大麻二酚对肿瘤中离子通道的作用

谢亚男 蔚丹 万方*

(内蒙古农业大学生命科学学院, 呼和浩特 010010)

摘要 大麻是一种古老的药用植物, 常被用于缓解疼痛和癫痫发作, 但大麻素的成瘾性限制了它的临床使用。大麻的提取物大麻二酚没有精神活性, 且不良反应明显小于Δ9-四氢大麻酚, 因此受到广泛青睐。离子通道是贯穿细胞膜的亲水性蛋白质孔道, 可维持机体生命活动, 也与肿瘤的发生发展密切相关。该文主要关注大麻二酚作用的部分瞬时受体电位离子通道、电压依赖性阴离子选择性通道1和T型钙离子通道。大麻二酚是一个多靶点药物, 对离子通道的作用受到广泛关注, 但其作用机制和结合位点尚不清晰。目前已有关于大麻二酚作用于离子通道的综述及离子通道和肿瘤关系的综述, 但鲜有大麻二酚对肿瘤中的离子通道作用的总结。该文主要总结了大麻二酚可能结合的离子通道及其在肿瘤细胞中的可能作用。

关键词 大麻二酚; 离子通道; 肿瘤

Effects of Cannabidiol on Ion Channels in Tumors

XIE Yanan, YU Dan, WAN Fang*

(*College of Life Sciences, Inner Mongolia Agricultural University, Hohhot 010010, China*)

Abstract *Cannabis sativa* is an ancient medicinal plant commonly used to relieve pain and epileptic seizures. But the addictive nature of cannabinoids limits its clinical application. Cannabidiol, an extract of cannabis, is not psychoactive and has significantly less adverse reactions than Δ9-tetrahydrocannabinol, so it is widely favored. Ion channels are hydrophilic protein pores that run through the cell membrane, maintaining the body's life activities, and they are also closely related to the occurrence and development of tumors. This article focuses on some transient receptor potential channels, voltage-dependent anion channel 1 and T type calcium channel affected by cannabidiol. Cannabidiol is a multi-target drug that is known to bind to ion channels, but its mechanism of action and binding sites are not clear. Although there are reviews on cannabidiol's effect via ion channels, and on the relationship between ion channels and tumors, there is little literature summarizing the effect of cannabidiol via ion channels in tumors. This article mainly summarizes the possible ion channels bound by cannabidiol and their roles in tumor cells.

Keywords cannabidiol; ion channels; tumor

大麻(*Cannabis sativa*)是一种古老的药用植物, 在医药应用已有数千年历史, 临床常被用于治疗癫痫和缓解疼痛, 然而大麻素的成瘾性限制了它的临床使用[1]。

大麻的主要化学成分是大麻二酚(cannabidiol, CBD)和Δ9-四氢大麻酚(Δ9-tetrahydrocannabinol, THC), 也含有少量其他同源大麻素[2]。CBD和THC联用具有协同作用, 在临床试验及个别病例中展现

收稿日期: 2023-03-09 接受日期: 2023-05-11
国家自然科学基金(批准号: RZ1900003098)资助的课题
*通讯作者。Tel: 13404813212, E-mail: fwan@imau.edu.cn
Received: March 9, 2023 Accepted: May 11, 2023
This work was supported by the National Natural Science Foundation of China (Grant No.RZ1900003098)
*Corresponding author. Tel: +86-13404813212, E-mail: fwan@imau.edu.cn

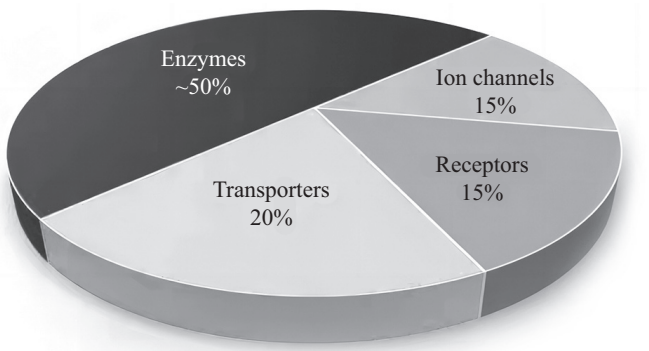


图1 大麻二酚不同分子靶点的比例(根据参考文献[12]修改)

Fig.1 The proportion of Cannabidiol's different molecular targets (modified from reference [12])

出了良好的抗癌功效[3]。在从植物大麻中提取并纯化大麻成分的过程中, 由于提纯工艺不同, CBD和THC成品中不可避免地会含有少量其他同源大麻素。CBD及THC均作用于内源性大麻素系统(endocannabinoid system, ECS), 该系统由大麻素受体(cannabinoid receptor, CBR)、内源性大麻素、内源性大麻素类酶和转运系统组成[4]。大麻素受体主要包含两种经典受体, 即大麻素受体1(cannabinoid receptor type 1, CB1)和大麻素受体2(cannabinoid receptor type 2, CB2)。ECS参与调控生物体内平衡的重要过程, 在肿瘤的发生发展中可抑制肿瘤细胞增殖、侵袭和迁移[5-6]。过去几十年中, ECS逐渐成为治疗各类癌症的新靶标[7]。CBD及THC则作用于CB1和CB2[8], CB1和CB2的不同组织分布, 导致受体活化的选择性和细胞特异性效应。CB1在中枢神经系统、外周神经末梢、血管内皮及脾脏中高表达, CB2在多种肿瘤细胞及免疫细胞如淋巴细胞、巨噬细胞、脾脏及淋巴结等[9]中高表达。这两种受体亚型都在多种肿瘤组织中高表达, 有研究表明, CB2在肿瘤发展中起关键作用。CBD和THC对大麻素受体的亲和力不同, THC对CB1和CB2的亲和力较高, 主要通过作用于CB1和CB2发挥作用, 具有精神成瘾性, 这也限制了其临床应用。CBD对CB1和CB2的亲和力较低, 不具有精神成瘾性, 在肿瘤细胞中存在其他作用靶点。

近年来, 越来越多的数据证明, CBD可以有效杀伤肿瘤细胞。CBD可选择性诱导肿瘤细胞凋亡, 具有安全性高、毒副作用不明显等特点, 在临床试验中高达1 500 mg/d的口服剂量或700 mg/d连续用药6周均未有明显的毒副作用[10]。CBD与化疗药物联合使用还可以减弱化疗药的毒副作用, 值得进一步研究。CBD口服生物利用度仅为6%, 极少量能到达全身血液循环, 但到达体内的药物分子与血浆蛋白结合率却高达94%, 游离态的CBD很少[11], 故而吸入或注射显然是更好的给药途径。

生物体内的ECS也可产生结合CB1和CB2的配体。研究者曾认为, 大麻素仅与CB1和CB2结合, 后发现大麻素与其他膜蛋白, 包括其他受体、转运蛋白、酶和离子通道等[12]之间也存在相互作用(图1)。近年来, CBD相关研究结果表明, 其可能通过作用于多种离子通道来影响细胞的生理活动[10-12]。本文主要总结CBD与离子通道的互作, 并阐述其结合位点及胞内效应。

