Cancer Biology and Endocannabinoid System

Subjects: Oncology

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The various components of the endocannabinoid system (ECS), such as the cannabinoid receptors (CBRs), cannabinoid ligands, and the signalling network behind it, are implicated in several tumour-related states, both as favourable and unfavourable factors.

Keywords: Cannabinoid receptors ; Cancer Biology ; Endocannabinoid system

1. Introduction

Historically, cannabinoids have primarily been used as palliative care agents in oncology. However, the various components of the endocannabinoid system (ECS), such as the cannabinoid receptors (CBRs), cannabinoid ligands, and their signalling network are interlinked with several tumour-related states, both as favourable and unfavourable factors. This vast network of molecules is an attractive pharmacological target, and its full potential is yet to be reached. Understanding the specific ways ECS components can regulate the cell cycle, proliferation and cell death considering their interactions with the immune system is necessary for advancing the current state of the art in cannabinoid-based anti-cancer therapeutic approaches.

2. The Interplay between Cancer Biology and the Endocannabinoid System

So far, seven receptors that respond to endogenous and exogenous cannabinoid ligands in humans have been described in literature [1], namely the main cannabinoid receptors 1 and 2 (CB1R, coded by *CNR1* gene [2] and CB2R, coded by *CNR2* gene [3]), as well as G protein-coupled receptors 18 (N-arachidonyl glycine receptor, GPR18 [4]), 55 (GPR55 [5]) and 119 (Glucose-dependent insulinotropic receptor, GPR119 [6]) and the transient receptor potential cation channel subfamily V members 1 and 2 (TRPV1 [7], TRPV2 [8]). All these receptors might be useful anti-cancer targets individually, as well as in various heteromerization scenarios. A simple STRING analysis [9], showed that cannabinoid receptors CB1R and CB2R directly interact with each other using several evidence platforms, as well with GPR18, GPR55 and TRPV1 (Figure 1a). Additional cluster analysis extended to five primary-interaction shell genes showed that GPR119 is only indirectly connected with the other receptors while TRPV2 seems to form a separate network entity (Figure 1b). The extended network is enriched in interactions (PPI enrichment *p*-value: 2.39×10^{-12}), meaning that these seven receptors in general interact more than is expected for a random set of molecules of similar size and can be considered, at least partially, as a biologically connected group [9].

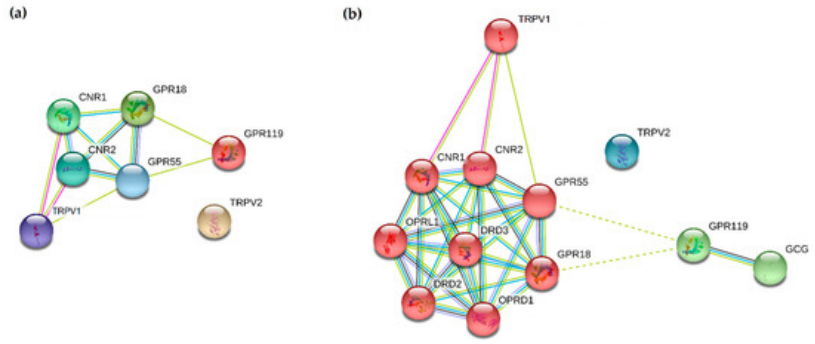

Figure 1. STRING interaction analysis of cannabinoid receptors. (**a**) Direct STRING analysis network was built based on high confidence (0.7) evidence from experimental interaction data (pink), co-expression (black), gene neighbourhood (green) and co-occurrence (blue) data, curated databases (light blue), protein homology (purple), and predictive and knowledge text mining (light green); (**b**) The network was extended to 5 primary-interaction shell genes to explore their indirect interactions and clustering (PPI enrichment *p*-value: 2.39×10^{-12}) using the intersection of 12 genes present on all analysed platforms. Red nodes—*CNR1/CNR2* cluster, green nodes—GPR119 cluster, blue nodes—TRPV2 cluster.

