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REVIEW ARTICLE

Targeting the endocannabinoid system as a potential anticancer approach

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ABSTRACT

The endocannabinoid system is currently under intense investigation due to the therapeutic potential of cannabinoid-based drugs as treatment options for a broad variety of diseases including cancer. Besides the canonical endocannabinoid system that includes the cannabinoid receptors CB_1 and CB_2 and the endocannabinoids *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol, recent investigations suggest that other fatty acid derivatives, receptors, enzymes, and lipid transporters likewise orchestrate this system as components of the endocannabinoid system when defined as an extended signaling network. As such, fatty acids acting at cannabinoid receptors (e.g. 2-arachidonoyl glyceryl ether [noladin ether], *N*-arachidonoyldopamine) as well as endocannabinoid-like substances that do not elicit cannabinoid receptor activation (e.g. *N*-palmitoylethanolamine, *N*-oleoylethanolamine) have raised interest as anticancerogenic substances. Furthermore, the endocannabinoid-degrading enzymes fatty acid amide hydrolase and monoacylglycerol lipase, lipid transport proteins of the fatty acid binding protein family, additional cannabinoid-activated G protein-coupled receptors, members of the transient receptor potential family as well as peroxisome proliferator-activated receptors have been considered as targets of antitumoral cannabinoid activity. Therefore, this review focused on the antitumorigenic effects induced upon modulation of this extended endocannabinoid network.

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Introduction

Endocannabinoid action has been primarily defined by the two endocannabinoids *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) and the cannabinoid receptors CB_1 and CB_2. Currently, the definition of the endocannabinoid system is becoming expanded on several levels. Accordingly, besides the classical cannabinoid receptors and endocannabinoids, the current extended definition of the endocannabinoid system encompasses other fatty acid derivatives such as 2-arachidonoyl glyceryl ether (noladin ether, 2-AGE), *O*-arachidonoylethanolamine (virodhamine), *N*-arachidonoyldopamine (NADA), oleic acid amide (oleamide, OA) as well as other non-CB G protein-coupled receptors such as GPR55, members of the transient receptor potential (TRP) family, e.g. transient receptor potential vanilloid 1 (TRPV1), and peroxisome proliferator-activated receptors (PPARs) (for review see Iannotti et al. 2016). In addition, proven to take part in the complex endocannabinoid signaling network are endocannabinoid-synthesizing enzymes such as the AEA-synthesizing enzymes *N*-acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), α/β-hydrolase domain-containing protein 4 (ABDH4), glycerophosphodiesterase-1 (GDE1), tyrosine–protein phosphatase non-receptor type 22 (PTPN22), and the 2-AG-producing diacylglycerol lipase-α and -β (DAGLα and -β) as well as degrading enzymes of AEA and 2-AG, fatty acid amide hydrolase [FAAH], and of 2-AG, monoacylglycerol lipase [MAGL] (for review see Di Marzo 2009; Petrosino and Di Marzo 2010). The components of the "classical" as well as expanded endocannabinoid system are indicated in Figure 1 and will be explained in the respective chapters accordingly. Moreover, an overview of transport as well as degradation pathways of endocannabinoids is provided in Figure 2.

Initial investigations concerning tumor-regressive effects of cannabinoid compounds were published in 1975 (Munson et al. 1975) long before the discovery of the endocannabinoid system. In this early study, Δ^8-tetrahydrocannabinol and Δ^9-tetrahydrocannabinol (THC) as well as cannabinol (CBN) were found to suppress tumor growth in a murine Lewis lung

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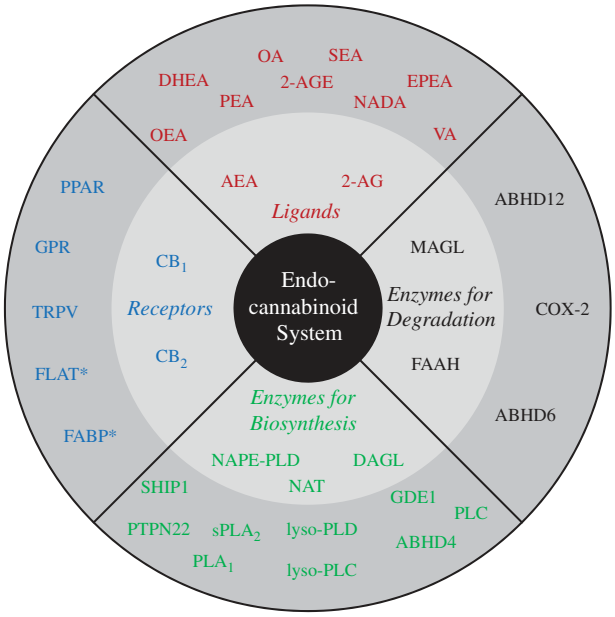

Figure 1. Components of the endocannabinoid system. The inner circle (light gray) represents the 'classical' endocannabinoid system. The outer circle (dark gray) includes components of the extended endocannabinoid system. * FLAT and FABP are transport proteins of endocannabinoids and endocannabinoid-like substances, respectively. 2-AG: 2-arachidonoylglycerol; 2-AGE: noladin ether, 2-arachidonoyl glyceryl ether; ABHD4, 6 and 12: α/β-hydrolase domain-containing protein 4, 6 and 12; AEA: *N*-arachidonoylethanolamine, anandamide; CB_1 and CB_2: cannabinoid receptors type-1 and -2; COX-2: cyclooxygenase-2; DAGL: diacylglycerol lipase; DHEA: *N*-docosahexaenoylethanolamine; EPEA: *N*-eicosapentaenoylethanolamine; FAAH: fatty acid amide hydrolase; FABP: fatty acid binding protein; FLAT: FAAH-like anandamide transporter; GDE1: glycerophosphodiester phosphodiesterase 1; GPR: G protein-coupled receptor; MAGL: monoacylglycerol lipase; NADA: *N*-arachidonoyldopamine; NAPE-PLD: *N*-acyl-phosphatidylethanolamine-specific phospholipase D; NAT: *N*-acyltransferase; OA: oleamide; OEA: *N*-oleoylethanolamine; PEA: *N*-palmitoylethanolamine; PLA_1: phospholipase A_1; PLC: phospholipase C; PLD: phospholipase D; PPAR: peroxisome proliferator-activated receptor; PTPN22: tyrosine-protein phosphatase non-receptor type 22; SHIP1: phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1; SEA: *N*-stearoylethanolamine; $sPLA_2$: soluble phospholipase A_2; TRPV: transient receptor potential vanilloid type; VA: virodhamine, *O*-arachidonoylethanolamine.

adenocarcinoma model. In agreement with these *in vivo* results, THC was later proven as inhibitor of DNA synthesis in Lewis lung carcinoma cells (White et al. 1976). Initial studies that investigated the role of cannabinoid receptors for growth inhibition of cancer cells were presented in 1998 (De Petrocellis et al. 1998). In subsequent years, anticancer effects of cannabinoids were confirmed by *in vitro* and *in vivo* studies (Galve-Roperh et al. 2000; Guzmán et al. 2001; Gómez del Pulgar et al. 2002). Particularly, in the decade 2000–2010, massive work was done by various groups worldwide at the preclinical level.

Concerning the clinical use of cannabinoid compounds in cancer therapy, nabilone was reported to be superior to prochlorperazine in the treatment of chemotherapy-induced emesis in the late 1970s (Herman et al. 1979) and has therefore been used as second-line antiemetic drug. Thus, today, capsules of THC and nabilone, a synthetic analog of THC, are approved for treatment of chemotherapy-induced emesis. Besides such palliative applications, only one clinical pilot study published in 2006 addressed probable curative effects, and indicated intracranially administered THC to be safe in glioblastoma patients (Guzmán et al. 2006). A recent explorative phase II study with recurrent glioblastoma patients revealed combined treatment of dose-intense temozolomide with a combination of the phytocannabinoids THC and cannabidiol (CBD) as add-on to confer a median survival of >550 d versus 369 d in the temozolomide + placebo group and a significantly higher 1 year survival rate in the cannabinoid group (83% versus 53% in the placebo cohort) (GWP 2017). Meanwhile, accumulating preclinical data further suggest beneficial effects for cancer therapies to be caused by modulation of a variety of components of the non-canonical endocannabinoid system. The present review, therefore, focusses on anticancerogenic effects by modulating pharmacotherapeutic targets of the endocannabinoid system also beyond the early definition.

The endocannabinoid system

Classical cannabinoid receptors

The inhibitory effect of cannabimimetic drugs such as THC on intracellular cyclic adenosine monophosphate (cAMP) production was already discovered in the middle of the 1980s with investigations from Allyn Howlett (Howlett 1984, 1985, 1986) that resulted in the concept of a cannabinoid receptor in neuronal cells (Devane et al. 1988). The scientific interest in cannabinoid action was further increased with cloning and expression of a central seven-transmembrane G protein-coupled cannabinoid receptor, referred to as CB_1 (Matsuda et al. 1990), followed by the molecular characterization of a peripheral cannabinoid receptor expressed on spleen and blood cells and referred to as CB_2 (Munro et al. 1993). Notably, at that time, these discoveries had already put forward the hypothesis of endogenously synthesized substances that activate these receptors as 'endocannabinoids' (Di Marzo et al. 1994). Among the two cannabinoid receptors, CB_1 was found to be predominantly expressed in the mammalian brain