离子通道功能障碍与肿瘤细胞不受控制的增殖、抵抗凋亡、侵袭及迁移等特征密切相关[13-14]。CBD对多种离子通道均有作用, 经过对现有文献的检索得出, CBD可能结合的离子通道受体包括TRPV1(transient receptor potential vanilloid 1)、TRPV2(TRP vanilloid 2)、TRPV3(TRP vanilloid 3)、TRPV4(TRP vanilloid 4)、TRPM8(TRP melastatin 8)、TRPA1(TRP ankyrin 1)、电压依赖性阴离子选择性通道1(voltage-dependent anion channel 1, VDAC1)、T型CaV3[15-20]。CBD可对上述离子通道产生的影响总结于表1。

1 TRP家族

瞬时受体电位(transient receptor potential, TRP)离子通道是一类在哺乳动物的外周和中枢神经系统分布很广泛的通道蛋白, 在进化中比较保守。根据氨基酸序列同源性分为6个亚家族, 分别是: TRPA(TRP

表1 CBD作用的离子通道的总结

Table 1 Ion channel summary of CBD action

靶点 Target	作用 Effect	亲和力及激活/拮抗能力 Affinity and activation/antagonism	研究对象 Research target
TRPV1 [15]	+	EC_{50}=3.5 μmol/L	HEK293 cells/human
TRPV2 [16]	+	EC_{50}=31.7 μmol/L	HEK293 cells/human
		EC_{50}=3.7 μmol/L	HEK293 cells/rat
TRPV3 [17]	+	EC_{50}=3.7 μmol/L	HEK293 cells/rat
TRPV4 [17]	+	EC_{50}=0.8 μmol/L	HEK293 cells/rat
TRPA1 [16]	+	EC_{50}=81.4 μmol/L	HEK293 cells/rat
TRPM8 [18]	-	IC_{50}=0.14 μmol/L	HEK293 cells/rat
VDAC1 [19]	-	K_d=11.2 μmol/L	Liver VDAC1 channel in planar lipid bilayer/sheep
T-type (Cacna1G) [20]	-	IC_{50}=0.82 μmol/L	HEK293 cells/human
T-type (Cacna1H) [20]	-	IC_{50}=0.78 μmol/L	HEK293 cells/human
T-type (Cacna1I) [20]	-	IC_{50}=3.70 μmol/L	HEK293 cells/human

+: 激活; -: 拮抗。

+: activation; -: antagonism.

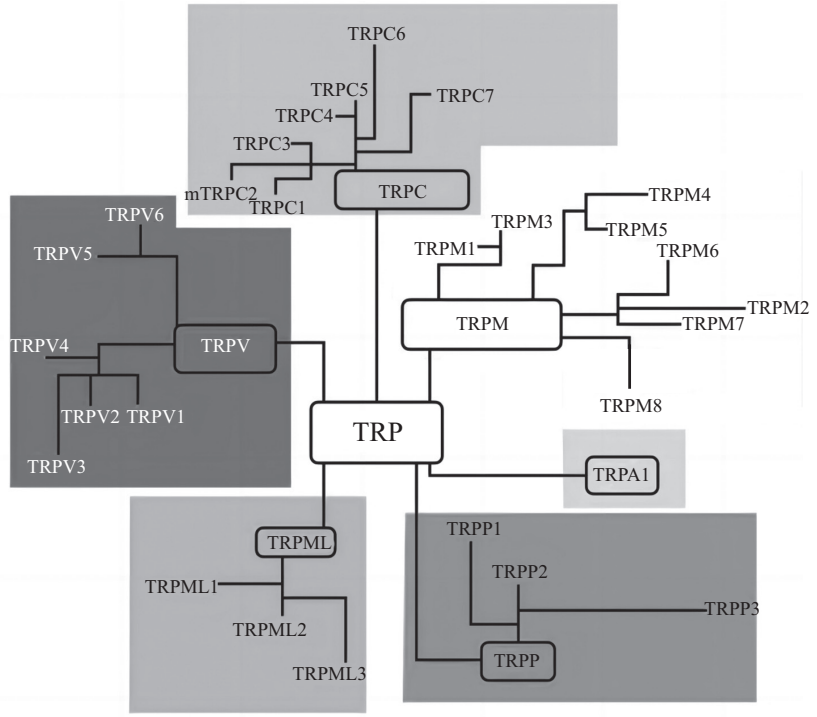


图2 TRP家族分支(来自https://zhuanlan.zhihu.com/p/368163927)

Fig.2 Branches of the TRP family (sourse from https://zhuanlan.zhihu.com/p/368163927)

ankyrin)、TRPV(TRP vanilloid)、TRPM(TRP melastatin)、TRPC(TRP canonical)和TRPML(TRP mucolipin)、TRPP(TRP polycystin), 共28个成员[21](图2)。具体又分为两大类, 第一类为TRPA、TRPV、TRPM、TRPC; 第二类为TRPML、TRPP[22]。

类似于电压门控钾离子通道, TRP离子通道由同源或异源的四个亚基组成, 每个亚基由一个跨膜区域(6个跨膜螺旋S1~S6)、胞内N-端和胞内C-端组成(图3)。在通道的跨膜区域S1~S6中, S1~S4形成电压感受结构域(voltage sensor-like domain, VSLD), S5、S6及两者中间的一段螺旋(孔螺旋)形成中心离子传导孔, 离子由此进出, S5和孔螺旋之间的区域压盖在孔道的上方[23]。TRPV、TRPM和TRPC通道家族中S6连接的C末端是一段长约25个氨基酸的保守结构域, 被称为TRP区域。该结构域既参与亚基的组装, 也是TRP通道门控变构的关键结构域[24-27]。

在TRP区域中包含一段高度保守的氨基酸序列WK-FQR, 通过一段连接蛋白link与S6螺旋连接[28-29]。

通过Uniport/PDB中蛋白的结构图发现这一V形疏水区域也存在于与CBD结合的其他几个TRP家族成员中, 据此可推测CBD对这一家族成员的结合与文献报道的CBD与TRPV2结合的方式相似, 主要由通道中S5和S6螺旋形成的V形疏水区域中的亮氨酸、缬氨酸和苯丙氨酸所介导[30](图4)。

TRP离子通道具有一定的离子选择性, 通过维持细胞内外阳离子平衡和信号转导来调节细胞的存活、增殖、分化和迁移[34]。

1.1 TRPV家族

TRPV家族的命名是基于第一个通道TRPV1的发现。TRPV1被一种天然存在的类似香草酸的分子——辣椒素(vanilloid)所激活。最初TRPV1通道被称为VR1, 但由于其结构和已发现的TRP家族极其相似, 被重新命名为TRPV1[35]。随后克隆了该家族的另外5个成员TRPV2~6。其中TRPV1~4为第一类, 参与热敏作用, 非选择性传导阳离子, 具有适中的钙选择性, P_{Ca}/P_{Na}为1~10; TRPV5~6为第二类, 具有高度的钙选择性, P_{Ca}/P_{Na}大于100, 参与肾脏Ca^{2+}吸收与重吸收[22,36]。