Nodes are labelled with Human Gene Nomenclature Committee (HGNC) gene symbols: *CNR1*—Cannabinoid receptor 1 gene, *CNR2*—Cannabinoid receptor 2 gene, DRD2—dopamine receptor D2, DRD3—dopamine receptor D3, GCG—glucagon, GPR18—N-arachidonyl glycine receptor (G-protein coupled receptor 18), GPR55—G-protein coupled receptor 55, GPR119—Glucose-dependent insulinotropic receptor (G protein-coupled receptor 119), OPRD1—Opioid Receptor Delta 1, OPRL1—Opioid Related Nociceptin Receptor 1, TRPV1 and TRPV2—transient receptor potential cation channel subfamily V members 1 and 2.

Changes in expression and activation of these CBRs, as well as their ability to form distinct functional heteromers with many other receptors alter the cell's tumuorigenic potential and their signalling properties, leading to pharmacologically different outcomes upon their stimulation [10][11][12]. Thus, the same ECS component can exert both protective and pathogenic effects in different tumour subtypes, which are often pathologically driven by different biological factors.

Cannabinoid receptors are widely expressed on normal and cancer cells. The interactive open-access databases the Human Protein Atlas [13][14] and UALCAN [15][16] were used to analyse the Cancer Genome Atlas (TCGA) [17] transcriptome data and assess their expression in various cancer subtypes. In silico analyses showed that cannabinoid receptors were generally not prognostically significant, but are enriched (mostly at the RNA level where more data is available) in some cancer subtypes: CNR1 in glioma (Figure 2a), CNR2 in testicular cancer (Figure 2b), GPR119 in pancreatic cancer, where it is also a favourable prognostic factor ($p < 0.001$, Figure 2c [18]) and **TRPV2** in melanoma, while it is an unfavourable prognostic factor in renal ($p < 0.001$, Figure 2d [19]) and testicular cancer ($p < 0.001$, Figure 2e [20]).

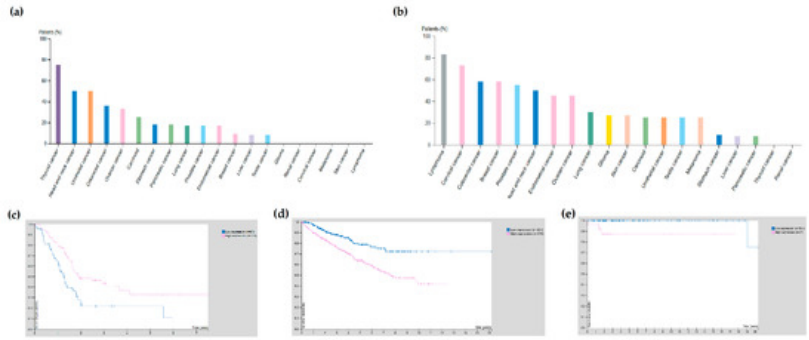

Figure 2. The expression of *CNR1*, *CNR2*, *GPR119* and *TRPV2* in cancer according to the Human Protein Atlas database [13]. (**a**) Expression of *CNR1* in cancer subtypes; (**b**) expression of *CNR2* in cancer subtypes; (**c**) survival curves of pancreatic cancer patients according to the expression of *GPR119* favourable prognostic factor, $p < 0.001$); (**d**) survival curves of renal cancer patients according to the expression of *TRPV2* (unfavourable prognostic factor, $p < 0.001$); (**e**) survival curves of testicular cancer according to the expression of *TRPV2* (unfavourable prognostic factor, $p < 0.001$).

The receptors are also significantly over- or under-expressed in some cancer subtypes compared to normal tissue which might be useful for diagnostics and specific anti-cancer approaches (Table 1) [16]. Interestingly, all cannabinoid receptors were found to be significantly under-expressed in colon adenocarcinoma.

Table 1. Comparison of cannabinoid receptors' genetic expression in normal vs. tumour tissue according to the UALCAN database [16] analysis of TCGA data.

