanonical cannabinoid receptors activate multiple networks in other tumors activated in HPVOPC, including the HER2, AKT/mTOR, and other pathways. *CNR1* and *CNR2* expression were both upregulated in HPV-positive head and neck squamous cell carcinomas (HNSCC) and HPV-negative HNSCC (ie, $P < .001$), and the expression of *CNR2* was higher in HPV-positive HNSCC compared with normal samples in a TCGA dataset (84). Small interfacing RNA–mediated *CNR1* knockdown in HPV-positive HNSCC cell lines UD-SCC-2, UM-SCC-47, and 93VU147T decrease proliferation and doxycycline inducible sh*CNR1*- and sh*CNR2*-stable UD-SCC-2 cell lines demonstrating decreased proliferation with induction of shCNR1 and shCNR2 (84). Selective CB_1 agonist ACEA, CB_2 agonist HU-308, and THC increase proliferation in a broad range of HPVOPC cells in dose ranges consistent with recreational cannabis exposure (85,86). Following knockdown of the expression of CB_1, the effect of the selective CB_1 agonist ACEA on HNSCC cell growth was attenuated, and knockdown of CB_2 expression reversed CB_2 agonist HU-308-induced growth in HNSCC cells (84). Meanwhile, selective CB_1 antagonist Rimonabant and CB_2 antagonist SR144528 inhibit proliferation in HPVOPC cell lines. Flow cytometric assessment of Annexin V expression shows that CB_1 or CB_2 agonists ACEA, HU-308, and THC inhibit apoptosis of serum-starved HPVOPC cells, and CB_1 or CB_2 antagonist Rimonabant and SR144528 induce apoptosis. Using a transwell migration assay, CB_1 or CB_2 agonists ACEA, HU-308, and THC increase cell migration ability in multiple cell lines, and migration was significantly reduced with CB_1 antagonist Rimonabant and CB_2 antagonist SR144528. Western blotting shows that ACEA, HU-308, and THC increase active,