CBD对TRPV1~4均具有不同程度的激活作用[30], 其相对应的EC_{50}分别是3.5 μmol/L、3.7 μmol/L、3.7 μmol/L、0.8 μmol/L[15-17]。

1.1.1 TRPV1 TRPV1主要在感觉神经元中表达, 能被辣椒素、质子、毒素和大于42 °C的温度所激活, 因此其在生理上对热和化学伤害感受很关键。该通道具有多种生理功能, 涉及多种生理和病理过程, 与癌症疼痛有关[37]。香草酸的结合位点是由S3、S4、S4-S5连接子及相邻的S5和S6亚基形成, 该位点在不结合配体状态下通常与磷脂酰肌醇结合[23]。

CBD可直接激活TRPV1受体。有研究表明, 在乳腺癌细胞系中, CBD通过激活TRPV1导致Ca^{2+}内流诱导内质网应激, 提高细胞内ROS水平并破坏蛋白质折叠, 从而加剧肿瘤细胞死亡[38]。在三阴性乳

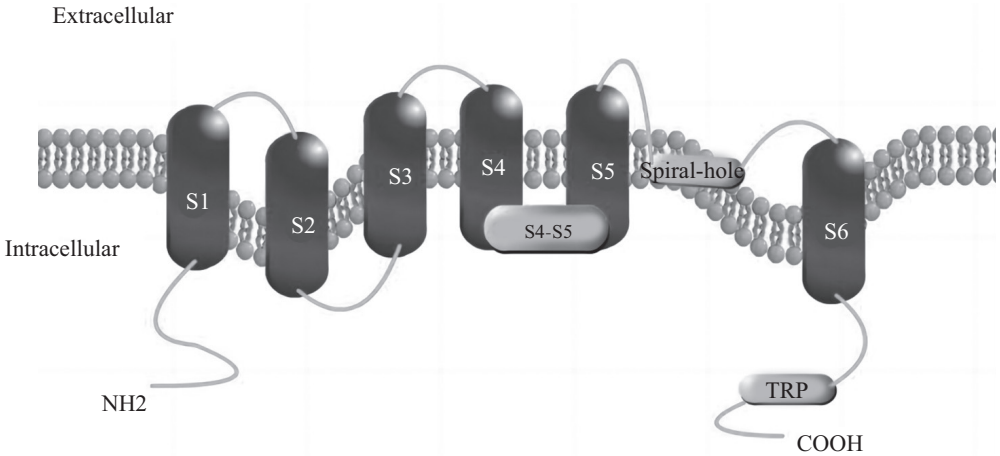
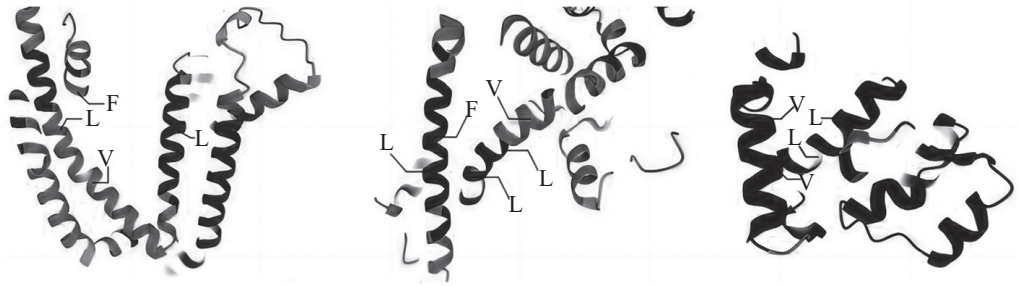


图3 TRPV/TRPM/TRPC亚家族结构示意图

Fig.3 Schematic of TRPV/TRPM/TRPC subfamily structure



UniPort ID: Q9Y5S1 [31]; UniPort ID: O75762 [32]; PDB ID: 8E4Q [33].

图4 CBD与TRPV2/TRPA1/TRPM8的结合位点

Fig.4 The binding site of CBD to TRPV2/TRPA1/TRPM8

腺癌细胞中CBD通过激活TRPV1诱导细胞凋亡[39]。CBD还通过激活TRPV1增强小胶质细胞的吞噬作用[40]。

1.1.2 TRPV2 TRPV2与TRPV1序列相似性最高, 具有50%的序列同源性[41], 在各种类型组织包括神经元和非神经元组织中广泛表达, 参与调节神经发育和免疫应答等多种重要的生理功能。

TRPV2高表达在多种肿瘤细胞中是一个致癌因素, 在少数肿瘤细胞中则发挥抑癌作用(表2)。其在骨髓癌、前列腺癌、三阴性乳腺癌等癌症中过表达, 并与癌细胞存活、增殖和迁移的信号通路有关。TRPV2是治疗胶质母细胞瘤的重要靶点, CBD可通过激活TRPV2, 进而提高神经胶质瘤细胞的化学敏感性并诱导人胶质瘤细胞系凋亡[42]。CBD激活TRPV2可提高乳腺癌细胞对化疗药物的敏感性, 从而在体内外对肿瘤生长产生更大的抑制作用[43]。CBD还通过激活慢性髓系白血病细胞中的TRPV2诱导线粒体功能障碍、线粒体自噬并抑制细胞增殖[44-45]。

1.1.3 TRPV3和TRPV4 TRPV3、TRPV4与TRPV1同源。TRPV3可在31~39 ℃温度范围内被激活, 在各种组织和器官中均表达, 在皮肤、口腔和胃肠道的上皮细胞中表达水平较高, 在皮肤相关疾病中具有重要功能[22]。TRPV3与CBD结合的药理作用尚未得到很好的研究。有研究表明, CBD通过激活TRPV3改变细胞内Ca^{2+}稳态, 并改善胃肠道炎症[17]。TRPV3在非小细胞肺癌中过表达, 与肺癌的进展相关, 激活TRPV3可促进肺癌细胞增殖[53], 因此其激动剂用于抗肿瘤的作用机制, 值得进一步研究。

TRPV4在体内有多种表达模式, 在多种免疫细胞上均有表达, 可直接介导胞外Ca^{2+}内流, 也通过影响膜电位等因素间接参与Ca^{2+}内流。过去的研究发现, TRPV4在多数肿瘤中表达水平增多, 仅在食管癌和前列腺癌等极少数肿瘤中表达水平减少[36]。TRPV4在调节肿瘤细胞的增殖、分化、凋亡及迁移中扮演重要角色[54-55], 在乳腺癌中促进细胞迁移和血管生成[56-58]; 在肺癌中促进血管生成和成熟, 抑制肿瘤生长[59]; 在肝癌中促进细胞迁移, 抑制细胞凋亡[60-62]; 在膀胱癌中促进肿瘤形成[63]; 在皮肤癌中促进肿瘤形成, 抑制细胞分化[64-65]。TRPV4还是神经胶质瘤潜在的生物标志物和治疗靶点, CBD通过激活TRPV4诱导致死性线粒体自噬, 从而抑制人神经胶质瘤细胞增殖[66]。

