Kidney (Renal) Cancer

Excerpt from www.cancer.ca:

Kidney cancer is a malignant tumour that starts in the cells of the kidney. Malignant means that it can spread, or metastasize, to other parts of the body.

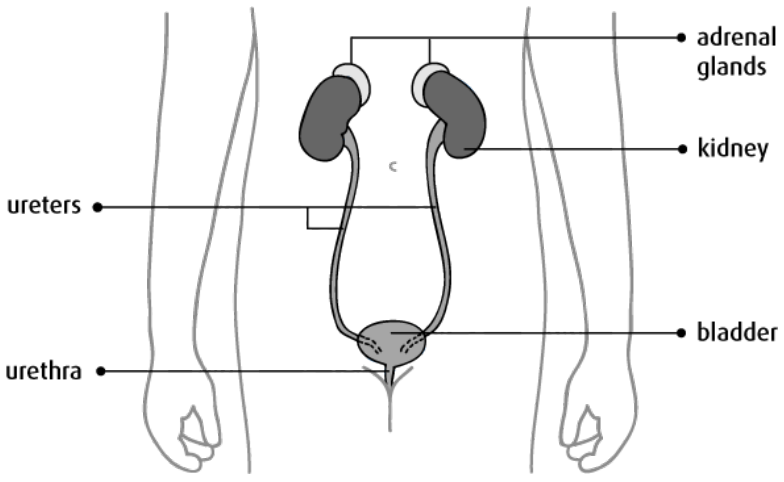
The kidney is part of the urinary system. The 2 kidneys are on either side of the backbone, deep inside the upper part of the abdomen. On the top of each kidney is an adrenal gland. The kidneys make urine by filtering water and waste material from the blood. Inside each kidney is a network of millions of small tubes called nephrons. Each nephron is made up of a tubule and a corpuscle. Tubules are tiny tubes that collect the waste materials and chemicals. Corpuscles have a clump of tiny blood vessels that filter the blood.

Cells in the kidney sometimes change and no longer grow or behave normally. These changes may lead to benign conditions such as cysts. They can also lead to benign tumours such as renal adenoma. Benign conditions and tumours are not cancerous. But in some cases, changes to kidney cells can cause cancer.

Most often, kidney cancer starts in cells that line the tubules. This type of cancer is called renal cell carcinoma. There are several different types of renal cell carcinoma.

Rare types of kidney cancer can also develop. These include renal sarcoma and adult Wilms tumour.

Location of the Kidneys



Cannabinoids Induce Cancer Cell Proliferation via Tumor Necrosis Factor α-Converting Enzyme (TACE/ADAM17)-Mediated Transactivation of the Epidermal Growth Factor Receptor

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Abstract

Cannabinoids, the active components of marijuana and their endogenous counterparts were reported as useful analgetic agents to accompany primary cancer treatment by preventing nausea, vomiting, and pain and by stimulating appetite. Moreover, they have been shown to inhibit cell growth and to induce apoptosis in tumor cells. Here, we demonstrate that anandamide, Δ^9-tetrahydrocannabinol (THC), HU-210, and Win55,212-2 promote mitogenic kinase signaling in cancer cells. Treatment of the glioblastoma cell line U373-MG and the lung carcinoma cell line NCI-H292 with nanomolar concentrations of THC led to accelerated cell proliferation that was completely dependent on metalloprotease and epidermal growth factor receptor (EGFR) activity. EGFR signal transactivation was identified as the mechanistic link between cannabinoid receptors and the activation of the mitogen-activated protein kinases extracellular signal-regulated kinase 1/2 as well as prosurvival protein kinase B (Akt/PKB) signaling. Depending on the cellular context, signal cross-communication was mediated by shedding of proAmphiregulin (proAR) and/or proHeparin-binding epidermal growth factor-like growth factor (proHB-EGF) by tumor necrosis factor α converting enzyme (TACE/ADAM17). Taken together, our data show that concentrations of THC comparable with those detected in the serum of patients after THC administration accelerate proliferation of cancer cells instead of apoptosis and thereby contribute to cancer progression in patients.

Introduction

Cannabinoids have been used in medicine for more than a century. Recently interest in their therapeutic value has been fuelled by suggestions to apply these drugs in cancer treatment to improve analgesia and to relieve insomnia (1) . Because of their neuroprotective properties, cannabinoids have also been proposed to be useful drugs for the therapy of neurodegenerative diseases like Parkinson‘s disease, Huntington disease, and multiple sclerosis (2) . Orally applicable Δ^9-tetrahydrocannabinol (THC; Dronabinol, Marinol) and its synthetic derivative Nabilone (Cesamet) have been approved by the United States Food and Drug Administration to stimulate the appetite of patients with AIDS and to reduce the nausea of cancer patients undergoing chemotherapy (1 , 3 , 4) .

Moreover, recent investigations propose that drugs activating the endogenous cannabinoid system might be used in cancer therapy to slow down or block cancer growth (4) . The endogenous

cannabinoid anandamide (AEA) acts antiproliferatively in MCF-7, EFM-19, T47D, and DU145 cells (5) . Interestingly, cannabinoid-induced inhibition of proliferation in breast cancer cells results from cycle arrest at the G_1-S phase transition and is independent of apoptosis (3 , 5) . Furthermore, depending on drug concentration, the timing of drug delivery, and cellular context, cannabinoids may either inhibit or stimulate the function of immune cells. Although high concentrations of cannabinoids block immune cells, Derocq *et al.* (8) demonstrated proliferation in human B cells after cannabinoid stimulation at nanomolar concentrations (6, 7, 8) . In addition, murine hematopoietic cells depend on AEA for normal growth in serum-free medium (9) .

