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COMMENTARY

The putative cannabinoid receptor GPR55 promotes cancer cell proliferation

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Cannabinoids, the active ingredients in marijuana, have dramatic effects on various organ systems. They exert their effects through two receptor types: CB1, primarily located in the brain, and CB2, primarily located in the immune system. Vertebrates also produce their own cannabinoid-like substances called endocannabinoids, including anandamide and 2-arachidonoylglyceral. Interestingly, some effects of endocannabinoids could not be explained by the signals through either CB1 or CB2. Recently, the orphan G protein-coupled receptor 55 (GPR55) was proposed to be an atypical cannabinoid receptor. In this issue of *Oncogene*, two groups demonstrated that GPR55 is expressed in various cancer types in an aggressiveness-related manner, suggesting a novel cancer biomarker and a potential therapeutic target.
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Cannabinoids were initially isolated from the plant *Cannabis Sativa*, and a great number of natural and synthetic active components have been subsequently identified as cannabinoid ligands. Cannabinoid receptors, CB1 and CB2, were identified based on their binding to cannabinoids (Das *et al*., 1995). However, plant cannabinoids are not a part of evolution of vertebrates, and the cannabinoid receptors are not made for getting 'high'. Indeed, scientists have discovered endogenous ligands for these receptors, endocannabinoids including anandamide and 2-arachidonylglycerol (Devane *et al*., 1992; Mechoulam *et al*., 1995; Sugiura *et al*., 1996). It has been recently proposed that the orphan G-protein couple receptor GPR55 is engaged and activated by lysophosphatidylinositol (LPI; Oka *et al*., 2010) and anandamide (Lauckner *et al*., 2008). In addition to their dramatic effects on the nervous, immune and other systems, recent studies have shown that various agonists of the classical cannabinoid receptors CB1 and CB2 possess antitumor effects, and have been approved to treat cancer or to eliminate the side effects of chemotherapy (Alexander *et al*., 2009; Oesch and Gertsch, 2009). Interestingly, in this issue of *Oncogene*, two groups demonstrated that GPR55 is expressed in various cancer types in an aggressiveness-related manner and have a critical role in regulating cancer-cell proliferation (Andradas *et al*., 2011; Piñeiro *et al*., 2011).

Since the identification and cloning of the orphan G-protein coupled receptor GPR55 in 1999, investigations on its biological and pharmacological role have also led to interests in employing GPR55 as a potential therapeutic target for various diseases (Sharir and Abood, 2010). GPR55 expression has been widely detected in the nervous system and peripheral tissues, including frontal cortex, cerebellum, striatum, hypothalamus, brain stem, dorsal root ganglia neurons, spleen, tonsil, adrenal, bone, endothelial cells, large intestine and adipose tissue. The recently developed commercial antibodies against GPR55 will allow the detection of the expression of GPR55 at the protein level in normal and tumor tissues. Although GPR55 could bind anandamide, it seems that LPI is the putative ligand of GPR55; activated downstream signaling was always observed when exogenous LPI was added into several types of cultured cells, which express transfected or native GPR55 (Oka *et al*., 2010; Sharir and Abood, 2010). Though the proposal that GPR55 is a true cannabinoid receptor remains controversial, it is still proper to consider GPR55 as an atypical cannabinoid receptor.

The physiological and pharmacological role of GPR55 remains poorly understood. Male GPR55$^{-/-}$ mice show a significant increase in the volume and thickness of trabecular bone and the presence of unresorbed cartilage, suggesting a possible application of selective GPR55 antagonists to treating osteoporosis (Whyte *et al*., 2009). On the other hand, female GPR55$^{-/-}$ mice were resistant to inflammatory and neuropathic pain (Staton *et al*., 2008). The increased circulating levels of LPI in patients with ovarian cancer and the pro-proliferative effects of LPI on Ras-transformed cell lines indicate a possible role of GPR55 in cancer progress. However, there had been no direct evidence until most recently when it was reported that the LPI-GPR55

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signaling pathway played a role in modulating migration, orientation and polarization of breast cancer cells MDA-MB-231 and MCF-7 (Ford *et al*., 2010).

The current two studies provided strong evidence that GPR55 promotes cancer cell proliferation (Andradas *et al*., 2011; Piñeiro *et al*., 2011). In one study, Andradas *et al*. found that most human cancer cell lines contain detectable levels of GPR55 mRNA. Higher GPR55 expression is associated with more aggressive phenotypes (higher histological grades and higher proliferative rates) in human breast tumors, pancreatic tumors and glioblastomas. Overexpression of GPR55 enhanced proliferation of HEK293 cells via extracellular signal-regulated protein kinase. Moreover, knockdown of GRP55 expression in T98G glioma cells reduced tumor growth. In another study, Piñeiro *et al*. demonstrated GPR55 expression in several prostate and ovarian cancer cell lines, and that GPR55 has a critical role in LPI-induced cancer growth and activation of intracellular signaling pathways. Furthermore, in prostate cancer cells, LPI was shown to synergize with cPLA2 and extracellular exportation of LPI by the ABCC1 transporter is responsible for the activation of GPR55 and promotion of cell proliferation.

This demonstration of pro-proliferative effects of GPR55 on cancer cells contributes to a better understanding of tumor progress and better development of therapeutic strategy for cancer. Many cannabinoid preparations have been successfully used for treating neuropathic pain, multiple sclerosis, schizophrenia and various other disorders. Based on their antiproliferative, antimetastatic, antiangiogenic and pro-apoptotic effects, the CB1/CB2 agonists were recently proposed to be novel agents for the treatment of various cancer types. More importantly, canabinoids are effective in eliminating side effects of chemotherapy, such as nausea, vomiting and lack of appetite (Alexander *et al*., 2009). Delta-9-tetrahydrocannabinol (THC), the most active component of phytocannabinoids and most commonly used preparation of cannabinoids in clinical settings, has been shown to have protumor and antitumor effects in a dose- or cell type-dependent manner in *in vitro* and *in vivo* models (Alexander *et al*., 2009). Interestingly, THC has been shown to be a GPR55 agonist in some studies but not in others (Sharir and Abood, 2010). Given that cannabinoids exhibit antitumor effects as CB1/CB2 agonists and protumor effects as GPR55 agonists, and different cancer cells express different ratio of CB1/CB2 to GPR55, it is reasonable to propose that examination of the coexpression status of CB1/CB2 and GPR55 should be a novel approach for selecting cancer types that are more suitable for a specific therapy.

As the investigation of the physiological and pathological functions of GPR55 is just at the beginning, many questions remain to be answered. How many types of cancer cells express GPR55 in a cancer progress-dependent manner? Would GPR55 expression in immune system functionally regulate inflammatory immune responses, especially under stress conditions? Are there any other endogenous ligands for GPR55? Does the function of cannabinoid ligands on GPR55 in normal tissues depend on cell types and/or environment? And does the expression level of GPR55 and its overlapping expression with CB1/CB2 underlie the divergent effects? With the development of selective agonists/antagonists and antibodies (especially those suitable for flow cytometry) as well as gene-modified mice, these questions are sure to be answered in the near future.

Conflict of interest

The authors declare no conflict of interest.

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