1.2 TRPM家族

TRPM家族与其他几个亚家族有类似的结构区域, 该亚家族的大多数成员最初是从肿瘤组织中克隆的, 与肿瘤发生、增殖和分化高度相关。该家族成员与温度感觉、镁(Mg^{2+})稳态和味觉有关。TRPM亚家族具有显著不同的激活模式、阳离子选择性和组织分布, 可根据结构相似性分为四类: TRPM1和TRPM3为第一类; TRPM4和TRPM5为第二类; TRPM2、TRPM6和TRPM7为第三类; TRPM8为第四类[21]。CBD可拮抗TRPM8, IC_{50}为0.14 μmol/L[18]。

TRPM8是一种有冷感知能力的非选择性阳离子通道, 参与热感、痛觉、体温调节和多种癌症的发生发展。在TRPM亚家族中, TRPM8对Ca^{2+}的选择性最强, 选择性比(P_{Ca}/P_{Na})为3.3[22]。TRPM8存在于哺乳动物的脂肪组织、神经元组织中[67], 参与调

表2 TRPV2在不同肿瘤中表达的致癌和抑癌作用

Table 2 Oncogenic and tumor suppressor effects of TRPV2 expression in different tumors

肿瘤 Tumor	致癌 Tumor promoter	抑癌 Tumor suppressor
Mantle cell lymphoma [46]	+	/
Multiple myeloma [47]	+	/
Bladder carcinoma [48]	+	/
Prostate adenocarcinoma [49]	+	/
Hepatocarcinoma [50]	+	/
Myeloid acute leukemia [51]	/	-
Glioblastoma [52]	/	-

+: 激活; -: 拮抗; /: 未有报道。

+: activation; -: antagonism; /: not reported.

节机体递质释放以及细胞增殖、分化、代谢及凋亡等重要生理功能[68]。

有研究发现, TRPM8在食管癌[69]、前列腺癌[70]、舌癌[71]、肾癌[72]、胰腺癌[73-75]等癌症中高表达。在人肾癌细胞A498中沉默*TRPM8*后, 由TRPM8介导的自噬调节可能通过JNK信号通路抑制细胞增殖并促进其凋亡[72]。在胰腺癌中, TRPM8表达水平越高, 细胞分化程度越差, TRPM8的高表达使进入细胞内的钙离子增多, 促进胰腺癌迅速进展[76]。

有研究表明, 在前列腺癌细胞中, CBD降低其*TRPM8*的mRNA水平, CBD的促凋亡作用可部分归因于拮抗TRPM8, 并伴有雄激素受体的下调、p53的激活和活性氧ROS水平的升高[77]。TRPM8与肿瘤生长密切相关, 但有关CBD与TRPM8的数据非常少, 因此需要进一步研究。

1.3 TRPA家族

TRPA1是哺乳动物TRPA亚家族中唯一的成员, 与其他TRP家族结构相比, TRPA1缺乏TRP结构域, 在N-末端结构域中包含14~17个特征性锚蛋白重复序列, 因此被称为锚蛋白[22]。

TRPA1属于非选择性阳离子通道, 它的激活可增加Na^+、H^+、Ca^{2+}等胞外阳离子内流量。TRPA1可由多种内源和外源性化合物激活, 既可被还原性分子(如半胱氨酸和赖氨酸)激活, 也可以被非亲电分子大麻素激活, 还受到各种内源性配体(如H_2O_2、缓激肽、硝酸脂质等)的调节[22]。该通道主要的生理功能包括感受冷、热和疼痛等伤害性刺激等, 在胰岛、胃肠道、心脏及肺等多种器官中分布, 且在感觉神经元和非神经细胞中也广泛表达。另有部分研究表明, TRPA1多数情况会与TRPV1共表达[78-79], 特别在感觉神经节中大量共表达[80], 两者紧密联系, 可相互调节[81]。关于疼痛感受的动物实验表明, TRPA1与TRPV1参与炎性反应, 并在炎性疼痛中发挥重要作用[82], 全身敲除这两个通道可以抑制慢性胰腺炎诱发的热痛敏和机械痛敏[83]。敲除*TRPA1*通道可以显著降低小鼠结肠炎引起的机械性痛觉过敏性, 因此TRPA1可能是结肠炎性疼痛的治疗靶点[84-85]。

虽然未检索到CBD作用于肿瘤细胞中TRPA1的研究, 但已知CBD可激活TRPA1[16], CBD对表达TRPA1的神经元产生强烈的兴奋作用[86], 而TRPA1又与癌症疼痛有关, 可作为乳腺癌疼痛治疗的靶点进行研究[87]。因此推测CBD也可通过作用于其他肿瘤细胞中的TRPA1通道缓解癌症患者的疼痛。有关CBD与TRPA1的数据非常少, 因此两者之间在肿瘤细胞中的相关机制仍然值得进一步研究。

2 VDAC家族

电压依赖性阴离子选择性通道(voltage-dependent anion channel, VDAC)是线粒体孔蛋白家族, 位于线粒体外膜, 共有VDAC1、VDAC2和VDAC3等3个家族成员, 其序列在进化中是高度保守的, 占线粒体外膜总蛋白的10%[88], 其中VDAC1亚型占比最高, 约为5%, 然后依次是VDAC2和VDAC3。每个VDAC通道都是由一个单独的VDAC蛋白(约285个氨基酸, 30~32 kDa)形成的宽β桶结构蛋白构成。这种单一多肽形成了一个开放时直径为2.5~3.0 nm、封闭时直径约为1.9 nm的大孔径的开放通道[89]。VDAC1在细胞质膜上也有表达, 但其在细胞质膜上的确切功能尚不清楚[90-95]。VDAC家族允许代谢物和许多离子通过, 是负责线粒体和细胞之间交流的主要孔道, 平衡细胞代谢和细胞死亡。在磷脂膜上, VDAC通道大部分时间在−20 mV~+20 mV的低电压下都是开放的, 对小离子(如: Cl^-、K^+、Na^+)略有选择性, 对阴离子有偏好, 并且具有高渗透性[91,96-98]。而通常施加超过20 mV的正电势或负电势时, VDAC会从开放状态转换为闭合状态, 此时对阳离子具有选择性, 渗透性降低, ATP和ADP则无法通过[89]。

VDAC家族是低聚的, 在细胞凋亡时VDAC1低聚程度增加[99-100]。VDAC通道控制细胞质和线粒体之间代谢产物的进出, 转运琥珀酸盐、苹果酸盐、丙酮酸盐和NADH等代谢产物, 在开放状态时, VDAC能够高速传递ATP分子[88]。因此, VDAC的结构、表达水平或状态改变都会破坏这些代谢产物的转运。