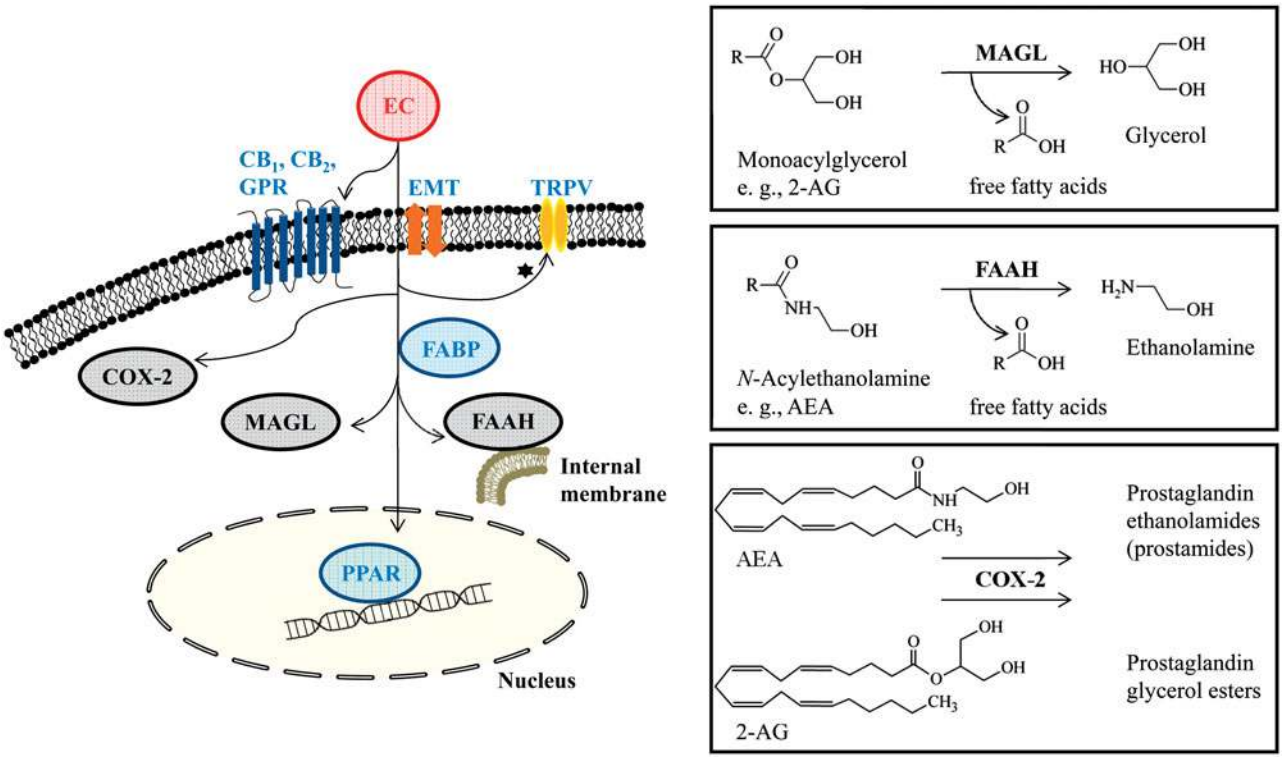

Figure 2. Signaling and degradation pathways of endocannabinoids in the extended endocannabinoid system. Left: *studies have suggested an intracellular binding site for capsaicin as well as AEA at the TRPV1 (Jung et al. 1999; Ross 2003). Right: chemistry of three different degradation pathways of endocannabinoids. CB_1 and CB_2: cannabinoid receptors type-1 and -2; COX-2: cyclooxygenase-2; EC: endocannabinoid; EMT: endocannabinoid membrane transporter; FAAH: fatty acid amide hydrolase; FABP: fatty acid binding protein; GPR: G protein-coupled receptor; MAGL: monoacylglycerol lipase; PPAR: peroxisome proliferator-activated receptor; TRPV: transient receptor potential vanilloid type.

(Herkenham et al. 1990). As functional consequence of a pertussis toxin-sensitive $G_{i/o}$ protein coupling, activation of CB_1 was shown to be linked to inhibition of adenylyl cyclase activity, conferring intracellular reduction of cAMP levels (Das et al. 1995) and to inhibition of N-type voltage-dependent calcium channels (Pan et al. 1996). Similar effects on cAMP levels were obtained from experiments addressing the mode of intracellular action induced upon CB_2 receptor activation. Accordingly, a pertussis toxin-sensitive inhibition of forskolin-induced cAMP production was found to be mediated via CB_2 receptor activation (Slipetz et al. 1995). As a specific CB_1-associated effect, a pertussis toxin-sensitive increased activation of the inactivating potassium A currents near resting levels of hippocampal neurons was described in the 1990s (Deadwyler et al. 1993). Other early investigations found further differences between the two receptors regarding their specific susceptibility toward different substances. Accordingly, inhibition of adenylyl cyclase activity in CB_2-overexpressing Chinese hamster ovarian cells could not, or could only marginally, be proven for AEA and THC (Bayewitch et al. 1995).

Endocannabinoids and endocannabinoid-like substances

Within the first half of the 1990s, AEA and 2-AG (Figure 3) were identified as endogenously synthesized fatty acid derivatives acting at cannabinoid-activated receptors (Devane et al. 1992; Mechoulam et al. 1995). On the one hand, AEA is a partial agonist at the CB_1 receptor with high affinity comparable with the phytocannabinoid THC (Devane et al. 1992; Mackie et al. 1993; Sugiura et al. 1999; Di Marzo and De Petrocellis 2012). On the other hand, AEA was shown to be an almost inactive agonist at the CB_2 receptor in some studies (Gonsiorek et al. 2000; Sugiura et al. 2000; Di Marzo and De Petrocellis 2012). In contrast, 2-AG acts as a full agonist with a moderate affinity at both CB receptors (Sugiura et al. 1999; Gonsiorek et al. 2000; Sugiura et al. 2000; Savinainen et al. 2001). The endocannabinoids *N*-homo-y-linolenylethanolamine and *N*-7,10,13,16-docosatetraenylethanolamine (Figure 3) were also demonstrated to bind to the CB_1 receptor with similar K_i values in a centrifugation-based ligand binding assay as AEA (Hanus et al. 1993).

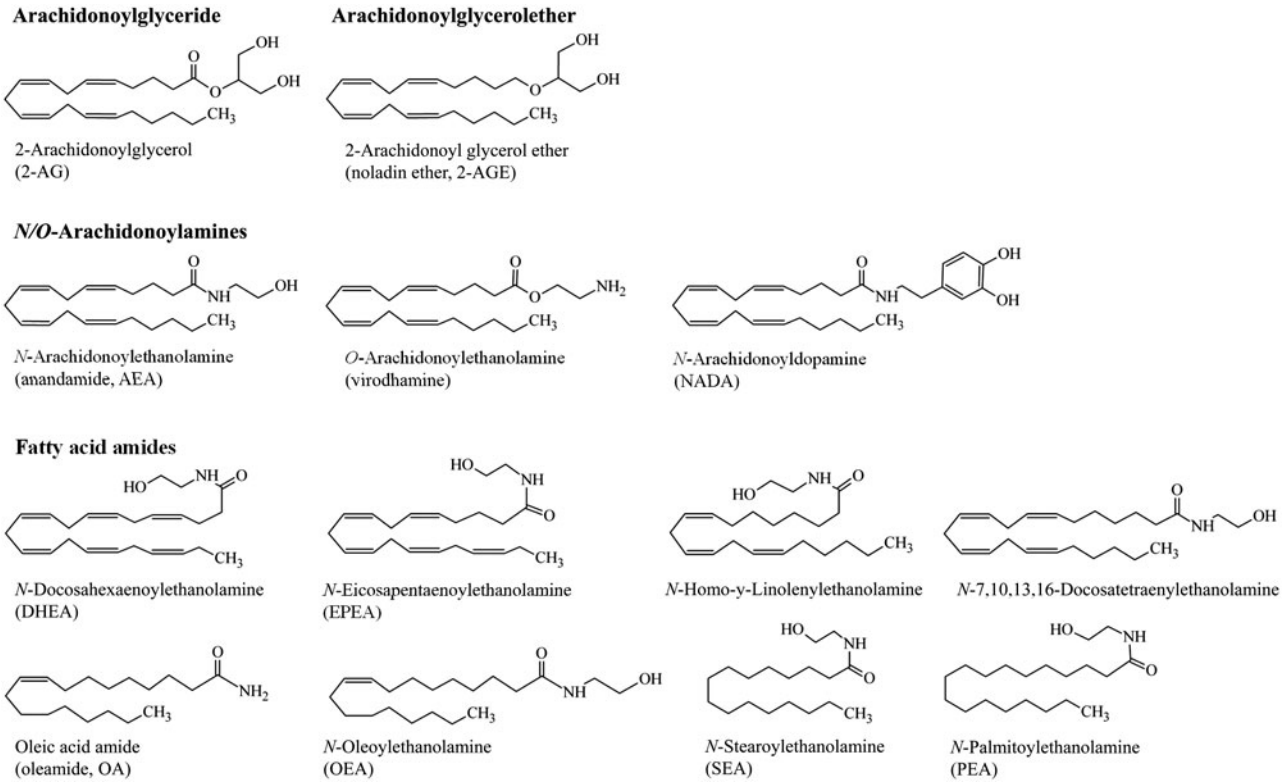

Figure 3. Chemical structures of endocannabinoids and endocannabinoid-like substances. Components are classified into groups depending on their chemical background.

NADA, virodhamine and noladin ether were synthesized and subsequently characterized as additional endocannabinoids at the beginning of the twenty-first century (Figure 3) (Bisogno et al. 2000; Hanus et al. 2001; Huang et al. 2002; Porter et al. 2002). NADA was initially described as a cannabinoid receptor agonist with a 40-fold higher affinity to CB_1 as compared to CB_2 (Bisogno et al. 2000). In contrast to these findings, another recent study found NADA as an ineffective agonist at the CB_1 receptor as assessed by analyses of CB_1 receptor-mediated activation of potassium channels or p42/44 mitogen-activated protein kinase (MAPK) phosphorylation in different cellular models but to promote mobilization of calcium via Gq-dependent processes (Redmond et al. 2016). Moreover, NADA was shown to increase the intracellular calcium concentration via binding at TRPV1 (Huang et al. 2002). Furthermore, NADA was identified as an effective inhibitor of MAGL (Björklund et al. 2010). As a substrate for FAAH (Bisogno et al. 2000), NADA exerts a lower hydrolysis rate as compared with AEA. Data of the latter study further suggested the inhibitory action of NADA on FAAH to be due to a competitive mechanism thereby leading to increased concentrations of other endocannabinoids and endocannabinoid-like substances (Bisogno et al. 2000).

Noladin ether, a structural ether analog of 2-AG (Figure 3), possesses a higher stability than 2-AG bearing an ester structure (Hanus et al. 2001). Concerning receptor affinities, noladin ether was found to be a CB_1 receptor agonist, while acting as weak CB_2 receptor and partial TRPV1 agonist (Hanus et al. 2001; Duncan et al. 2004). Noladin ether could be detected in rat and porcine brain (Hanus et al. 2001; Fezza et al. 2002). However, Oka et al. (2003) could not detect endogenous noladin ether in brains of various mammalian species, thereby raising a controversial debate on its role as endogenous cannabinoid receptor ligand.

