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The use of cannabinoids as anticancer agents

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ABSTRACT

It is well-established that cannabinoids exert palliative effects on some cancer-associated symptoms. In addition evidences obtained during the last fifteen years support that these compounds can reduce tumor growth in animal models of cancer. Cannabinoids have been shown to activate an ER-stress related pathway that leads to the stimulation of autophagy-mediated cancer cell death. In addition, cannabinoids inhibit tumor angiogenesis and decrease cancer cell migration. The mechanisms of resistance to cannabinoid anticancer action as well as the possible strategies to develop cannabinoid-based combinational therapies to fight cancer have also started to be explored. In this review we will summarize these observations (that have already helped to set the bases for the development of the first clinical studies to investigate the potential clinical benefit of using cannabinoids in anticancer therapies) and will discuss the possible future avenues of research in this area.

Contents

1. Introduction

Δ^9-tetrahydrocannabinol (THC), the main active component of *Cannabis sativa* exerts its effects by mimicking endogenous substances – the endocannabinoids anandamide (Devane et al., 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995) – that bind specific cannabinoid receptors located in the plasma membrane (Pertwee et al., 2010). Two major cannabinoid-specific receptors – CB_1 and CB_2 – have been identified (Matsuda et al., 1990; Munro et al., 1993). The transient receptor potential cation channel subfamily V member 1 (TRPV1), the orphan G protein-coupled receptor GPR55 and peroxisome proliferator-activated receptors (PPARs) have been proposed to act as endocannabinoid receptors, although their

Abbreviations: 2-AG, 2-arachidonoylglycerol; ALK, anaplastic lymphoma kinase; ATF-4, activating transcription factor 4; CB_1, cannabinoid CB_1 receptor; CB_2, cannabinoid CB_2 receptor; CBD, cannabidiol; CHOP, C/EBP homologous protein; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; MDK, midkine; mTORC1, mammalian target of rapamycin complex 1; THC, Δ^9-tetrahydrocannabinol; TRIB3, tribbles-homologue 3; TRPV1, transient receptor potential cation channel subfamily V member 1 (TRPV1); VEGF, vascular endothelial growth factor.

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precise contribution in the context of the endocannabinoid signaling is still a matter of debate (Pertwee et al., 2010). Most of the cannabinoids effects in the central nervous system rely on CB_1 receptor activation (Pertwee et al., 2010), Nevertheless expression of CB_1 receptor is not restricted to the central nervous system and this receptor is widely expressed in many different locations in the organism (Pertwee et al., 2010) The CB_2 receptor was initially described to be present in the immune system (Pertwee et al., 2010), although different studies have shown that it is also present in cells from other origins including astrocytes and certain populations of neurons (Atwood and Mackie, 2010; Fernandez-Ruiz et al., 2007). Of note, expression of CB_1 and CB_2 receptors occurs in many types of cancer cells, an event that not necessarily correlates with the expression of these receptors in non-transformed cells from the tissue from which cancer cells originated (Fernandez-Ruiz et al., 2007; Guzman et al., 2006; Sarfaraz et al., 2008).

The endocannabinoid system – constituted by the endocannabinoids, their receptors and the proteins involved in the synthesis, transport and degradation of endocannabinoids – exerts numerous regulatory functions in the organism (Katona and Freund, 2008); (Pacher et al., 2006; Pertwee, 2009). Accordingly, the pharmacological manipulation of the endocannabinoid system is being investigated for the treatment of many different diseases. In a cancer context, cannabinoids have been shown to alleviate nausea and vomit induced by chemotherapy (Guzman, 2003; Pertwee, 2009) and several cannabinoid-based medicines [Marinol (THC) and Cesamet (nabilone, a synthetic analogue of THC)] are approved for this purpose. Cannabinoids also inhibit pain, and Sativex (a standardized cannabis extract) has been approved in Canada for the treatment of cancer-associated pain. Other potential palliative effects of cannabinoids in oncology include appetite stimulation and attenuation of wasting (Pertwee et al., 2010).

In addition to these palliative actions of cannabinoids in cancer patients, THC and other cannabinoids exhibit antitumor effects in animal models of cancer (Guzman, 2003; Sarfaraz et al., 2008); (Pisanti et al., 2013; Velasco et al., 2012).