THC, the endogenous cannabinoid AEA and synthetic cannabinoids like HU-210 and Win55,212-2 interact with specific G protein-coupled receptors (GPCRs). Two subtypes of the cannabinoid receptors, CB1 and CB2, have been cloned and characterized (10 , 11) . The CB1 receptor, which is responsible for the well-known psychotropic effects of cannabinoids, is highly expressed in the central nervous system, but lower levels are also present in immune cells and peripheral tissues including testis, whereas the CB_2 receptor is predominantly expressed in immune cells (12, 13, 14) . Both cannabinoid receptors are coupled to heterotrimeric $G_{i/o}$-proteins and activate the mitogen-activated protein kinases (MAPK) extracellular signal-regulated kinase (ERK)1/2 and p38 as well as the Akt/PKB survival pathway (5 , 15) . Extensive research efforts have addressed the question how cannabinoids induce MAPK activation. Thus far, the accumulation of ceramides after cannabinoid stimulation has been implicated in the induction of the ERK/MAPK signal, whereas other reports suggested intracellular ceramide levels not to be required for cannabinoid-induced MAPK activation (5 , 12) . Previously we and others have shown that a wide variety of GPCR agonists leads to the activation of MAPK via transactivation of the epidermal growth factor receptor (EGFR) (16, 17, 18, 19) . This mechanistic concept involves the proteolytic processing of a membrane-spanning proEGF-like growth factor by a zinc-dependent metalloprotease of the ADAM family (18, 19, 20, 21) .

The aim of this study was to identify critical elements that link the cannabinoid receptors to activation of the ERK/MAPK and the Akt/PKB pathway. Hence, we tested whether cannabinoid receptors transactivate the EGFR in cancer cell lines, thereby activating downstream mitogenic signaling events.

Our results demonstrate that treatment of NCI-H292 (lung cancer), SCC-9 (squamous cell carcinoma), 5637 (bladder carcinoma), U373-MG (glioblastoma), 1321N1 (astrocytoma), and A498 (kidney cancer) cells with cannabinoids such as THC, AEA, HU-210, and Win55,212-2 leads to rapid EGFR tyrosine phosphorylation, phosphorylation of the adaptor protein Src homology 2 domain-containing (SHC), and downstream activation of ERK1/2 and Akt/PKB. EGFR transactivation is specifically mediated by cannabinoid-induced cleavage of proAmphiregulin (proAR) and/or proHeparin-binding epidermal growth factor-like growth factor (proHB-EGF) at the cell surface by tumor necrosis factor α-converting enzyme (TACE/ADAM17). Importantly, THC induced EGFR- and metalloprotease-dependent cancer cell proliferation. Thus, this cross-communication of CB1/CB2 receptors and the EGFR provides a molecular explanation of how cannabinoid receptors are linked to MAPK and Akt/PKB activation in a wide variety of human cancer cell lines.

In the light of these results, the use of cannabinoids in cancer therapy has to be reconsidered, because relatively high concentrations of THC induce apoptosis in cancer cells, whereas nanomolar concentrations enhance tumor cell proliferation and may, therefore, accelerate cancer progression in patients.

http://cancerres.aacrjournals.org/content/64/6/1943.long

J Histochem Cytochem. Dec 2010; 58(12): 1129–1134.
doi: 10.1369/jhc.2010.957126
PMCID: PMC2989249

Cannabinoid CB_1 Receptor Is Downregulated in Clear Cell Renal Cell Carcinoma

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Abstract

Several studies in cell cultures and in animal models have demonstrated that cannabinoids have important antitumoral properties. Because many of these effects are mediated through cannabinoid (CB) receptors CB_1 and CB_2, the study of their expression in human neoplasms has become of great interest in recent years. Fresh and formalin-fixed tissue samples of 20 consecutive clear cell renal cell carcinomas (CCRCCs) were collected prospectively and analyzed for the expression of both CB receptors by using RT-PCR, Western blot (WB), and immunohistochemical techniques. RT-PCR assays demonstrated the expression of mRNA encoding the CB_1 in tumor tissue and in adjacent non-neoplastic kidney. Conversely, WB and IHC revealed a marked downregulation of CB_1 protein in tumor tissue; CB_2 was not expressed. The obtained data suggest a possible implication of the endocannabinoid system in renal carcinogenesis. A posttranscriptional downregulation of CB_1 and the absence of expression of CB_2 characterize CCRCC. **(J Histochem Cytochem 58:1129–1134, 2010)**

Clin Biochem. 2013 May;46(7-8):638-41. doi: 10.1016/j.clinbiochem.2012.12.023. Epub 2013 Jan 12.

Cannabinoid CB1 receptor is expressed in chromophobe renal cell carcinoma and renal oncocytoma.

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Author information

Abstract

OBJECTIVE:

To analyze the mRNA and protein expression of cannabinoid receptors CB1 and CB2 in chromophobe renal cell carcinoma (ChRCC) and renal oncocytoma (RO).

DESIGN AND METHODS:

Fresh and formalin-fixed tissue samples of ChRCC and RO were analyzed by using real-time quantitative RT-PCR and immunohistochemical techniques (n=40).

RESULTS:

Quantitative RT-PCR analysis showed that CB1 mRNA was underexpressed by 12-fold in ChRCC and had a variable expression in RO. CB1 protein showed intense positive immunostaining in both neoplasms. Both CB2 mRNA and protein were not expressed in tumor and non tumor renal tissue.

CONCLUSION:

This distinct immunoprofile may eventually be used as an additional tool with practical interest in the differential diagnosis of renal tumors.

PMID:
23318578
[PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/23318578