Virodhamine, an ester derivative of arachidonic acid (AA) and ethanolamine, was shown to act as CB_1 receptor antagonist and CB_2 receptor agonist (Porter et al. 2002). A non-enzymatic transformation of *N*-acylethanolamines into the corresponding *O*-acyl esters and vice versa was reported to be catalyzed by bases as well as acids (Markey et al. 2000). De Petrocellis et al. (2004) have suggested a switch from CB_1- to CB_2-mediated responses and vice versa by the conversion of AEA into virodhamine, and by virodhamine into AEA, respectively. In a further investigation, virodhamine has been shown to inhibit the activity of FAAH in a concentration-dependent manner (Steffens et al. 2005). The authors of this study further suggested that, similar to

2-AG, virodhamine serves as substrate hydrolyzed by MAGL. Later Brantl et al. (2014) provided evidence for 2-AG and virodhamine as probable enzymatic substrates of MAGL. In fact, both endocannabinoids were demonstrated to elicit platelet activation which resembled AA-induced aggregation and was blocked by the cyclooxygenase-1 (COX-1) inhibitor acetylsalicylic acid and by a thromboxane A_2 receptor antagonist accordingly. Moreover, platelet activation by 2-AG and virodhamine was inhibited by the MAGL inhibitor JZL184, suggesting both endocannabinoids to stimulate platelets via a MAGL-triggered mechanism leading to free AA and its COX-1-dependent metabolism to proaggretory thromboxane A_2 (Brantl et al. 2014). Finally, AEA, 2-AG, NADA, noladin ether, and virodhamine have been identified as GPR55 agonists (Ryberg et al. 2007; Akimov et al. 2017).

Brown et al. (2010) have suggested that *N*-docosahexaenoylethanolamine (DHEA) as well as *N*-eicosapentaenoylethanolamine (EPEA) likewise act as endocannabinoids (Figure 3). In fact, both compounds were shown to activate CB_1 and CB_2 receptors *in vitro* with a significant potency. However, other studies also demonstrated cannabinoid receptor-independent effects for DHEA and EPEA (Rovito et al. 2013; Park et al. 2016). Therefore, DHEA and EPEA will be discussed in context with antitumorigenic effects of endocannabinoid-like substances that do not elicit cannabinoid receptor activation such as *N*-palmitoylethanolamine (PEA), *N*-oleoylethanolamine (OEA), *N*-stearoylethanolamine (SEA), and OA (Bisogno et al. 1998; Maccarrone et al. 2002) (Figure 3).

Further cannabinoid targets

In recent years, a number of additional receptors have been identified as targets of cannabinoid compounds. Among these, several ion channels of the TRP family, as well as G protein-coupled orphan receptors have emerged as initial platforms of diverse cannabinoid effects. Furthermore, intracellular receptors, such as members of the PPAR family, have been shown to be involved in cannabinoid action.

TRP channels

TRP channel interactions with cannabinoid compounds have been investigated thoroughly during recent decades. Thus, TRP channels have been assigned as 'ionotropic cannabinoid receptors' (Di Marzo et al. 2002). Within this group of ion channels, TRPV1 has been reported as additional receptor for AEA (Zygmunt et al. 1999) and CBD (Bisogno et al. 2001; Ligresti et al. 2006). In recent years, TRPV2 was identified as target for CBD (Qin et al. 2008; Nabissi et al 2013) and THC (De Petrocellis et al. 2011). In addition, TRPV3 activation was proven for CBD and tetrahydrocannabivarin (THCV), whereas TRPV4 was shown to be activated by THCV and cannabidivarin (CBDV) (De Petrocellis et al. 2012). The latter study further found the cannabinoid compounds cannabigerovarin and cannabigerolic acid to desensitize TRPV3 and TRPV4. TRP channels of the ankyrin type-1 (TRPA1) were identified as targets of cannabigerol (CBG), CBD, and CBN (De Petrocellis et al. 2008). Another TRP channel susceptible to cannabinoid action is the TRP channel of melastatin type-8, which was found to be activated upon treatment with CBD, CBG, THC acid, and CBN (De Petrocellis et al. 2008).

G protein-coupled receptors

In recent years, several G protein-coupled receptors (GPR) have been deorphanized as cannabinoid-activated receptors. Thus, accumulating data revealed the GPR55 as important cannabinoid target. Besides activation by lysophosphatidylinositol (LPI), GPR55 has been described to be activated upon stimulation with the cannabinoids abnormal CBD (abn-CBD), a synthetic regioisomer of CBD, O-1602 (specific GPR55 agonist), R(+)-methanandamide (hydrolysis-stable analog of AEA), JWH-015 (specific CB_2 receptor agonist), and THC (Johns et al. 2007; Lauckner et al. 2008). In this context, Ryberg et al. (2007) presented a comprehensive analysis monitoring GTPγS binding in GPR55-overexpressing cells allowing a comparison of GPR55-activating properties among different cannabinoids. In this study, CBD was found to act antagonistic at the GPR55, whereas AEA and virodhamine elicited agonistic activities at this receptor. Recently, *N*-arachidonoylglycine (NAGly), a derivative of AEA that lacks affinity to cannabinoid receptors (Sheskin et al. 1997), and THC have been shown to act as agonists at GRP55 in the microglial cell line BV-2 (McHugh et al. 2014). In contrast to CB_1 and CB_2, which have been described as $G_{i/o}$ protein-coupled receptors, GPR55 was demonstrated to elicit intracellular action via G_q protein coupling (Lauckner et al. 2008).

Despite apparent discrepancies in the literature concerning cannabinoid-induced GPR18 activation, some data provide evidence for this orphan receptor as a further cannabinoid-triggered target. NAGly, O-1602, abn-CBD, THC, and AEA have been described as GPR18 agonists in GPR18-overexpressing HEK293 cells accordingly (McHugh et al. 2012). Notably, NAGly action at GPR18 was shown to appear in a pertussis toxin-sensitive manner via inhibition of forskolin-induced cAMP production similar to cannabinoid receptors (Kohno et al. 2006). Recently, CBD was found to antagonize NAGly- and

THC-induced GPR18 activation (McHugh et al. 2014). However, these findings have been evaluated critically due to studies that could not confirm ligand-elicited GPR18 signaling responses by NAGly (Finlay et al. 2016). Furthermore, a number of investigations presented data that clearly contradict the findings of GPR18 as a target of NAGly, AEA and abnCBD (Yin et al. 2009; Lu et al. 2013; Finlay et al. 2016).

Concerning further GPR family members, GPR119 was found to be triggered by the endocannabinoid-like substances OEA and PEA (Overton et al. 2006). Moreover, NAGly has been described as a ligand at GPR92 (Oh et al. 2008). Finally, a recent publication has provided evidence for CBD to act as an inverse agonist at GPR12 (Brown et al. 2017).

Members of the PPAR family

Several studies have found the endocannabinoid-like substances EPEA, DHEA, SEA, OEA, and PEA to be agonists at PPARα (Fu et al. 2003; Lo Verme et al. 2005; Artmann et al. 2008; Tellez et al. 2013). In this context, OEA was reported to induce satiety and to reduce body-weight gain via PPARα activation (Fu et al. 2003). In addition, PEA was reported to exert its anti-inflammatory effects via PPARα (Lo Verme et al. 2005). Concerning the effect of phytocannabinoids such as THC on PPARα, the current literature provides conflicting data. On the one hand, THC, although devoid of binding affinity, was shown to upregulate and to enhance the basal transcriptional activity of PPARα in breast cancer cells (Takeda et al. 2014). On the other hand, THC failed to induce transcriptional activity of PPARα in cervical carcinoma cells (Sun et al. 2007). Notably, the latter study revealed other cannabinoids, such as WIN55,212–2, AEA, OEA, virodhamine, and noladin ether to significantly increase transcriptional activity of PPARα in luciferase reporter assays.

THC has been described as agonist at PPARγ, thereby causing vasorelaxation (O'Sullivan et al. 2005, 2006) as well as antiproliferative effects on hepatocellular carcinoma cells *in vitro* and *in vivo* (Vara et al. 2013). A vasorelaxant effect causally linked to binding and activating of PPARγ was further confirmed for CBD (O'Sullivan et al. 2009). Furthermore, AEA was demonstrated to activate PPARγ thereby conferring the differentiation of fibroblast into adipocytes (Bouaboula et al. 2005).

Other studies provided evidence for an indirect activation of PPARγ by cannabinoid-induced cyclooxygenase-2 (COX-2) expression and subsequent prostaglandin (PG)-evoked PPARγ activation. Accordingly, in lung cancer cells, a cytosol-to-nucleus-translocation of PPARγ was found to be caused by CBD via enhanced COX-2-dependent production of PGD_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 (Ramer et al. 2013). A similar pathway involving PPARγ-activating PGs has been reported for the cannabinoid R(+)-methanandamide (Eichele et al. 2009).

Biosynthesizing enzymes

Nowadays, a two-step pathway, assigned as transacylation-phosphodiesterase pathway, is generally accepted for the biosynthesis of AEA and other *N*-ethanolamines (NAEs) (Schmid 2000; Wang and Ueda 2009). In this context, the first reaction step is carried out by *N*-acyltransferases (NATs) that catalyze the *N*-acylation of phosphatidylethanolamine in a calcium-dependent or -independent manner (Jin et al. 2007; Wang and Ueda 2009). The conversion to NAEs is performed either in a second single step reaction by *N*-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) or in sequential steps by α/β-hydrolase domain-containing protein 4 (ABHD4) followed by glycerophosphodiester phosphodiesterase 1 (GDE1) or soluble phospholipase A_2 ($sPLA_2$) and subsequent turnover by lysophospholipase D (lyso-PLD). A further sequential mechanism includes the action of phospholipase C (PLC) and downstream of phosphatases such as PTPN22 and phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1 (SHIP1) (Di Marzo et al. 1994; Sun et al. 2004; Simon and Cravatt 2006; Liu et al. 2008; Simon and Cravatt 2008; Di Marzo and Piscitelli 2015).

2-AG synthesis was discovered to be mediated by cleavage of membrane phospholipids via phospholipase C as well as by the turnover of diacylglycerol (DAG) via DAGLα and -β (Prescott and Majerus 1983; Stella et al. 1997). As a second synthesizing pathway, Sugiura et al. (1995) reported a combined action of phospholipase A_1 (PLA_1) and lyso-PLC. Moreover, 2-AG was described to be also formed from AA-containing lysophosphatidic acid through dephosphorylation (Nakane et al. 2002).