当氧化磷酸化产生的ATP不能被转运时, 细胞通过上调糖酵解来支持细胞生存。VDAC作为多种蛋白质的支架, 通过与Bcl-2家族成员或己糖激酶(hexokinase, HK)相互作用支持糖酵解, 进而防止细胞凋亡, 从而参与细胞生存或死亡的选择, 并与癌细胞之间密切相关。VDAC家族是抗癌和线粒体代谢改变所导致的其他疾病重要的潜在治疗靶点[88]。

VDAC1是抗癌的重要靶点。相比于正常细胞系，许多人类肿瘤细胞系中VDAC1的表达水平较高[101]。在肿瘤细胞中HK的表达水平也较高，HK有四种不同异构体(I、II、III和IV)，其中HK-I和HK-II可与线粒体外膜上的VDAC1专一性结合[102]。VDAC1和HK之间的直接相互作用有利于细胞产生能量并防止细胞死亡，破坏它们的关联是靶向VDAC1治疗癌症的主要方向。有研究证明，CBD可调节线粒体外膜上VDAC1和HK-II的耦联，从而导致线粒体功能和致癌信号通路的强烈转变，进而引发激素难耐性前列腺癌细胞的死亡[103]。

3 钙电压门控通道亚基

电压门控钙离子通道(voltage-gated calcium channels, VGCCs)的功能核心是CaVα1亚基(calcium voltage-gated channel subunit alpha1)。在哺乳动物中有10个不同的基因分别编码CaVα1亚基，CaVα1亚基分别是Cacna1A~I和1S。这10个α1亚基与辅助亚基结合，在基因表达的调节、细胞内钙稳态等多种功能中发挥作用[104]。VGCCs是细胞中Ca^{2+}内流的主要途径，参与细胞增殖、代谢、凋亡等生理学过程[105]。根据其序列同源性可分为三组，分别编码三类主要的CaVα1蛋白：第一组1S、1F、1C、1D编码CaV1(L型)；第二组1A、1B、1E编码CaV2(N、P/Q、R型)；第三组1G、1H、1I编码CaV3(T型)[106-108]。CBD可抑制所有CaV3(T型)钙离子通道[20]，不同于编码*CaV1*和*CaV2*基因的家族成员，T型钙通道属于低电压依赖型(low-voltage-activated, LVA)钙通道，具有低阈值激活和缓慢失活的生理学特性[109]，在神经系统中分布广泛[110]。

这10个钙离子通道亚基在特定组织和细胞类型中有独特的生物活性。T型钙通道中，Cacna1G在瘢痕组织和瘢痕疙瘩成纤维细胞中特异性高表达；Cacna1H在大脑、丘脑、杏仁核、基底节区、小脑浦肯野细胞中高表达；Cacna1I主要分布于下丘脑和感觉神经内[111]。

由于CaV通道的独特亚细胞定位、蛋白质关联和功能特性，从不同CaV通道进入的钙会激活不同的信号通路，因此某些CaV通道通常与细胞某些功能相关。由*Cacna1G*、*Cacna1H*和*Cacna1I*基因编码的CaV3(T型)通道是许多神经元起搏的基础[112-113]。

T型钙离子通道在神经系统中表达水平较高，同时在多种肿瘤如神经胶质瘤、胚胎瘤、视网膜母细胞瘤、肾细胞癌、尤因肉瘤等中也有表达(depmap portal——https://depmap.org/portal/)。虽未检测到CBD与CaV3(T型)通道在肿瘤细胞中互作的研究，但CBD抑制神经细胞中所有T型钙离子通道，因此推测，CBD应也可作用于肿瘤中的T型钙离子通道，具体机制有待进一步研究。

4 总结与展望

癌症治疗过程中有一定的挑战性，很多化疗药有一定的副作用，在治疗过程中会杀伤正常细胞。越来越多的研究表明，CBD具有副作用小、不具有精神成瘾性的优点，已被批准为减少化疗副作用的药物。TRP家族近年来成为了抗肿瘤新药的研发靶点，它们在人体内分布非常广泛，作为肿瘤的治疗靶点可能对正常细胞产生副作用。CBD的副作用非常小，利用它靶向TRP家族或可避免这一问题，是非常合适且有前景的。

参考文献 (References)

[1] BONINI S A, PREMOLI M, TAMBARO S, et al. *Cannabis sativa*: a comprehensive ethnopharmacological review of a medicinal plant with a long history [J]. J Ethnopharmacol, 2018, 227: 300-15.

[2] SCOTT K A, DALGLEISH A G, LIU W M. The combination of cannabidiol and Δ9-tetrahydrocannabinol enhances the anticancer effects of radiation in an orthotopic murine glioma model [J]. Mol Cancer Ther, 2014, 13(12): 2955-67.

[3] SINGH Y, BALI C. Cannabis extract treatment for terminal acute lymphoblastic leukemia with a philadelphia chromosome mutation [J]. Case Rep Oncol, 2013, 6(3): 585-92.

[4] JOSHI N, ONAIVI E S. Endocannabinoid system components: overview and tissue distribution [J]. Adv Exp Med Biol, 2019, 1162: 1-12.

[5] RAMER R, SCHWARZ R, HINZ B. Modulation of the endocannabinoid system as a potential anticancer strategy [J]. Front Pharmacol, 2019, 10: 430.

[6] MULLER C, MORALES P, REGGIO P H. Cannabinoid ligands targeting TRP channels [J]. Front Mol Neurosci, 2018, 11: 487.

[7] LAEZZA C, PAGANO C, NAVARRA G, et al. The endocannabinoid system: a target for cancer treatment [J]. Int J Mol Sci, 2020, 21(3): 747.

[8] THOMAS A, BAILLIE G L, PHILLIPS A M, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists *in vitro* [J]. Br J Pharmacol, 2007, 150(5): 613-23.

[9] KISKOVA T, MUNGENAST F, SUVAKOVA M, et al. Future aspects for cannabinoids in breast cancer therapy [J]. Int J Mol Sci, 2019, 20(7): 1673.

[10] CONSROE P, LAGUNNA J, ALLENDER J, et al. Controlled

clinical trial of cannabidiol in Huntington's disease [J]. Pharmacol Biochem Behav, 1991, 40(3): 701-8.

[11] BIRNBAUM A K, KARANAM A, MARINO S E, et al. Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy [J]. Epilepsia, 2019, 60(8): 1586.

[12] IBEAS BIH C, CHEN T, NUNN A V W, et al. Molecular targets of cannabidiol in neurological disorders [J]. Neurotherapeutics, 2015, 12(4): 699-730.

[13] NATALIA P, ROMAN S, YAROSLAV S. Ion channels in cancer: are cancer hallmarks oncochannelopathies [J]? Physiol Rev, 2018, 98(2): 559-621.

[14] LEHENKYI V, PREVARSKAYA N. Oncogenic TRP channels [J]. Adv Exp Med Biol, 2011, 704(704): 929.