2. Endocannabinoid system: role in tumor generation and progression

A relatively large body of data has accumulated during the last decade about the role of endocannabinoid system in tumor generation and progression (see Table 1 for a brief summary of some of these observations). In many cases, these reports show that levels of endocannabinoids and their receptors are increased in cancer, a situation that frequently correlates with tumor aggressiveness (Malfitano et al., 2011). Accordingly, anandamide and 2-AG have been shown to be over-expressed in several types of tumors including glioblastoma multiforme (GBM), meningioma, pituitary adenoma, prostate and colon carcinoma and endometrial sarcoma (Pisanti et al., 2013). In addition, circulating endocannabinoid levels have been associated with increased disease progression in a mouse model of metastatic melanoma and in human samples of this pathology (Sailler et al., 2014). A similar situation has been proposed for cannabinoid receptors and endocannabinoid degrading enzymes. Thus, CB1 receptor was found to be upregulated in Hodgkin lymphoma cells (Benz et al., 2013) and in chemically induced cellular hepatocarcinoma (Mukhopadhyay et al., 2015). CB1 receptor levels are also increased and correlate with disease severity in human epithelial ovarian tumors (Messalli et al., 2014) and have been proposed to be a factor of bad prognosis following surgery in stage IV colorectal cancer (Jung et al., 2013).

Regarding CB2 receptor, a correlation between its expression, histologic grade and prognosis has been demonstrated in breast cancer (Caffarel et al., 2006) and glioma (Sanchez et al., 2001). In this latter tumor type a combined up-regulation of CB1 and CB2 receptors has been proposed to occur together with a decrease on the levels of the enzymes involved in endocannabinoid degradation compared to healthy controls (Wu et al., 2012). Similarly, expression of CB1 and CB2 is enhanced in mantle cell lymphoma, while FAAH expression is reduced compared to non-malignant B-cells (Ek et al., 2002; Islam et al., 2003; Wasik et al., 2014).

Recently, a role for the non-canonical cannabinoid receptor GPR55 in cancer development has been described. Higher histological grades of human glioblastomas, breast, pancreatic and skin cancers have been reported in association with increased GPR55 expression. Moreover, silencing of GPR55 reduced the proliferation of tumor cells in a xenograft mouse model of glioblastoma (Andradas et al., 2011; Perez-Gomez et al., 2013).

Altogether, these data suggest that the endocannabinoid system may play a pro-tumorigenic role and in agreement with this hypothesis genetic ablation of CB1 and CB2 receptors decreases UV light induced skin carcinogenesis (Zheng et al., 2008) and CB2 receptor overexpression enhances the predisposition to leukemia after leukemia virus infection (Joosten et al., 2002). Moreover, genetic ablation of CB1 receptor

Table 1
Changes in the expression of cannabinoid (CB) receptors or endocannabinoids (ECB)-degrading enzymes in human cancer.

Tumor type	CB receptors or ECB degrading enzymes	References
Hodgkin lymphoma	CB1 levels increased	(Benz et al., 2013)
Non-Hodgkin lymphoma	CB1 levels increased	(Gustafsson et al., 2008)
Chemically-induced cellular hepatocarcinoma	CB1 levels increased	(Mukhopadhyay et al., 2015)
Hepatocellular carcinoma	CB1 and CB2 expression correlates with improved prognosis of patients with hepatocellular carcinoma	{Xu, 2006 #378}
Human epithelial ovarian tumors	CB1 levels increased. Correlation with disease severity	(Messalli et al., 2014)
Stage IV colorectal cancer	CB1 levels are a factor of bad prognosis following surgery	(Jung et al., 2013)
Colon cancer	CB1 levels decreased, CB1 genetic ablation increases the growth of colon carcinomas	(Wang et al., 2008)
Pancreatic cancer	CB1 and CB2 levels increased and MAGL and FAAH levels decreased associated with bad prognosis	(Michalski et al., 2008)
Prostate cancer	CB1 levels increased associated with severity of disease and poor prognosis	(Chung et al., 2009)
Prostate cancer	FAAH tumor levels (but not CB1) directly correlate with severity of the diseases	(Thors et al., 2010)
Breast cancer	CB2 levels increased. Correlation with disease severity	{Caffarel, 2010 #15;Caffarel, 2006 #16;Perez-Gomez et al., 2015 #349}
Glioma	CB2 levels increased with degree in gliomas	(Sanchez et al., 2001)
Mantle cell lymphoma	CB1 and CB2 levels increased and FAAH levels decreased	(Ek et al., 2002; Islam et al., 2003; Wasik et al., 2011)
UV light induced skin carcinogenesis	CB1 and CB2 genetic ablation decrease UV light induced skin carcinogenesis	(Zheng et al., 2008)
Leukemia	CB2 overexpression enhances the predisposition to leukemia after leukemia virus infection.	(Joosten et al., 2002)
Glioma, breast cancer, skin cancer	GPR55 increased levels associated with higher histological tumor grade	(Andradas et al., 2011; Perez-Gomez et al., 2013)