Degradation enzymes

As alternative targets to combat cancer diseases, the main enzymes of endocannabinoid turnover have attracted the interest in recent years. FAAH was discovered as a catabolic enzyme for AEA degradation (Deutsch and Chin 1993) and was shown to likewise hydrolyze 2-AG (Di Marzo et al. 1998; Goparaju et al. 1999). Later, FAAH was further found to degrade the endocannabinoid-like substances OA (Cravatt et al. 1996), OEA and PEA (Desarnaud et al. 1995; Saghatelian et al. 2004). Instead, the major enzyme of 2-AG

degradation is MAGL (Blankman et al. 2007). However, in some cells, ABHD6 and ABHD12 were demonstrated to hydrolyze 2-AG (Blankman et al. 2007). AEA as well as 2-AG were reported to be oxidized by COX-2 and processed by PG synthases to PG ethanolamides (PG-EAs, prostamides) and PG glycerol esters (PG-Gs), respectively (Yu et al. 1997; Kalgutkar et al. 1999; Kozak et al. 2000).

Transport proteins

The mode of action underlying the cellular uptake and transport of endocannabinoids is still a matter of debate (Fowler 2012, 2014; Deutsch 2016). In this context, the FAAH-like anandamide transporter (FLAT), a splice variant of the endocannabinoid degradation enzyme FAAH, heat shock protein 70 (HSP70), albumin as well as members of the fatty acid binding protein (FABP) family have been identified to be involved in the transport of endocannabinoids and endocannabinoid-like substances (Maccarrone et al. 2010; Fu et al. 2011; Fowler 2012).

In recent years, FABPs have been investigated as intracellular carriers that deliver endocannabinoids and endocannabinoid-like substances to their catabolic enzymes. In fact, members of the cytosolic FABP family, which comprises 10 subtypes with a tissue-specific distribution (for review see Thumser et al. 2014), were reported to bind AEA and 2-AG, as well as OEA and PEA (Kaczocha et al. 2009, 2012; Sanson et al. 2014; Huang et al. 2016). Meanwhile, inhibition of some members of the FABP family has been shown to increase endocannabinoid concentrations. Accordingly, a knockout (KO) of liver FABP1 in male mice was shown to increase brain levels of AEA, 2-AG, OEA, and PEA in the animals (Martin, Chung, Landrock, Landrock, Huang, et al. 2016). Interestingly, in another study with female FABP1 KO mice, levels of AEA and 2-AG remained unaltered as compared with wild-type animals, whereas brain levels of PEA and OEA were found to be decreased (Martin, Chung, Landrock, Landrock, Dangott, et al. 2016). Collectively, these data suggest a gender-specific regulation. An *in vitro* study with neuroblastoma cells overexpressing FABP5 demonstrated a potentiated uptake and hydrolysis of AEA (Kaczocha et al. 2009). In another work of the same group, mice lacking FABP5 and FABP7 were shown to possess elevated levels of AEA, PEA, and OEA and to exhibit reduced nociception in different pain models (Kaczocha et al. 2015). Antinociceptive effects were reversed by antagonists to CB_1, PPARα, and TRPV1 in a modality-specific manner. In line with these data, chemically synthesized FABP inhibitors caused antinociceptive effects in rodents in a CB_1- and PPARα-dependent manner associated with elevated brain levels of AEA (Kaczocha et al. 2014), implying FABPs as novel targets for the development of analgesic and anti-inflammatory drugs.

Another possible transport protein for endocannabinoids and endocannabinoid-like substances is FLAT, which was reported to be located in the cytosol as well as in the membrane (Fu et al. 2011). In line with this notion, the FLAT inhibitor ARN272 has been shown to increase AEA plasma concentration in mice and to decrease intracellular AEA concentration in cortical neurons (Fu et al. 2011).

Antitumorigenic effects associated with the endocannabinoid system

An overwhelming number of studies have shown antitumorigenic effects induced by endocannabinoids and activation of the endocannabinoid system. In the following chapters the outcome of selected investigations in this field will be presented accordingly. However, in this context, it is likewise worthy to note that some studies also reported a protumorigenic impact of cannabinoids on cancer cells *in vitro* and *in vivo* with the respective data being reviewed recently (Ramer and Hinz 2016).

Regulation of cannabinoid receptors and endocannabinoids in cancer tissue

Several studies have provided evidence for an upregulation of cannabinoid receptors in cancer tissue (for review see Ramer and Hinz 2016). In addition, correlation analyses revealed a link between high CB_1 receptor expression and poor prognosis in terms of pancreatic (Michalski et al. 2008), prostate (Chung et al. 2009), ovarian (Messalli et al. 2014), and colorectal cancer (Jung et al. 2013). For HER2-positive breast cancer (Pérez-Gómez et al. 2015) as well as for head and neck squamous cell carcinoma (Klein Nulent et al. 2013), an association between a high CB_2 receptor expression and poor patients' outcome was published recently. An overview of the regulations of cannabinoid receptors in malignant tissues is given in Table 1.

The majority of data concerning the levels of endocannabinoids in cancer (summarized in Table 2) suggest these fatty acid derivatives to be upregulated in malignancies when compared to healthy tissue. Thus, AEA and 2-AG were found elevated in adenomatous polyps and in colorectal carcinomas compared to the tissues of the respective neighboring healthy mucosa (Ligresti et al. 2003). Other cancer entities reported to contain enhanced levels of endocannabinoids are prostate cancer (Schmid et al. 2002; Nithipatikom et al. 2004), pituitary adenomas (Pagotto et al. 2001), and colorectal

Table 1. Regulation of cannabinoid receptors in cancer tissues sorted by chronological order of the publications.

Receptor	Regulation	Association with patients' prognosis	Tumor	References
CB_2	↑	Markedly enhanced in grade IV glioblastomas compared with CB_1	Glioblastoma	Sánchez et al. (2001)
CB_1	↑	n.d.	Mantle cell lymphoma	Islam et al. (2003)
CB_2	↑	Grade III versus I-II ER-negative versus ER-positive PR-negative versus PR-positive HER2-positive versus negative	Breast cancer	Caffarel et al. (2006)
CB_1, CB_2	↔	Unrelated to malignancy	Glioblastoma	Held-Feindt et al. (2006)
CB_1	↑ (45%)	Disease-free survival significantly better	Hepatocellular carcinoma	Xu et al. (2006)
CB_2	↑ (52%)	with high versus low CB_1 and CB_2		
CB_1	↓	Significant relationship between low CB_1 receptor expression and longer survival	Pancreatic cancer	Michalski et al. (2008)
CB_1	↓	Downregulation of CB_1 receptor in grade II–III	Colon carcinoma	Wang et al. (2008)
CB_2	↔	Unrelated to malignancy		
CB_1	↑	Associated with severity and outcome	Prostate cancer	Chung et al. (2009)
CB_2	↑	n.d.	Endometrial cancer	Guida et al. (2010)
CB_1	↔			
CB_1	↓	n.d.	Clear cell renal carcinoma	Larrinaga et al. (2010)
CB_1, CB_2	↑	Associated with advanced stages	Glioblastoma	Wu et al. (2012)
CB_1	↓[a]	(i) In stage IV colorectal cancer, high versus low CB_1 expression correlated with a poorer overall survival (ii) In stage I/II or III following surgery no association with patients´ survival	Colorectal cancer	Jung et al. (2013)
CB_2	↑	Associated with reduced disease-specific survival and reduced overall survival	Head and neck squamous cell carcinoma	Klein Nulent et al. (2013)
CB_1	↔	Unrelated to malignancy		
CB_1	↑	n.d.	Colorectal cancer	Chen et al. (2015)
CB_2	↔			
CB_1	↑	Associated with increased malignancy	Ovarian cancer	Messalli et al. (2014)
CB_1	↑	Correlates with Gleason score	Prostate cancer	Fowler (2015)
CB_1	↑	n.d.	Hepatocellular carcinomas	Mukhopadhyay et al. (2015)
CB_2	↑	Association between elevated CB_2 expression in HER2-positive breast tumors and poor patient prognosis	Breast cancer	Pérez-Gómez et al. (2015)
CB_2	↑	n.d.	Bladder cancer	Bettiga et al. (2017)
CB_1	↔			

[a]Low CB_1 more frequently in stage IV than in stages I–III; ↔: not regulated; ↑: upregulated; ↓: downregulated; n.d.: not determined; CB_1 and CB_2: cannabinoid receptors of type-1 and -2; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor.

cancer (Chen et al. 2015). An upregulation of 2-AG was also shown in meningiomas and glioblastomas (Petersen et al. 2005). Interestingly, an early investigation by Maccarrone et al. (2001) showed lower levels of AEA, OEA, PEA, SEA but not of 2-AG in human meningiomas and gliomas. Taken together, elevated levels of cannabinoid receptors seem to exhibit a tendency to adverse outcome for cancer patients. However, cannabinoid receptors as well as endocannabinoids are not uniformly upregulated in malignant tissue and thus do not serve as reliable disease markers.

Regulation of the degradation enzymes FAAH and MAGL

In the majority of the currently available studies, FAAH and MAGL levels were found to be elevated in cancer versus healthy tissues. Endsley et al. (2008) have reported higher expression levels of FAAH in prostate cancer. In another study, a correlation between FAAH expression and disease severity has been identified (Thors et al. 2010). Increased levels of MAGL were reported in ovarian tumors as well as in colorectal cancer tissues (Nomura et al. 2010; Ye et al. 2011). On the one hand, a recent publication revealed MAGL and 2-AG to be strongly upregulated in colorectal cancer tissues (Pagano et al. 2017). Furthermore, elevated expression of MAGL was likewise reported in ductal breast tumors compared with less malignant breast tumors (Gjerstorff et al. 2006). However, high-expression levels of both enzymes correlated with a positive survival prognosis in pancreatic ductal adenocarcinomas (Michalski et al. 2008). On the other hand, Wu et al. (2012) have identified a downregulation of FAAH and MAGL in glioma versus healthy tissue, as well as a lower concentration of the synthesizing enzyme NAPE-PLD and unchanged concentrations of DAGL, resulting in decreased AEA and increased 2-AG concentrations. Another study found a downregulation of MAGL in endometrial carcinoma compared with healthy tissue

Table 2. Regulation of endocannabinoids and endocannabinoid-like substances in cancer tissues sorted by chronological order of the publications.