Cancer Type	Receptor	Cancer Subtype	Expression in Tumour vs. Normal Tissue	*p* Value
Breast cancer	CNR1	Breast invasive carcinoma	Under-expressed	7.09E-11
	CNR2	Breast invasive carcinoma	Under-expressed	1.55E-02
	GPR18	Breast invasive carcinoma	Over-expressed	3.60E-07
Gastrointestinal malignancies	CNR1	Cholangiocarcinoma	Over-expressed	3.16E-02

		Colon adenocarcinoma	Under-expressed	1.58E-07
		Hepatocellular carcinoma	Over-expressed	3.52E-11
		Rectum adenocarcinoma	Under-expressed	9.80E-03
	CNR2	Colon adenocarcinoma	Under-expressed	6.57E-04
		Rectum adenocarcinoma	Under-expressed	2.83E-02
	GPR18	Colon adenocarcinoma	Under-expressed	3.30E-06
	GPR55	Colon adenocarcinoma	Under-expressed	2.16E-04
	GPR119	Colon adenocarcinoma	Under-expressed	1.55E-05
		Hepatocellular carcinoma	Under-expressed	3.58E-05
		Pancreatic adenocarcinoma	Over-expressed	1.73E-02
		Rectum adenocarcinoma	Under-expressed	2.84E-03
	TRPV1	Hepatocellular carcinoma	Over-expressed	4.75E-06
		Stomach adenocarcinoma	Over-expressed	1.32E-03
	TRPV2	Cholangiocarcinoma	Over-expressed	5.71E-07
		Hepatocellular carcinoma	Over-expressed	4.27E-09
		Stomach adenocarcinoma	Over-expressed	1.22E-08
Gynaecological malignancies	CNR1	Uterine corpus endometrial carcinoma	Under-expressed	1.54E-02
	GPR18	Cervical squamous cell carcinoma	Over-expressed	1.18E-03
	GPR55	Cervical squamous cell carcinoma	Over-expressed	1.64E-09
		Uterine corpus endometrial carcinoma	Under-expressed	9.88E-07
Prostate cancer	CNR1	Prostate adenocarcinoma	Under-expressed	3.45E-06
	TRPV1	Prostate adenocarcinoma	Over-expressed	1.05E-04

	TRPV2	Prostate adenocarcinoma	Under-expressed	3.56E-02
Thoracic tumours	CNR1	Lung adenocarcinoma	Under-expressed	1.62E-12
		Lung squamocellular carcinoma	Under-expressed	4.06E-07
	TRPV1	Lung adenocarcinoma	Over-expressed	<1E-12
		Lung squamous cell carcinoma	Over-expressed	6.11E-10
	TRPV2	Lung adenocarcinoma	Under-expressed	<1E-12
		Lung squamous cell carcinoma	Under-expressed	1.62E-12
Thyroid cancer	CNR1	Thyroid carcinoma	Under-expressed	3.05E-02
	CNR2	Thyroid carcinoma	Under-expressed	1.72E-05
	GPR18	Thyroid carcinoma	Under-expressed	3.94E-03
	GPR55	Thyroid carcinoma	Over-expressed	2.24E-04
	TRPV1	Thyroid carcinoma	Under-expressed	3.74E-02
Central nervous system malignancies	GPR18	Glioblastoma multiforme	Over-expressed	1.60E-06
	TRPV1	Glioblastoma multiforme	Under-expressed	4.78E-02
Melanoma (primary vs. metastasis)	CNR2	Skin cutaneous melanoma	Over-expressed	1.22E-06
	GPR18	Skin cutaneous melanoma	Over-expressed	1.61E-09
	GPR119	Skin cutaneous melanoma	Under-expressed	1.95E-02
	TRPV2	Skin cutaneous melanoma	Under-expressed	3.81E-02

2.1. Breast Cancer

Breast cancer (BC) remains the most common malignant disease in women in Western countries. Although the rates of mortality have declined since the late 1990s primarily due to adjuvant systemic therapy and earlier detection by palpation and mammograms, some breast tumours remain resistant to conventional therapies. In addition, actual treatments have side effects that substantially affect the patients' quality of life [21][22][23][24] and many plants have been evaluated as supplementary and alternative anticancer medicines [25][26]. As BC is a highly heterogeneous disease in terms of molecular portraits, prognosis, and treatment [23], there are three main BC subtypes based on classical molecular profiles:

hormone receptor-positive, Human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative tumours. The current state-of-the art suggests that cannabinoid-based approaches may offer a therapeutic benefit in these three BC subtypes [27].