[15] BISOGNO T, HANUS L, DE PETROCELLIS L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide [J]. Br J Pharmacol, 2001, 134: 845-52.

[16] QIN N, NEEPER M P, LIU Y, et al. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons [J]. J Neurosci, 2008, 28(24): 6231-8.

[17] PETROCELLIS L D, ORLANDO P, MORIELLO A S, et al. Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation [J]. Acta Physiologica, 2012, 204(2): 255-66.

[18] PETROCELLIS L D, VELLANI V, SCHIANO-MORIELLO A, et al. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8 [J]. J Pharmacol Exp Ther, 2008, 325(3): 1007-15.

[19] RIMMERMAN N, BEN-HAIL D, PORAT Z, et al. Direct modulation of the outer mitochondrial membrane channel, voltage-dependent anion channel 1 (VDAC1) by cannabidiol: a novel mechanism for cannabinoid-induced cell death [J]. Cell Death Dis, 2013, 4(12): 949.

[20] ROSS H R, NAPIER I, CONNOR M. Inhibition of recombinant human t-type calcium channels by Δ9-tetrahydrocannabinol and cannabidiol [J]. J Biol Chem, 2008, 283(23): 16124-34.

[21] PREMKUMAR L S. Transient receptor potential channels as targets for phytochemicals [J]. ACS Chem Neurosci, 2014, 5(11): 1117-30.

[22] SAMANTA A H T M V. Transient receptor potential (TRP) channels [J]. Subcell Biochem, 2018(87): 141-65.

[23] KWON D H, ZHANG F, SUO Y, et al. Heat-dependent opening of TRPV1 in the presence of capsaicin [J]. Nat Struct Mol Biol, 2021, 28(7): 554-63.

[24] FRANCISCO J T, AINARA L C, GREGORIO F B, et al. The region adjacent to the c-end of the inner gate in transient receptor potential melastatin 8 (TRPM8) channels plays a central role in allosteric channel activation [J]. J Biol Chem, 2014, 289(41): 28579-94.

[25] RAMSEY I S, DELLING M, CLAPHAM D E. An introduction to TRP channels [J]. Annu Rev Physiol, 2006, 68(1): 619-47.

[26] LATORRE R, ZAELZER C, BRAUCHI S. Structure-functional intimacies of transient receptor potential channels [J]. Q Rev Biophys, 2009, 42(3): 201-46.

[27] GEES M, OWSIANIK G, NILIUS B, et al. TRP channels [J]. Compr Physiol, 2012, 2(1): 563-608.

[28] CLAPHAM D E, RUNNELS L W, STRUBING C. The TRP ion channel family [J]. Nat Rev Neurosci, 2001, 2(6): 387-96.

[29] OWSIANIK G, TALAVERA K, VOETS T, et al. Permeation and selectivity of TRP channels [J]. Annu Rev Physiol, 2006, 68(1): 685-717.

[30] PUMROY R A, SAMANTA A, LIU Y, et al. Molecular mechanism of TRPV2 channel modulation by cannabidiol [J]. eLife, 2019, 8: 48792.

[31] MCCLEVERTY C J, KOESEMA E, PATAPOUITAN A, et al. Crystal structure of the human TRPV2 channel ankyrin repeat domain [J]. Protein Sci, 2006, 15(9): 2201-6.

[32] PAULSEN C E, ARMACHE J P, GAO Y, et al. Structure of the TRPA1 ion channel suggests regulatory mechanisms [J]. Nature, 2015, 520(7548): 511-7.

[33] YIN Y, ZHANG F, FENG S, et al. Activation mechanism of the mouse cold-sensing TRPM8 channel by cooling agonist and PIP2 [J]. Science, 2022, 378: 6616.

[34] DADON D, MINKE B. Cellular functions of transient receptor potential channels [J]. Int J Biochem Cell Biol, 2010, 42(9): 1430-45.

[35] CATERINA M J, SCHUMACHER M A, TOMINAGA M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway [J]. Nature, 1997, 389(6653): 816-24.

[36] VENNEKENS R, OWSIANIK G, NILIUS B. Vanilloid transient receptor potential cation channels: an overview [J]. Curr Pharm Des, 2008, 14(1): 18-31.

[37] SZALLASI A, SHETA M. Targeting TRPV1 for pain relief: limits, losers and laurels [J]. Expert Opin Investig Drugs, 2012, 21(9): 1351-69.

[38] HARPE A, BEUKES N, FROST C L. CBD activation of TRPV1 induces oxidative signalling and subsequent ER stress in breast cancer cell lines [J]. Biotechnol Appl Biochem, 2022, 69(2): 420-30.

[39] LIGRESTI A, MORIELLO A S, STAROWICZ K, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma [J]. J Pharmacol Exp Ther, 2006, 318(3): 1375-87.

[40] HASSAN S, ELDEEB K, MILLNS P J, et al. Cannabidiol enhances microglial phagocytosis via transient receptor potential (TRP) channel activation [J]. Br J Pharmacol, 2014, 171(9): 2426-39.

[41] 田甜. TRPV2通道结构与功能研究进展[J]. 科技视界(TIAN T. [J]. Science & Technology Vision), 2017(7): 88,93.

[42] NABISSI M, MORELLI M B, SANTONI M, et al. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents [J]. Carcinogenesis, 2013, 34(1): 48-57.

[43] ELBAZ M, AHIRWAR D, XIAOLI Z, et al. TRPV2 is a novel biomarker and therapeutic target in triple negative breast cancer [J]. Oncotarget, 2016, 9(71): 33459-70.

[44] SIVEEN K S, NIZAMUDDIN P B, UDDIN S, et al. TRPV2: a cancer biomarker and potential therapeutic target [J]. Dis Markers, 2020, 2020: 1-10.

[45] MAGGI F, MORELLI M B, TOMASSONI D, et al. The effects of cannabidiol via TRPV2 channel in chronic myeloid leukemia cells and its combination with imatinib [J]. Cancer Sci, 2022, 113(4): 1235-49.

[46] ROBERT S B, REBEKAH J J, RENATA W, et al. Protein profiling of plasma membranes defines aberrant signaling pathways in mantle cell lymphoma [J]. Mol Cell Proteomics, 2009, 8(7): 1501-15.

[47] MORELLI M B, OFFIDANI M, ALESIANI F, et al. The effects of cannabidiol and its synergism with bortezomib in multiple myeloma cell lines. A role for transient receptor potential vanilloid type-2 [J]. Int J Cancer, 2014, 134(11): 2534-46.

[48] CAPRODOSSI S, LUCCIARINI R, AMANTINI C, et al. Transient receptor potential vanilloid type 2 (TRPV2) expression in normal urothelium and in urothelial carcinoma of human bladder: correlation with the pathologic stage [J]. Eur Urol, 2008, 54(3): 612-20.