Endocannabinoid	Regulation	Association with patients' prognosis	Tumor	References
AEA	↓	n.d.	Meningioma, glioma	Maccarrone et al. (2001)
OEA	↓			
PEA	↓			
SEA	↓			
AEA	↑	n.d.	Pituitary adenomas	Pagotto et al. (2001)
2-AG	↑			
2-AG	↑	n.d.	Colorectal carcinoma	Ligresti et al. (2003)
AEA	↑			
AEA	↑	n.d.	Gliomas (grade IV)	Petersen et al. (2005)
2-AG	↑		Meningiomas (grade I)	
2-AG	↑	n.d.	Endometrial carcinoma	Guida et al. (2010)
AEA	↓	Associated with advanced stages	Glioma	Wu et al. (2012)
2-AG	↑			
PEA[a]	↑	Significantly correlated with	Various cancers	Sailler et al. (2014)
OEA[a]	↑	the number of metastases		
AEA	↑	n.d.	Colorectal cancer	Chen et al. (2015)
AEA	↑	n.d.	Hepatocellular carcinomas	Mukhopadhyay et al. (2015)
2-AG[b]	↑	n.d.	Diffuse large B-cell lymphoma	Zhang et al. (2016)

↑: upregulated; ↓: downregulated. Non-regulations of endocannabinoids reported in the cited publications are not listed. 2-AG: 2-arachidonoylglycerol; AEA: *N*-arachidonoylethanolamine, anandamide; OEA: *N*-oleoylethanolamine; PEA: *N*-palmitoylethanolamine; SEA: *N*-stearoylethanolamine.
[a]Measured in patients' plasma.
[b]Measured in patients' serum.

(Guida et al. 2010). The mRNA levels of NAPE-PLD as well as of FAAH were further found to be increased in colorectal cancer tissue (Chen et al. 2015). Due to these opposite results obtained in different tumor entities, a functional contribution of FAAH and MAGL regulations as well as of endocannabinoid-synthesizing enzymes to cancer progression is still unclear. Monitoring of these molecules does therefore not provide a reliable prognosis of the disease.

Antitumorigenic effects of endocannabinoids

Antitumorigenic action of AEA

A number of studies provide evidence for endocannabinoids to counteract tumor progression (for review see Petrosino and Di Marzo 2010). An overview of antitumorigenic mechanisms and actions of endocannabinoids is given in Table 3.

In this context, AEA was found to elicit CB_1 receptor-dependent antiproliferative effects on nerve growth factor-challenged breast cancer cells (De Petrocellis et al. 1998). An antiproliferative impact of AEA was later confirmed using glioma (Jacobsson et al. 2000, 2001) and colon carcinoma cells (Ligresti et al. 2003). Other tumor entities that were found to be susceptible for AEA's CB_1 receptor-dependent antiproliferative action are prostate cancer cell lines activated with epidermal growth factor (Mimeault et al. 2003) as well as breast cancer cells (Laezza et al. 2006). A recent publication could further demonstrate AEA to inhibit tumor cell invasion and to elicit an antimetastatic effect on lung cancer cells *in vivo* (Winkler et al. 2016). In the latter study, the anti-invasive effect of AEA was found to be causally linked to AEA-induced upregulation of tissue inhibitor of matrix metalloproteinases-1 (TIMP-1). Furthermore, AEA was found to elicit apoptosis of human gastric adenocarcinoma (Ortega et al. 2016), colorectal cancer (Patsos et al. 2010), as well as head and neck squamous cell carcinoma cells (Park et al. 2015). In terms of melanoma cells, a contribution of the CB_1 receptor to AEA's proapoptotic effect could be proven (Adinolfi et al. 2013).

In addition, stable analogs of AEA were found to confer inhibition of cancer cell growth and spread. As such, arachidonoyl-2′-chloroethylamide (ACEA) revealed antiproliferative properties on colorectal carcinoma cells (Ligresti et al. 2003). Moreover, R(+)-methanandamide was demonstrated to induce apoptosis in cervical and lung cancer cell lines (Eichele et al. 2009) and glioma cells (Hinz et al. 2004a; Eichele et al. 2006). Notably, these proapoptotic effects of R(+)-methanandamide on cervical cancer (Eichele et al. 2009) and glioma cells (Hinz et al. 2004a) were not sensitive toward antagonists of cannabinoid receptors as well as TRPV1. On the contrary, R(+)-methanandamide-induced apoptosis of mantle cell lymphoma cells was found to depend on activation of both CB_1 and CB_2 receptors (Gustafsson et al. 2006). A recent study was further able to demonstrate AEA as well as R(+)-methanandamide to confer a proapoptotic action on prostate cancer cells via CB_1 (Orellana-Serradell et al. 2015).

Whereas the proapoptotic effects of R(+)-methanandamide on glioma cells were found to be mediated via lipid raft microdomains bypassing cannabinoid

Table 3. Growth inhibitory action of endocannabinoids and synthetic derivatives sorted by chronological order of the publications.

Substance	Receptor/pathway	Impact on cell fate	Cancer cell type	References
AEA	CB_1	Proliferation ↓	*Breast cancer cells:* EFM-19, MCF-7	De Petrocellis et al. (1998)
2-AG R(+)-methanandamide	n.d.	Proliferation ↓	*Breast cancer cells:* EFM-19	
AEA	CB_1/Raf-translocation↑, p42/44 MAPK ↑, prolactin receptor ↓, trk NGF receptor ↓	Proliferation ↓	*Breast cancer cells:* MCF-7	Melck et al. (1999)
AEA	Superoxide anion production ↑, activation of PP32-like protease ↑, CB receptors n.d.	Proliferation ↓	*Pheochromocytoma cells:* PC-12	Sarker et al. (2000)
Met-F-AEA	CB_1	Proliferation ↓	*K-ras transformed rat thyroid epithelial cells:* KiMol	Bifulco et al. (2001)
AEA 2-AG	CB_1,CB_2 and TRPV1, ceramide ↑	Proliferation ↓	*Rat glioma cells:* C6	Jacobsson et al. (2001)
AEA 2-AG ACEA AEA 2-AG	CB_1 n.d.	Proliferation ↓	*Differentiating colon carcinoma cells:* CaCo-2 *Non-differentiating colon carcinoma cells:* DLD-1	Ligresti et al. (2003)
AEA	CB_1, ceramide ↑	Proliferation ↓ apoptosis ↑	*Prostatic cancer cells:* LNCaP, DU145, PC3	Mimeault et al. (2003)
R(+)-methanandamide	Independent of CB_1, CB_2 and TRPV1, ceramide ↑, COX-2 ↑, PGE_2 ↑	Apoptosis ↑	*Human neuroglioma cells:* H4	Hinz et al. (2004a, 2004b)
R(+)-methanandamide	Depends on COX-2 cytochrom C ↑, caspase-3/-9↑, PARP↑	Apoptosis ↑	*Human neuroglioma cells:* H4	Eichele et al. (2006)
R(+)-methanandamide	CB_1 and CB_2, ceramide ↑, p38 phosphorylation ↑	Apoptosis ↑	*Mantle cell lymphoma cells:* Rec-1	Gustafsson et al. (2006)
Met-F-AEA	CB_1, $p21^{waf}$ ↑, Cdc25A↓, cyclin *E*–Cdk2 kinase complex activation ↓	Proliferation ↓	*Breast cancer cells:* MDA-MB-231	Laezza et al. (2006)
R(+)-methanandamide	Independent of CB_1, CB_2 and TRPV1, ceramide ↑, COX-2 ↑, activation of PPARγ↑	Apoptosis ↑	*Human cervical cancer cells:* HeLa	Eichele et al. (2009)
R(+)-methanandamide	CB_2	Apoptosis ↑	*Prostatic cancer cells:* LNCaP, DU145, PC3	Olea-Herrero et al. (2009)

(*continued*)

Table 3. Continued

Substance	Receptor/pathway	Impact on cell fate	Cancer cell type	References
Met-F-AEA	n.d.	Apoptosis ↑	*Thyroid carcinoma cells:* ARO, FB1	Cozzolino et al. (2010)
	CB_1		*Thyroid carcinoma cells:* NPA, FRO	
	Activation of p53 ↑, $p21^{waf}$ ↑, cyclin A ↓		*Thyroid carcinoma cells:* NPA	
AEA	Independent of CB_1, CB_2, COX-2-dependent	Apoptosis ↑	*Apoptosis-resistant colon cancer cells:* HCT116 $Bax^{-/-}$, SW480, HCA7	Patsos et al. (2010)
AEA	CB_1	Proliferation ↓	*Prostate cancer cells:* PC3	Nithipatikom et al. (2011)
2-AG	n.d.	Proliferation ↑		
2-AG (+ hydrolase inhibitors Diazomethylarachidonoyl ketone, Octylthio-1,1,1-trifluoropropan-2-one)		Proliferation ↓		
Met-F-AEA	PPARγ/RXRα-dependent CB_1 upregulation	Proliferation ↓	*Colorectal cancer cells:* SW620, DLD1	Proto et al. (2012)
AEA	CB_1, COX-2, LOX, lipid rafts	Apoptosis ↑	*Human melanoma cells:* A375	Adinolfi et al. (2013)
AEA 2-AG R(+)-methanandamide	CB_1	Apoptosis ↑	*Prostate cancer cells:* PC3, *Primary prostate cancer cells*	Orellana-Serradell et al. (2015)
AEA 2-AG R(+)-methanandamide	AKT ↓, p42/44 MAPK ↑, BCL-2 ↓, activation of caspase-3 ↑		*Primary prostate cancer cells*	
AEA	reactive oxygen species ↑, independent of CB_1 and TRPV1	Proliferation ↓	*Head and neck squamous cell carcinoma cells:* SNU-1041, SNU-1066, PCI-1	Park et al. (2015)
2-AG R(+)-methanandamide	n.d.	Proliferation ↔		
AEA R(+)-methanandamide	n.d.	Apoptosis ↑	*Gastric adenocarcinoma cells:* AGS	Ortega et al. (2016)

n.d.: not determined; 15d-PGJ_2: 15-deoxy-delta-12,14-prostaglandin J_2; 2-AG: 2-arachidonoylglycerol; ACEA: arachidonoyl-2′-chloroethylamide; AEA: *N*-arachidonoylethanolamine, anandamide; AKT: protein kinase B; BCL-2: B-cell lymphoma 2; CB_1 and CB_2: cannabinoid receptors of type-1 and -2; Cdc25A: cell division cycle 25 homolog A; COX-2: cyclooxygenase-2; Met-F-AEA: 2-methyl-arachidonyl-2'-fluoro-ethylamide; LOX: lipoxygenase; MAPK: mitogen-activated protein kinase; PARP: Poly [ADP-ribose] polymerase; PG: prostaglandin; PGD_2: prostaglandin D_2; PGE_2: prostaglandin E_2; PPAR: peroxisome proliferator-activated receptor; RXR: retinoid X receptor; trk NGF receptor: high affinity nerve growth factor receptor; TRPV: transient receptor potential vanilloid type.

receptors or TRPV1 (Hinz et al. 2004a,b), the inhibitory impact of R(+)-methanandamide on invasion of cervical and lung cancer cells was found to be mediated via CB_1, CB_2, and TRPV1 (Ramer and Hinz 2008). Here a causal link between R(+)-methanandamide-attenuated invasion and a CB_1-, CB_2-, and TRPV1-dependent upregulation of TIMP-1 could be proven in cervical and lung cancer cells.