2.2. Gastrointestinal Malignancies

Gastrointestinal cancers (GIC) represent a vast family of malignant diseases including rectal cancer, biliary cancer, gastric cancer, esophageal cancer, pancreatic cancer, colorectal cancer, anal cancer, early colon cancer, familial risk colorectal cancer, and hepatocellular carcinoma. Standard treatment approaches depend on various clinical and genetic factors and are constantly evolving to meet the patients' needs. Despite all invested efforts, colorectal cancer (CRC) is still the third most common malignant disease in the world with around 1.8 million new cases in 2018, and in second place by mortality induced by cancer with around 0.9 million deaths [28]. The ECS's involvement in the development, progression and treatment of CRC has been evaluated in terms of the implication of cannabinoid receptors, endo- and synthetic cannabinoids, as well as various ECS-induces signalling molecules [29][30].

2.3. Gynecological Malignancies

Gynaecological malignancies make up approximately one out of six cancers in women [31]. Although they are usually grouped together, cancers of the female reproductive system comprise a diverse group of cancers with distinct risk factors, signs and symptoms, clinical presentations and treatment modalities, each named after the anatomical part in which the cancer started: cervical, ovarian, uterine (endometrial cancer and uterine sarcoma), vaginal, vulvar, and fallopian tube [32]. Since they play important roles in the regulation of cell proliferation, differentiation and survival, endocannabinoids (ECS) have emerged as a cell regulatory mechanism involved in protection against cancer development. In addition, endocannabinoids are actively involved in all aspects of female reproduction such as oocyte production [33] and their impairment has been associated with various gynaecological pathological conditions such as ectopic pregnancies (N-arachidonoylethanolamine (AEA), CB1R, fatty acid amide hydrolase (FAAH)) and cancer. The expression of CB1R, CB2R, N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and FAAH was shown in normal human ovaries, while AEA was found in the follicular fluid after ovarian stimulation by hormones [34].

2.4. Prostate Cancer (PC)

Prostate cancer is one of the most common malignant cancers in men. It is the second most frequently diagnosed cancer and one of the leading causes of cancer death worldwide in the male population [35]. Standard treatment of localized PC is surgery or radiotherapy. Approximately one third of conventionally treated patients will develop metastases, at which point androgen withdrawal is the most effective form of systemic therapy. Unfortunately, androgen deprivation is associated with a gradual transition of PC cells through a spectrum of androgen dependence, followed by androgen sensitivity, and finally androgen independence, known as castration-resistant prostate cancer (CRPC). This stage of PC has a more aggressive phenotype and is unresponsive to further hormonal therapy, with a very poor prognosis [36][37]. Cannabinoids have shown a high anticancer activity in PC, but the specific molecular mechanisms responsible for these effects depend on the drug and tumour context.

2.5. Thoracic Tumours

In 2018, over two million new lung cancer (LC) cases were diagnosed, and over 1.3 million people have died from LC, making this disease the most common occurring malignant disease in the world, as well as the most common cause of cancer-related deaths [28]. Although LC is a model cancer for the success of molecular targeted therapies [38][39], due to the high cost of radiologically-based nation-wide screening programs [40][41], it is most often diagnosed in advanced disease stages when the level of cancer-related pain is high [42]. An individual combination of pharmacological and non-pharmacological approaches for each patient ensures the optimal palliative care which results in higher quality of life and longer survival. The role of the ECS is ambiguous in LC, as there have been sporadic reports connecting the use of cannabinoids to a higher risk of LC [43] and more reports that document its beneficiary properties. Although it is known that cannabis contains many similar toxins and carcinogens to tobacco [44] and regular marijuana use has been shown to induce various pulmonary problems [45][46], to date, there are no conclusive data associating it with an increased risk of lung cancer [47][48].

2.6. Thyroid Cancer (TC)

Fewer than 1% of all thyroid nodules are cancerous and, even when they are, most of thyroid cancers are very curable. In fact, the most common types of TC (papillary ~85%, follicular ~10%) are most curable in patients younger than 50, with a 98% cure rate if treated appropriately. On the other hand, there are rare forms such as anaplastic TC which are very aggressive (median survival 3–5 months) [49]. Even though these types of cancer are very rare (less than 2% of all thyroid

cancers) therapeutic options are needed for these aggressive forms of disease. The results of many studies suggest that manipulation of the ECS can be consider as an option to prevent propagation of thyroid tumour cells and that CB2R may be a therapeutic target for the treatment of the most aggressive types of TC. We note that in vivo TC studies with cannabinoids are scarce and more rigorous evaluation is needed to confirm the role of the ECS in this malignancy.