[49] MONET M, GKIKA D, LEHENKYI V, et al. Lysophospholipids stimulate prostate cancer cell migration via TRPV2 channel activation [J]. Biochim Biophys Acta, 2009, 1793(3): 528-39.

[50] LI N, LONG Y, FAN X, et al. Proteomic analysis of differentially expressed proteins in hepatitis B virus-related hepatocellular carcinoma tissues [J]. J Exp Clin Cancer Res, 2009, 28(1): 122.

[51] ZATKOVA A, MERK S, WENDEHACK M, et al. AML/MDS with 11q/MLL amplification show characteristic gene expression signature and interplay of DNA copy number changes [J]. Genes Chromosomes Cancer, 2009, 48(6): 510-20.

[52] NABISSI M, MORELLI M B, AMANTINI C, et al. TRPV2 channel negatively controls glioma cell proliferation and resistance to fas-induced apoptosis in erk-dependent manner [J]. Carcinogenesis, 2010, 31(5): 794-803.

[53] XIAOLEI L, QIANHUI Z, KAI F, et al. Overexpression of TRPV3 correlates with tumor progression in non-small cell lung cancer [J]. Int J Mol Sci, 2016, 17(4): 437.

[54] JIE P, HONG Z, TIAN Y, et al. Activation of transient receptor potential vanilloid 4 induces apoptosis in hippocampus through downregulating PI3K/Akt and upregulating p38 MAPK signaling pathways [J]. Cell Death Dis, 2015, 6(6): 1775.

[55] 李孝琼, 陈莉, 王昌梅. TRPV4对HeLa细胞增殖的作用[J]. 中华临床医师杂志(LI X Q, CHEN L, WANG C M. The effect of TRPV4 regulation on hela cells proliferation *in vitro* [J]. Chin J Clinicians), 2013, 7(7): 3.

[56] PLA A F, GRANGE C, ANTONIOTTI S, et al. Arachidonic acid-induced Ca^{2+} entry is involved in early steps of tumor angiogenesis [J]. Mol Cancer Res, 2008, 6(4): 535.

[57] FIORIO P A, ONG H L, CHENG K T, et al. TRPV4 mediates tumor-derived endothelial cell migration via arachidonic acid-activated actin remodeling [J]. Oncogene, 2012, 31(2): 200-12.

[58] PLA A F, GENOVA T, PUPO E, et al. Multiple roles of protein kinase a in arachidonic acid-mediated Ca^{2+} entry and tumor-derived human endothelial cell migration [J]. Mol Cancer Res, 2010, 8(11): 1466-76.

[59] ADAPALA R K, THOPPIL R J, GHOSH K, et al. Activation of mechanosensitive ion channel TRPV4 normalizes tumor vasculature and improves cancer therapy [J]. Oncogene, 2016, 35(3): 314-22.

[60] VRIENS J, JANSSENS A, PRENEN J, et al. TRPV channels and modulation by hepatocyte growth factor/scatter factor in human hepatoblastoma (HepG2) cells [J]. Cell Calcium, 2004, 36(1): 19-28.

[61] YANG S, LEI Z, MINGZHE Y, et al. TRPV4 channel inhibits TGF-β1-induced proliferation of hepatic stellate cells [J]. PLoS One, 2014, 9(7): 101179.

[62] ZHAN L, YANG Y, MA T T, et al. Transient receptor potential vanilloid 4 inhibits rat HSC-T6 apoptosis through induction of autophagy [J]. Mol Cell Biochem, 2015, 402(1/2): 9-22.

[63] MIZUNO H, SUZUKI Y, WATANABE M, et al. Potential role of transient receptor potential (TRP) channels in bladder cancer cells [J]. J Physiol Sci, 2014, 64(4): 305-14.

[64] LEE H, CATERINA M J. TRPV channels as thermosensory receptors in epithelial cells [J]. PflugersArch, 2005, 451(1): 160-7.

[65] FUSI C, MATERAZZI S, MINOCCI D, et al. Transient receptor potential vanilloid 4 (TRPV4) is downregulated in keratinocytes in human non-melanoma skin cancer [J]. J Invest Dermatol, 2014, 134(9): 2408-17.

[66] HUANG T, XU T, WANG Y, et al. Cannabidiol inhibits human glioma by induction of lethal mitophagy through activating TRPV4 [J]. Autophagy, 2021, 17(11): 3592-606.

[67] MA P Y, LI X Y, WANG Y L, et al. Natural bioactive constituents from herbs and nutraceuticals promote browning of white adipose tissue [J]. Pharmacol Res, 2022, 178: 106175.

[68] 苏林, 宋程程, 舒瑞辰, 等. 神经病理性痛大鼠冷痛觉过敏与背根神经节TRPM8膜转运的关系[J]. 中华麻醉学杂志(SU L, SONG C C, SHU R C, et al. Relationship between cold hyperalgesia and trafficking of TRPM8 to cell membrane in dorsal root ganglion of rats with neuropathic pain [J]. Chin J Anesthesiol), 2017, 37(5): 532-5.

[69] LAN X, ZHAO J, SONG C, et al. TRPM8 facilitates proliferation and immune evasion of esophageal cancer cells [J]. Biosci Rep, 2019, 39(10): BSR20191878.

[70] LIU T, LIAO Y, TAO H, et al. RNA interference-mediated depletion of TRPM8 enhances the efficacy of epirubicin chemotherapy in prostate cancer LNCaP and PC3 cells [J]. Oncol Lett, 2018, 15(4): 4129-36.

[71] 潘娴, 吴煜农, 傅振, 等. TRPM8在舌癌组织及TCA8113中的表达及其意义[J]. 口腔生物医学(PAN X, WU Y N, FU Z, et al. Expression of TRPM8 incarcinoma of to ngueand cell line TCA8113 [J]. Oral Biomedicine Vol), 2010, 1(3): 4.

[72] 付婷, 熊毅. TRPM8通道介导的自噬调节可能通过JNK信号通路影响肾癌细胞的存活[J]. 东南大学学报(FU T, XIONG Y. TRPM8-channel-mediated autophagy may regulate renal cancer cell survival through JNK signaling pathway [J]. J Southeast Univ), 2020, 39(3): 6.

[73] YEE N S, ZHOU W, LEE M. Transient receptor potential channel TRPM8 is over-expressed and required for cellular proliferation in pancreatic adenocarcinoma [J]. Cancer Lett, 2010, 297(1): 49-55.

[74] YEE N S, ZHOU W, LEE M, et al. Targeted silencing of TRPM7 ion channel induces replicative senescence and produces enhanced cytotoxicity with gemcitabine in pancreatic adenocarcinoma [J]. Cancer Lett, 2012, 318(1): 99-105.

[75] YEE N S, BOWN R D, LEE M S, et al. TRPM8 ion channel is aberrantly expressed and required for preventing replicative senescence in pancreatic adenocarcinoma: potential role of TRPM8 as a biomarker and target [J]. Cancer Biol Ther, 2012, 13(8): 592-9.