R(+)-methanandamide was further shown to increase lymphokine-activated killer (LAK) cell-mediated lysis of lung cancer cells via upregulation of intercellular adhesion molecule-1 (ICAM-1) on cancer cell surface (Haustein et al. 2014).

Another stable AEA analog with anticancer properties is 2-methyl-arachidonyl-2'-fluoro-ethylamide (Met-F-AEA). Met-F-AEA was shown to inhibit ras oncogene-dependent tumor growth in a CB_1-dependent manner (Bifulco et al. 2001) and to inhibit tumor angiogenesis and metastasis (Portella et al. 2003). In the latter study, Met-F-AEA inhibited the growth of cancers in a xenograft model using rat thyroid carcinoma and was able to block metastasis of Lewis lung carcinoma in mice. In another investigation, Met-F-AEA was demonstrated to elicit a growth inhibitory action on thyroid cancer cells by activation of p53 and upregulation of $p21^{CIP1/WAF1}$ expression (Cozzolino et al. 2010). The authors of the latter study found CB_1 receptor expression more abundant in cell lines with profound cytotoxic action of Met-F-AEA suggesting a contribution of CB_1 to these growth inhibitory effects. A CB_1-dependent antiproliferative effect of Met-F-AEA was later confirmed in colorectal cancer cells (Proto et al. 2012). Moreover, Met-F-AEA was demonstrated to elicit an antimetastatic effect in a murine model of breast cancer metastasis (Grimaldi et al. 2006) and to cause CB_1-dependent antiangiogenic properties (Pisanti et al. 2007).

Antitumorigenic action of 2-AG

Concerning the antitumorigenic action of exogenously added 2-AG, a number of studies revealed an antiproliferative action on several tumor entities. Accordingly, an early investigation found growth inhibitory properties of 2-AG on breast cancer cells via CB_1 receptor activation (Melck et al 2000). Tumor-regressive effects of 2-AG have likewise been reported for colorectal carcinoma (Ligresti et al. 2003) and glioma cells (Jacobsson et al. 2001). Recently, 2-AG was demonstrated to block invasion of lung cancer cells and to elicit antimetastatic effect on lung cancer cells in nude mice (Winkler et al. 2016). Furthermore, 2-AG and its ether derivate (noladin ether) have been described to elicit anti-invasive effects on androgen-independent prostate cancer cell lines (Nithipatikom et al. 2004) and to inhibit proliferation of prostate carcinoma cells (Nithipatikom et al. 2011). Later, the growth inhibitory action of 2-AG on prostate cancer cells could be substantiated and was shown to depend on CB_1-modulated p42/44 MAPK and protein kinase B (AKT) signaling pathways (Orellana-Serradell et al. 2015).

Antitumorigenic action of other endocannabinoids

In addition to the anticancer effects of AEA and 2-AG, two other endocannabinoids, NADA and noladin ether, have been reported to elicit tumor-regressive effects. Nevertheless, studies on their antitumorigenic effects are still rare. NADA was found to inhibit proliferation of breast cancer cells *in vitro* and *in vivo,* while maintaining the effects of 'classical' cannabinoids, such as hypothermia, hypolocomotion, catalepsy, and analgesia (Bisogno et al. 2000). Moreover, NADA and other *N*-acyl-dopamines were shown to act as profound antiproliferative and cell death-inducing agents in human osteosarcoma, neuroblastoma, breast adenocarcinoma, lymphoma, and leukemia cell lines (Akimov et al. 2015). Concerning the underlying mechanism, NADA was found to confer a CB_1-dependent antiproliferative effect on colorectal carcinoma cells (Ligresti et al. 2003) and to induce cell death via oxidative stress in pheochromocytoma cells (Ashba et al. 2016). In another study using pheochromocytoma cells, NADA-induced cell death was suppressed by a GPR55 antagonist (Akimov et al. 2017). Finally, NADA was demonstrated to confer neuroblastoma cell death via TRPV1 (Davies et al. 2010) and to inhibit oncogenic signaling of rat sarcoma (RAS) in myeloid leukemia cell lines by an as yet unknown mechanism (Wu et al. 2017).

Noladin ether inhibited proliferation of prostate cancer cells via nuclear factor (NF)-κB/cyclin D- and cyclin E-dependent pathways, thereby inducing a cell-cycle arrest to the G_0/G_1 phase (Nithipatikom et al. 2011). The same group has shown an anti-invasive effect of noladin ether, which was mediated by a downregulation of protein kinase A activity (Nithipatikom et al. 2004). Studies concerning probable antitumorigenic effects of virodhamine are currently still unavailable.

Antitumorigenic action of endocannabinoid-like substances

In investigations addressing antitumorigenic effects of the endocannabinoid-like substances OEA and PEA, both substances have been demonstrated to decrease the viability of neuroblastoma cells (Hamtiaux et al. 2011) and to elicit anti-invasive and antimetastatic properties in lung cancer cell models *in vitro* and *in vivo*

(Winkler et al. 2016). In case of OEA, the latter study was able to provide evidence for an involvement of TIMP-1 in the anti-invasive action of this substance. Moreover, PEA was shown to inhibit the proliferation of colon carcinoma cells via a PPARα-dependent inhibition of the AKT/mechanistic target of rapamycin (mTOR) pathway (Sarnelli et al. 2016). On the mechanistic level, PEA has been demonstrated to confer an entourage effect on AEA activity via downregulation of FAAH expression and activity (Di Marzo et al. 2001) and via positive allosteric modulation of TRPV1 thereby supporting the antiproliferative action of AEA (De Petrocellis et al. 2002). Sailler et al. (2014) found plasma concentrations of circulating PEA and OEA to correlate with the number of metastases in several cancer entities. In the same study, lower OEA concentrations were shown to promote the migration of murine metastatic melanoma cancer cells, whereas higher concentrations inhibited this response. Finally, SEA, another cannabinoid receptor-inactive saturated fatty acid amide, has been demonstrated to elicit proapoptotic effects in rat glioma cells via increasing intracellular calcium and mitochondrial uncoupling (Maccarrone et al. 2002). As PEA, SEA likewise confer an entourage effect on AEA via inhibition of AEA degradation by FAAH (Maccarrone et al. 2002).

Antiproliferative effects have been observed for DHEA and EPEA in prostate cancer cells. Dependent on the cell lines tested both cannabinoid receptor-dependent and -independent pathways were shown to underlie decreased proliferation (Brown et al. 2010). Moreover, DHEA and EPEA as well as their parent fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) induced prostate cell-cycle arrest and increased apoptosis, with DHEA and EPEA being significantly more potent than their parent fatty acids in inhibiting prostate cancer cell growth and proliferation by these substances (Brown et al. 2010). A few years later, Rovito et al. (2013) presented data on an increased autophagy of breast cancer cells treated with DHEA and EPEA, which was mediated by PPARγ activation. Recently, DHEA was demonstrated to inhibit the proliferation of head and neck squamous cell carcinoma via increased synthesis of reactive oxygen species induced by the 5-lipoxygenase pathway (Park et al. 2016).

Concerning the sleep-inducing factor OA, a CB_1 receptor-dependent antiproliferative effect was presented in breast cancer cells (Bisogno et al. 1998). Moreover, OA enhanced the cytostatic effect of AEA, which was found to be antagonized by a CB_1 receptor antagonist (Bisogno et al. 1998). Using breast cancer cells, OA inhibited proliferation, induced cell-cycle arrest and decreased migration and invasion *in vitro* accompanied with antimetastatic effects *in vivo* (Zibara et al. 2015). In the latter context, antitumorigenic effects of OA were mediated via downregulation of various metastatic markers, such as vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-9 (Zibara et al. 2015). Nevertheless, more studies are necessary to define the precise role of endocannabinoid-like substances in modulating tumor progression.

Other cannabinoid receptor targets involved in cancer progression

Recently, the TRPV2 receptor was shown to be involved in CBD-induced autophagy of glioblastoma cells (Nabissi et al. 2015) and to be a mediator of enhanced sensitivity of cannabinoids toward chemotherapeutics (Nabissi et al. 2013; Morelli et al. 2014).

As a further important receptor involved in cancer progression, GRP55 was found to influence tumor growth induced upon activation of endogenous LPI synthesis (Andradas et al. 2011; Piñeiro et al. 2011; Pérez-Gómez et al. 2013). GPR55 was demonstrated to confer cancer progression by virtue of its ability to enhance proliferation, invasion, and angiogenesis (Henstridge et al. 2011; Ross 2011). In line with this notion, overexpression of GPR55 was found to enhance cancer progression, whereas knockdown of GPR55 was revealed to confer reduced viability of breast, glioma, and pancreatic cancer cells (Andradas et al. 2011). Recently, the CB_2 receptor has been found to cause a cross-action on GPR55 via formation of heteromers that determine proliferation of cancer cells (Balenga et al. 2014; Moreno et al. 2014). As a result of this receptor interaction with agonists and antagonists of one receptor being able to impair the signaling of the partner receptor, Moreno et al. (2014) have shown that high doses of THC decreased growth of tumors coexpressing CB_2 and GPR55 receptors and increased tumor growth in GPR55-silenced tumors. The authors of the latter study suggested that THC in low doses only activates CB_2, which is associated with a slight tumor growth, whereas at high doses, THC behaves as a GPR55 antagonist resulting in a cross-antagonism of the protumorigenic effects of CB_2 activation. Other publications were able to demonstrate CBD to counteract the promoting effect of GPR55 on colon carcinogenesis (Kargl et al. 2016; Hasenoehrl et al. 2018).