2.7. Central Nervous System Malignancies

There are over 130 types of brain tumours, as classified by the World Health Organisation. Brain tumours can differ in the cells they originate from, how quickly they are likely to grow and spread, and the location of the brain they affect. The most common types of adult brain tumours or gliomas include glioblastoma, astrocytoma, meningioma and pituitary adenoma. Gliomas are defined as the tumours that display histological, immunohistochemical, and ultrastructural evidence of glial differentiation. They are classified according to cellular features and grade of malignancy [50]. Glioblastoma multiforme (GBM), or grade IV astrocytoma, is the most frequent class of malignant primary brain tumours being the most aggressive form of cancer. Consequently, survival after diagnosis is low [50][51], due primarily to the high invasiveness and proliferation rate of GBM. Additionally, GBM exhibits a high resistance to standard chemotherapy and radiotherapy. Current standard therapeutic strategies for the treatment of GBM are only palliative including surgical resection and focal radiotherapy [51] [52]. It has been recently found that cannabinoids exert anti-glioma actions in laboratory animals and constitute a potential cannabinoid-based therapy for GBM [53].

2.8. Melanoma

Melanoma represents an aggressive form of malignant skin cancer which develops by transformation of melanocytes. Despite the introduction of targeted therapies and immunotherapy for the treatment of malignant melanoma, it is still associated with significant morbidity and mortality [28]. The application of the endocannabinoids AEA, 2-AG, as well as the endogenous signalling lipid PEA and inhibitor of FAAH involved in ECS metabolism were shown to increase cell death both in vitro and in vivo [54]. On the contrary, reports of a pro-tumourigenic effect of CB1R also exist [55]. This further emphasizes the interplay between the ECS, the specific cancer cell type and the immune microenvironment which needs to be considered when designing future studies. The dose of the applied cannabinoid, as well as its complex interaction with the primary anti-cancer therapy regimen via intersecting downstream signalling pathways might have a significant impact on the final outcome [56][57].

3. Legal and Ethical Aspects of ECS Exploitation in Oncology

While clinical trials employing phytocannabinoids as CBD or targeting other components of the ECS in cancer pose no more ethical issues than the ones that appear in almost every human-related oncological clinical trial [57], medical, ethical and legal ramifications of the use of exogenous psychotropic cannabinoids as THC are vast. Beside the favourable benefit-to-risk ratio, fully autonomous and informed consent and careful monitoring for safety and side effects, additional ethical considerations related to social context and lingering misconceptions are related to medicinal cannabis use.

Cannabinoids have an important role in palliative medicine due to their analgesic and antiemetic effects, but an increasing number of preclinical studies indicate their anticancer properties as well. Even though some cannabinoid-based drugs have been registered in several countries (e.g., nabiximols, dronabinol, nabilone), there have been studies demonstrating moderate- or low-quality evidence supporting the use of these agents in anti-cancer treatment [58]. The ethical and medical debates are still ongoing about the use of psychotropic cannabinoids as therapeutics in cancer patients. The proof of profound safety and efficacy in clinical trials is lacking and it is hard to assess the potential benefits and risks. Many aspects are still unknown about the way of administration, dosage, interaction with other drugs and adverse effects. The legal prohibition of medical marijuana on the other hand directly confronts the personal and autonomous freedom of choice. It might be said that medical facts are still too vague to overturn the informed decision that harms are not inflicted to third parties when marijuana is used for medicinal purpose and that possible harms cannot outweigh the suffering that can probably be removed by the drugs [59]. The social and political history of cannabis prohibition and the stigma it has perpetuated continues to stand in the way of detailed systematic research that will help elucidate many dilemmas pertaining to its use. To help guide the research in this exciting medical filed, the principles of biomedical ethics, i.e., respect for autonomy, beneficence, and justice, should be followed.

4. Conclusions

The use of ECS components as anti-cancer agents and targets, and the range of effects they might induce (cell death, regulation of angiogenesis and invasion or anticancer immunity), depend in great deal on the specific cannabinoid ligand acting in a specific cancer cell type. Although an attractive target, the use of ECS components in anti-cancer treatment is

interlinked with many legal and ethical issues that need to be considered. The legislation which outlines the permissive boundaries of their therapeutic use in oncology is still unable to follow the current scientific burden of evidence, but the number of ongoing clinical trials might tip the scale forward in the near future.

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