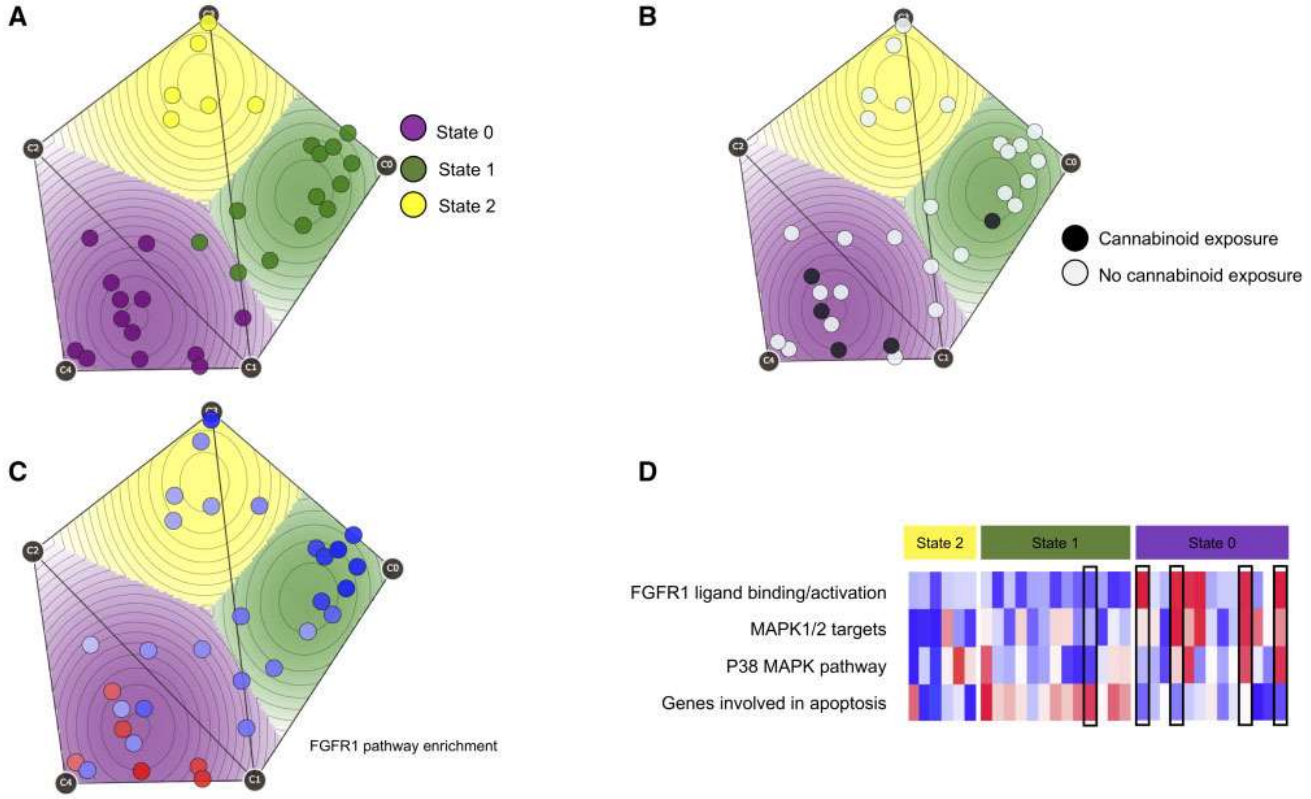

Figure 2. p38 MAPK activation in HPVOPC patients with cannabinoid exposure. **A)** Onco-GPS map showing clustering of cannabinoid exposed tumors in FGFR1 signaling state. B) Heat map demonstrating single-sample gene set enrichment analysis enrichment of 4 selected pathways. FGF signaling (high) and apoptosis (low) represent robust oncogenic characteristics of state 0 (purple) cannabis.

phosphorylated p38, p-p38, and MAPK downstream targets p-MAPKAPK2 and p-HSP27 with minimal to no change in the total p38, MAPKAPK2, and HSP27. Inactivation of p38 MAPK pathway using SB203580, a p38 MAPK-specific inhibitor, partially inhibited the proliferative effect of CB_1 and CB_2 agonists, indicating that CB_1- and CB_2-promoted proliferation in HPV HNSCC cells is only partially mediated by p38 MAPK activation, but other networks downstream of CB_1 and CB_2 other than p38 MAPK may also contribute to the growth effects of cannabinoid receptor activation. Similar data in murine xenografts demonstrate CB_1 and CB_2 promote proliferation of HPV-positive HNSCC cells using in vivo models and that cannabinoid receptor blockade inhibits tumor growth in vivo.

Serum samples of HPVOPC patients were assayed for cannabinoid metabolites, and 5 patients were noted to have cannabinoids (ie, THC and metabolites) present in pretreatment plasma samples (84). Single-sample gene set enrichment analysis using RNA sequencing data from primary tumors defined differential pathway activation. The P38 MAPK pathway was upregulated and apoptosis pathway was downregulated in cannabinoid patients, and FGFR1-associated pathways were upregulated. Tumors aggregate into 3 distinct oncogenic states, with almost all (ie, 4 out of 5) cannabinoid positive samples stratifying to the same state 0 group with higher enrichment of FGFR1 and MAPK signaling (ie, high) and apoptosis pathways (ie, low) (Figure 2) (87). These data show HPVOPC from patients with cannabinoid exposure demonstrates MAPK and FGFR1 pathway activation and apoptosis pathway inhibition.

In summary, HPVOPC and cannabis use are increasing, and epidemiologic data show daily cannabis use is associated with HPVOPC development, and THC upregulates MAPK networks that drive HPVOPC via CB_1 and CB_2 activation.

Conclusion

Cannabinoid receptors were first identified as GPCRs responsible for the effects of THC and led to the discovery of the endocannabinoid system comprised of receptors, endogenous ligands, and synthetic and degradative enzymes. THC produces a wide array of physiological effects, including control of cell fate, through interaction with the established CB_1 and CB_2 receptors and the endocannabinoid system. Additional candidate receptors such as GPR55 and GPR18 also exist. These sessions present multiple lines of preclinical evidence supporting that the cannabinoids THC and CBD act as broad-based antitumor agents controlling many aspects of cancer progression, including cell proliferation, apoptosis, invasion, metastasis, and immune surveillance. Importantly, evidence is provided that in certain MAPK-driven HPV-mediated oropharynx cancers, cannabinoid receptor agonists may promote tumor progression. An alternate mechanism explaining why cannabinoid agonist can both inhibit and stimulate tumor growth in specific cancers may relate to cannabinoid receptor downregulation. Past (88,89) and present (90) studies demonstrated that chronic treatment with cannabinoid agonists leads to downregulation of cannabinoid receptors and their activity. In a cancer, where tumor growth is driven by cannabinoid receptor activation, reducing the level and activity of the receptors by chronically treating with specific cannabinoids may ultimately lead to a decrease in

tumor progression. Cannabinoid antagonists have also been shown to have antitumor activity in specific cancers (74,91).

Important gaps in knowledge that require future research include increasing our understanding of the molecular mechanisms underlying cannabinoid antitumor activity; defining the basic biological role the endocannabinoid system plays in cancer progression; identifying molecular biomarkers of response to cannabinoid antitumor activity; designing the most appropriate cannabinoid-based combinational therapies with standard of care in preclinical models of cancers; and determining in which cancers (eg, HPVOPC) cannabinoid receptor agonists may drive cancer progression through specific MAPK-driven or additional networks. In these cases, treatment with a cannabinoid antagonist may be beneficial. Additionally, with the wide use of immunotherapy across cancer, a more detailed understanding of cannabinoid modulation of the immune system in the context of cancer progression is warranted. Finally, there is also significant need for well-developed clinical trials across cancers, which will ultimately determine whether cannabinoids may benefit cancer patients by inhibiting disease progression.

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