Transport proteins associated with cancer progression

The currently available data suggest inhibition of members of the FABP family as possible strategy against

cancer. Accordingly, increased levels of FABPs led in most cases to tumor growth and metastasis, conferring poor survival prognosis for cancer patients. An overview of FABP upregulation in cancer tissues is provided in Table 4.

In agreement with the hypothesis of FABPs as proteins with cancer-progressive properties, FABP1 has been identified to increase the angiogenic potential and migration in hepatocellular carcinoma via an upregulation of VEGF-A (Ku et al. 2016).

FABP4, another member of the FABP family, has been shown to increase the aggressiveness of acute myeloid leukemia (Yan et al. 2017) and metastatic prostate cancers (Herroon et al. 2013) and to support the proliferation of breast cancer (Guaita-Esteruelas et al. 2017) as well as other cancer types (Uehara et al. 2014; Guaita-Esteruelas et al. 2017).

FABP5 silencing was shown to decrease the expression of MMP-2 and MMP-9 in cervical cancer (Wang et al. 2016), while overexpression of FABP5 in oral squamous cell carcinoma increased MMP-9 (Fang et al. 2010). On the functional level, silencing of FABP5 suppressed tumor cell proliferation and invasiveness (Fang et al. 2010; Wang et al. 2016). FABP5 inhibition was further demonstrated to confer suppression of tumorigenesis of mammary carcinoma (Kannan-Thulasiraman et al. 2010; Levi et al. 2013; Zhang et al. 2015) and prostate cancer cells (Forootan et al. 2014). In another investigation, the same group suggested FABP5 to promote angiogenesis via PPARγ, which was in turn activated by transported fatty acids (Forootan et al. 2016). This assumption was partially confirmed by a study with rat Rama37 model cells transfected with FABP5 genes, which had increased metastatic activity via enhanced VEGF gene expression (Jing et al. 2001). Silencing of FABP5 was further found to decrease proliferation of prostate cancer cells (Kawaguchi et al. 2016).

In terms of FABP7, experiments using glioma cells transfected with an FABP7 expression vector exhibited increased migration compared to FABP7-negative glioma cells. This promigratory impact of FABP7 was found to be dependent on binding of AA to FABP7, decreased levels of PPARγ, and increased COX-2 activity (Mita et al. 2010). The latter study further demonstrated binding of DHA to FABP7 to confer shuttling of FABP7 to the nucleus associated with an inhibitory impact of migration.

Nevertheless, some studies also showed decreased levels of FABPs in some cancer cells (Tölle et al. 2009; Inoue et al. 2014; Wang et al. 2014) as well as antitumorigenic properties following overexpression of FABPs (Nevo et al. 2010; Song et al. 2012). As such, breast cancer cells expressing FABP3 were demonstrated to exhibit reduced invasiveness via binding of FABP3 to the integrin α-subunit (Nevo et al. 2010). Using an embryonic cancer cell line, another study found overexpression of FABP3 to exhibit a proapoptotic impact (Song et al. 2012).

As FABPs have been reported as transport systems of fatty acids of the endocannabinoid family, it is tempting to speculate that anticancer effects of FAPB inhibition may occur due to elevated endocannabinoid levels which, however, could not be proven yet.

Investigational anticancer drugs acting at the endocannabinoid system

FAAH inhibitors

In agreement with the diverse anticarcinogenic effects of endocannabinoids, inhibitors of FAAH that increase endocannabinoid levels, thereby enhancing the cannabimimetic action, were supposed to inhibit cancer cell proliferation. Inhibition of cancer cell proliferation by suppression of endocannabinoid turnover with the FAAH inhibitor *N*-arachidonoylserotonin (AA-5HT) was reported to occur in glioma (Jacobsson et al. 2001) and colorectal cancer cells (Ligresti et al. 2003). AA-5HT likewise inhibited the growth of thyroid cancer cells *in vitro* and *in vivo* (Bifulco et al. 2004). In a mouse model of chemically induced precancerous colon lesions, AA-5HT has been further proven to inhibit the formation of aberrant crypt foci (Izzo et al. 2008). In line with these observations, a combination of URB597, a highly selective, irreversible FAAH inhibitor (Alexander and Cravatt 2005), with AEA was reported to result in antiproliferative effects on neuroblastoma cells (Hamtiaux et al. 2011). Antiproliferative effects were further demonstrated for combinations of URB597 with Met-F-AEA on colorectal cancer cells (Proto et al. 2012), with PEA on melanoma cells and with Met-F-AEA on lung cancer cells (Hamtiaux et al. 2012). Beyond inhibition of cancer cell proliferation, several studies even found inhibition of FAAH to be associated with blockade of cancer cell invasion and metastasis. Accordingly, the FAAH inhibitor CAY10401 decreased prostate cancer cell invasion, which could be confirmed by knockdown of FAAH, whereas FAAH overexpression was associated with enhanced invasion (Endsley et al. 2008). Another study substantiated the anti-invasive properties of FAAH inhibition by an siRNA approach as well as by the FAAH inhibitors URB597 and AA-5HT using human lung cancer cells and revealed an upregulation of TIMP-1 to confer this response (Winkler et al. 2016). The contribution of cannabinoid receptors to anticancerogenic effects caused by FAAH inhibition is poorly investigated.

Table 4. Overexpression of FABP members in cancer tissues, its association with patients´ prognosis and observed co-regulations. In all studies, FABP expression levels in malignant tissues were verified against non-cancer tissues.

Over-expressed FABP	Cancer	References	Methods	Co-regulations	Prognoses for cancer patients
FABP1	Gastric cancer	Jiang et al. (2017)	Immuno-histochemical staining, LC-MS/MS	Overexpression of fatty acid synthase	n.d.
	Hepatocellular carcinoma	Ku et al. (2016)	Immuno-histochemical staining	Positive correlation with VEGF-A expression	n.d.
	Prostate cancer	Das et al. (2001)	RT-PCR	Downregulation of FABP4 and FABP5	n.d.
FABP2	Prostate cancer	Das et al. (2001)	RT-PCR	Downregulation of FABP4 and FABP5	n.d.
FABP3	Malignant glioma	Hyvönen et al. (2014)	Immuno-histochemical staining	–	Expression positively correlates with the histological grade of the tumor
	Non-small cell lung cancer	Tang et al. (2016)	Immuno-histochemical staining, RT-PCR	–	Associated with advanced tumor node metastasis stage and negative impact on the overall survival
FABP4	Breast cancer	Kim et al. (2015)	Immuno-histochemical staining	–	Associated with significantly shorter disease-free survival and overall survival
	Cerebellar liponeurocytoma	Anghileri et al. (2012)	Immuno-histochemical staining, RT-PCR	Overexpression additionally verified versus medulloblastoma	n.d.
	Non-small cell lung cancer	Tang et al. (2016)	Immuno-histochemical staining, RT-PCR	–	Associated with advanced tumor node metastasis stage and negative impact on the overall survival
	Oral squamous cell carcinoma	Lee et al. (2014)	Immuno-histochemical staining	–	n.d.
	Ovarian cancer	Nieman et al. (2011)	Immuno-histochemical staining	Overexpressed at the adipocyte-cancer cell interface	n.d.
		Tucker et al. (2014)	RT-PCR	Associated with upregulation of alcohol dehydrogenase 1B	n.d.
FABP5	Bladder cancer	Chen et al. (2011)	RT-PCR	Increased mRNA levels of PABPC1, DDX5, SF3B1, EIF3S6 and Cks2, decreased mRNA levels of TPM2 and TAGLN	n.d.
	Breast cancer	Liu et al. (2011)	Immuno-histochemical staining RT-PCR	–	Correlates with ER/PR-negative status, high tumor grade, and poor prognosis
		Powell et al. (2015)	Immuno-histochemical staining	High expression correlates with high levels of EGFR	Correlates with lower disease-free survival
	Cervical cancer	Wang et al. (2016)	Immuno-histochemical staining	–	Correlates with lymph node metastasis, lymphovascular space invasion, stage, tumor size, and poor prognosis
	Cholangiocarcinoma	Jeong et al. (2012)	Immuno-histochemical staining, MALDI-TOF-MS	–	Correlates with tumor size, lymph node metastasis, angioinvasion, and staging
	Hepatocellular carcinoma	Fujii et al. (2005)	Western blot	Upregulation of PCNA and EB1	n.d.
	Malignant glioma	Campos et al. (2011)	Immuno-histochemical staining, RT-PCR	–	Correlates with malignancy
	Oral squamous cell carcinoma	Fang et al. (2010)	Immuno-histochemical staining, Western blot	–	n.d.
	Prostate cancer	Adamson et al. (2003)	Immuno-histochemical staining	–	n.d.
		Kawaguchi et al. (2016)	bisulfite sequencing analysis, combined bisulfite restriction analysis, quantitative analysis of DNA methylation using RT-PCR, Western blot	Hypomethylation of FABP5 promoter, up-regulation of FABP5 transcription by Sp1 and c-Myc	n.d.

(*continued*)

Table 4. Continued

Over-expressed FABP	Cancer	References	Methods	Co-regulations	Prognoses for cancer patients
FABP6	Colorectal cancer	Ohmachi et al. (2006)	Immuno-histochemical staining	–	n.d.
FABP7	Breast cancer	Gromov et al. (2014)	2D-PAGE and 2D Western immunoblotting, immuno-histochemical staining, MALDI-TOF-MS	–	Associated with apocrine differentiation, nuclear localization associated with more aggressive stages of apocrine carcinomas
	Clear cell renal cell carcinoma	Zhou et al. (2015)	Immuno-histochemical staining	FABP7 mRNA expression inversely correlated with its DNA methylation	Expression correlates with advanced clinical stage and poor survival of patients
	Malignant glioma	Morihiro et al. (2013)	Immuno-histochemical staining, Western blot	–	Expression correlates with tumor grade
	Melanoma	Goto et al. (2006)	Immuno-histochemical staining, RT-PCR, Western blot	–	n.d.
	Teratoid/rhabdoid tumor	Grupenmacher et al. (2013)	RT-PCR	–	n.d.
FABP9	Prostate cancer	Al Fayi et al. (2016)	Immuno-histochemical staining	–	Correlates with reduced patient survival times, increased joint Gleason score and androgen receptor index

–: no co-regulation observed; n.d.: not determined; Cks2: cyclin-dependent kinases regulatory subunit 2; DDX5: DEAD box protein 5; EB1: APC-binding protein EB1; EGFR: epidermal growth factor receptor; EIF3S6: eukaryotic translation initiation factor 3 subunit E; FABP: fatty acid binding protein; LC-MS/MS: liquid chromatography-tandem mass spectrometry; MALDI-TOF-MS: matrix-assisted laser desorption/ionization-time of flight-mass spectrometry; PABPC1: polyadenylate-binding protein 1; PAGE: polyacrylamide gel electrophoresis; PCNA: proliferating cell nuclear antigen; RT-PCR: real-time polymerase chain reaction; SF3B1: splicing factor 3b subunit 1; TAGLN: transgelin; Sp1: transcription factor Sp1; TPM2: tropomyosin beta chain.

One study found a contribution of at least the CB_1 receptor to the antiproliferative effect of AA-5HT in colorectal carcinoma cells (Ligresti et al. 2003). Concerning the above mentioned anti-invasive effects of FAAH siRNA, URB597, and AA-5HT on lung cancer cells, an involvement of CB_2 and TRPV1 was found (Winkler et al. 2016).

MAGL inhibitors

The major enzyme of 2-AG turnover, MAGL, poses another attractive target of anticancer strategies. Accordingly, the MAGL inhibitor JZL184 and MAGL knockdown were demonstrated to confer antiproliferative and proapoptotic effects on colorectal cancer cells *in vitro* and *in vivo* (Ye et al. 2011). MAGL knockdown and treatment with JZL184 were further found to confer an inhibitory action on prostate carcinoma cell invasion as well as on the growth of prostate carcinoma xenografts *in vivo* (Nomura et al. 2011). Concerning the underlying mechanism, the latter investigation reported a partial contribution of the CB_1 receptor to the anti-invasive and growth inhibitory impact of MAGL inhibition. In addition to this cannabinoid action, add-back of MAGL products such as free fatty acid conferred a partial inhibition of the anti-invasive effect of MAGL inhibition. These findings support the hypothesis that MAGL activity provides procancerogenic lipid precursors for synthesis of lysophosphatidic acid and PGs which could be confirmed using diverse cancer cell lines (Nomura et al. 2010). Notably, the latter study could not find CB_1 and CB_2 receptor antagonists to rescue the migratory defects of MAGL knockdown cells, suggesting that the impact of MAGL on cancer aggressiveness did not involve endocannabinoid signaling.

Concerning effects of JZL184 on prostate cancer cells, a recent report found antiproliferative effects of the substance when cells were activated with epidermal growth factor with no effect in the absence of epidermal growth factor (Cipriano et al. 2014). In this study, the antiproliferative effect of JZL184 could not clearly be demonstrated to be dependent on cannabinoid receptor activation due to a high variability of CB_1 expression in different experimental series.

In agreement with MAGL inhibition as a concept of anticancer action, pristimerin, a naturally occurring triterpenoid and reversible MAGL inhibitor (King et al. 2009), was shown to likewise exert an anticancerogenic impact on various cancer cell lines and in animal models (for review see Yousef et al. 2017). Accordingly, pristimerin has been reported to inhibit tumor cell proliferation, survival, angiogenesis, and metastasis by modulation of various molecular targets, resulting in

decreased levels of cyclins and of phosphorylated forms of p42/44 MAPK, AKT, mTOR, and NF-κB proteins as well as increased concentrations of apoptosis-related proteins and reactive oxygen species (Yousef et al. 2017). However, concerning the anticarcinogenic action of pristimerin, an involvement of cannabinoid receptors has not been reported so far. Finally, the synthetic MAGL inhibitor URB602 was demonstrated to act anticancerogenically on colon cancer cells *in vitro* and *in vivo* via downregulation of VEGF and fibroblast growth factor 2 associated with inhibition of tumor angiogenesis (Pagano et al. 2017).

Investigational drugs acting at the endocannabinoid system – potential role as anticancer agents

FABP inhibitors

As outlined earlier, the inhibition of diverse FAPBs in cancer cells has been associated with antitumoral effects. Moreover, inhibition of some FABPs has been shown to increase endocannabinoid concentrations in cancer cells (Kaczocha et al. 2009; Björklund et al. 2014). From that background, the antitumorigenic impact of FABP inhibitors may amongst others be due to an interference with the transport of anticarcinogenic endocannabinoids and endocannabinoid-like substances to their degradation enzymes. However, although the FABPs may, therefore, provide interesting targets in cancer therapy, an actual involvement of enhanced levels of endocannabinoids to be involved in anticarcinogenic action of FABP inhibitors remains to be elucidated.

Most of the FAPB inhibitors synthesized so far have been developed for the treatment of obesity, atherosclerosis, diabetes, and metabolic syndrome (for review see Wang YT et al. 2016). Among these, the FABP4 inhibitor BMS309403 has been demonstrated to increase levels of AEA in neuroblastoma cells (Kaczocha et al. 2009), whereas the FABP5 inhibitor SB-FI-26 has been shown to increase AEA concentration in rat sarcoma cell lines (Björklund et al. 2014). In agreement with the anticarcinogenic action of endocannabinoids, inhibition of FABP4 by BMS309403 has been shown to decrease prostate tumor growth and lung metastasis *in vivo* via induction of apoptosis (Uehara et al. 2014). However, considering the likewise existing, albeit lower affinity of BMS309403 to FABP3, FABP5 and FABP7 (Sulsky et al. 2007; Tyukhtenko et al. 2015), the observed antitumorigenic effects could be generated by inhibition of FABP4 or by combined inhibition of various members of the FABP family. In a further investigation, SB-FI-26, a specific FABP5 inhibitor, was demonstrated to suppress prostate cell proliferation, migration, invasiveness, and colony formation (Al-Jameel et al. 2017). In this study, the SB-FI-26-mediated decrease in cellular fatty acid uptake was followed by inhibition of PPARγ, thereby preventing a downstream induction of cancer-promoting genes (Al-Jameel et al. 2017).

In contrast, FABP5 expression was shown to induce rather than inhibit antitumor activity in cancer-associated macrophages by enhancing interferon β (IFNβ) response in tumor cells (Rao et al. 2015). In the latter study, the substance EI-05 has been demonstrated to elevate FABP5 and IFNβ concentrations in macrophages, thereby conferring inhibition of mammary tumor growth *in vivo* (Rao et al. 2015).

Substrate-selective cyclooxygenase inhibitors

As outlined earlier, AEA and 2-AG are metabolized via COX-2 to PG-EAs and PG-Gs, respectively. The resulting prostanoids are considered to have other specific functions than classical prostanoids and to interact with other receptors as has been shown for $PGF_{2\alpha}$-EA previously (for review see Woodward et al. 2013). To investigate the role of PG-EAs and PG-Gs, specific COX-2 inhibitors, named substrate-selective cyclooxygenase inhibitors (SSCI), have been developed (Prusakiewicz et al. 2009; Hermanson et al. 2013). These substances inhibit the metabolism of AEA and 2-AG to PG-EAs and PG-Gs without affecting the metabolism of AA to PGs, which in turn avoids the side effects associated with classical NSAIDs such as gastrointestinal damage (for review see Hermanson et al. 2014). In this context, the SSCI LM-4131 was shown to increase brain 2-AG levels, whereas the (R)-enantiomers of ibuprofen, naproxen, and flurbiprofen, all considered as SSCIs, increased AEA and 2-AG levels (Duggan et al. 2011; Hermanson et al. 2013). As proposed for FABP inhibitors before, an investigation of endocannabinoid-elevating SSCIs would be an interesting strategy for further preclinical investigations to find novel drugs possessing antitumorigenic effects. An interesting candidate in this respect could be the recently developed dual FAAH/SSC inhibitor FluAM1 (Gouveia-Figueira et al. 2015).

Summary

The WHO considered cancer diseases as the second leading cause of death globally with 8.8 million deaths in 2015, among which lung cancer appears as the most deadly (1.69 million deaths per year) (http://www.who.int/mediacentre/factsheets/fs297/en/). Due to the increasing economic impact that has been estimated at

$1.16 trillion in 2010 (Stewart and Wild 2014), research on alternative treatment options for cancer diseases poses a major challenge for the future. Although clinical data concerning systemic anticancer effects of cannabinoid compounds are still missing to provide reliable bench-to-bedside conversion, a recently proceeded orphan drug designation for cannabinoids as a treatment option for glioma in the USA (FDA 2014, 2015) and Europe (EMA 2015) may represent a first step in this direction. Concerning the preclinical data on anticancer effects of cannabinoids, the main advantage of these substances may be their broad array of anticancer effects, which comprise inhibition of cancer proliferation, angiogenesis, invasion, and chemoresistance, as well as induction of apoptosis, autophagy and tumor immune surveillance. Thus, cannabinoids may complement the currently used pharmacological interventions as a broadly diversified strategy for inhibition of cancer progression, while counteracting the severe side effects of chemotherapeutics, such as emesis, cachexia and neurodegeneration (for review see Ramer and Hinz 2016).

Nowadays, governments of many countries have introduced specific laws that at least partially enable critically ill patients' access to cannabinoid compounds, which, however, appears to be in contrast to a lack of approvals by the respective regulatory agencies. Additionally, the growing popularity of cannabinoid drugs such as CBD, which are part of a growing market of nutraceuticals, implies a large potential for self-medication that, particularly in cancer patients, bears a potential risk for patient health due to uncertain drug quality and unknown drug interactions. Taken together, the clinical use of cannabinoid compounds currently appears paradoxical at several levels. Therefore, clinical studies concerning the effects of cannabinoids on cancer growth are warranted in order to direct the clinical use of cannabinoid compounds toward approved medications. Furthermore, basic research concerning the endocannabinoid system in physiological as well as pathological processes throughout recent decades has revealed several targets for systemic anticancer treatments, such as FAAH and MAGL, as well as endocannabinoids other than AEA and 2-AG, namely noladin ether and NADA, that elicit anticancer effects by their ability to modulate cannabinoid receptors. Other putative targets may be transport proteins of the FABP family. This success in preclinical research raises the hope that accumulating knowledge about the complex network of the endocannabinoid system in an extended definition may imply probable further attractive targets for anticancer therapies in the future.

As a matter of fact, however, the main shortcoming today is the discrepancy between a large body of evidence of systemic anticancerogenic effects of cannabinoids at the preclinical level and missing knowledge about the actual effects on patients undergoing cancer therapy. In particular, data concerning the safety and efficacy of cannabinoid dosing that confers tumor inhibition should be collected in urgently needed clinical studies.

Disclosure statement

The authors declare no conflict of interest.

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