[76] 董正. TRPM8离子通道在胰腺癌中高表达的临床意义[D]. 长春: 吉林大学, 2017.

[77] DE P L, LIGRESTI A, SCHIANO M A, et al. Non-THC cannabi-

noids inhibit prostate carcinoma growth *in vitro* and *in vivo*: pro-apoptotic effects and underlying mechanisms [J]. Br J Pharmacol, 2013, 168(1): 79-102.

[78] MAFTEI D, VELLANI V, ARTICO M, et al. Abnormal pain sensation in mice lacking the prokineticin receptor PKR2: interaction of PKR2 with transient receptor potential TRPV1 and TRPA1 [J]. Neuroscience, 2020, 427(1): 16-28.

[79] CAO D S, ZHONG L, HSIEH T H, et al. Expression of transient receptor potential ankyrin 1 (TRPA1) and its role in insulin release from rat pancreatic beta cells [J]. PLoS One, 2012, 7(5): 38005.

[80] AKOPIAN A N , RUPAREL N B , JESKE N A , et al. Transient receptor potential TRPA1 channel desensitization in sensory neurons is agonist dependent and regulated by TRPV1-directed internalization [J]. J Physiol, 2007, 583(1): 175-93.

[81] NIELSEN T A, ERIKSEN M A, GAZERANI P, et al. Psychophysical and vasomotor evidence for interdependency of TRPA1 and TRPV1-evoked nociceptive responses in human skin: an experimental study [J]. Pain, 2018, 159(10): 1989-2001.

[82] UTSUMI D, MATSUMOTO K, TSUKAHARA T, et al. Transient receptor potential vanilloid 1 and transient receptor potential ankyrin 1 contribute to the progression of colonic inflammation in dextran sulfate sodium-induced colitis in mice: links to calcitonin gene-related peptide and substance p [J]. J Pharmacol Sci, 2018, 136(3): 121-32.

[83] 毕凌波, 尹翠, 张奉明, 等. 转基因敲除TRA1/TRPV1离子通道表达在慢性胰腺炎疼痛中的调控作用[J]. 医学信息(BI L B, YIN C, ZHANG F M, et al. The regulatory role of transgenic knockout TRA1/TRPV1 ion channel expression in chronic pancreatitis pain [J]. Medical Information Aug), 2020, 33(15): 65-8.

[84] CATTARUZZA F, SPREADBURY I, MIRANDA-MORALES M, et al. Transient receptor potential ankyrin-1 has a major role in mediating visceral pain in mice [J]. Am J Physiol Gastrointest Liver Physiol, 2010, 298(1): G81-91.

[85] KOIVISTO A, CHAPMAN H, JALAVA N, et al. TRPA1: a transducer and amplifier of pain and inflammation [J]. Basic Clin Pharmacol Toxicol, 2014, 114(1): 50-5.

[86] KOWALSKI C W, RAGOZZINO F J, LINDBERG J E M, et al. Cannabidiol activation of vagal afferent neurons requires TRPA1 [J]. J Neurophysiol, 2020, 124(5): 1388-98.

[87] ALMEIDA A D, RIGO F K, PRA D D, et al. Role of transient receptor potential ankyrin 1 (TRPA1) on nociception caused by a murine model of breast carcinoma [J]. Pharmacol Res, 2020, 152: 104576.

[88] MAZURE N M. VDAC in cancer [J]. Biochim Biophys Acta Bioenerg, 2017, 1858(8): 665-73.

[89] ELIZABETH B D, MICHAEL F. VDAC channels [J]. IUBMB Life, 2001, 52(3): 113-8.

[90] BATHORI G, PAROLINI I, SZABO I, et al. Extramitochondrial porin: facts and hypotheses [J]. J Bioenerg Biomembr, 2000, 32(1): 79-89.

[91] VARDA S B, VITO D P, MARKUS Z, et al. VDAC, a multifunctional mitochondrial protein regulating cell life and death [J]. Mol Aspects Med, 2010, 31(3): 227-85.

[92] CESAR M, WILSON J E. All three isoforms of the voltage-dependent anion channel (VDAC1, VDAC2, and VDAC3) are present in mitochondria from bovine, rabbit, and rat brain [J]. Arch Biochem Biophys, 2004, 422(2): 191-6.

[93] PINTO V D, GUARINO F, GUARNERA A, et al. Characterization of human VDAC isoforms: a peculiar function for VDAC3 [J]? Biochimica et Biophysica Acta, 2010, 1797(6/7): 1268-75.

[94] MESSINA A, REINA S, GUARINO F, et al. VDAC isoforms in mammals [J]. Biochimica et Biophysica Acta, 2011, 1818(6): 1466-76.

[95] YAMAMOTO T, YAMADA A, WATANABE M, et al. VDAC1, having a shorter n-terminus than VDAC2 but showing the same migration in an sds-polyacrylamide gel, is the predominant form expressed in mitochondria of various tissues [J]. J Proteome Res, 2006, 5(12): 3336-44.

[96] BENZ, R. Permeation of hydrophilic solutes through mitochondrial outer membranes: review on mitochondrial porins [J]. Biochim Biophys Acta, 1994, 1197(2): 167-96.

[97] COLOMBINI M. Voltage gating in the mitochondrial channel, VDAC [J]. J Membr Biol, 1989, 111(2): 103-11.

[98] MANNELLA C A. Conformational changes in the mitochondrial channel protein, VDAC, and their functional implications [J]. J Struct Biol, 1998, 121(2): 207-18.

[99] SHAY G, DANYA B H, VARDA S B. Structure-based analysis of VDAC1: N-terminus location, translocation, channel gating and association with anti-apoptotic proteins [J]. Biochem J, 2012, 444(3): 475-85.

[100] NURIT K, DALIA T, VARDA S B. Oligomerization of the mitochondrial protein voltage-dependent anion channel is coupled to the induction of apoptosis [J]. Mol Cell Biol, 2010, 30(24): 5698-709.

[101] VARDA S B, DANYA B H. VDAC, a multi-functional mitochondrial protein as a pharmacological target [J]. Mitochondrion, 2012, 12(1): 24-34.

[102] NAKASHIMA R A, MANGAN P S, COLOMBINI M, et al. Hexokinase receptor complex in hepatoma mitochondria: evidence from N,N'-dicyclohexylcarbodiimide-labeling studies for the involvement of the pore-forming protein VDAC [J]. Biochemistry, 1986, 25(5): 1015-21.

[103] MAHMOUD A M, KOSTRZEWA M, MAROLDA V, et al. Cannabidiol alters mitochondrial bioenergetics via VDAC1 and triggers cell death in hormone-refractory prostate cancer [J]. Pharmacol Res, 2023, 189: 106683.

[104] KARIN J R, FRANK L H. The impact of splice isoforms on voltage-gated calcium channel α1 subunits [J]. J Physiol, 2004, 554(3): 609-19.

[105] ANDRADE A, BRENNECKE A, MALLAT S, et al. Genetic associations between voltage-gated calcium channels and psychiatric disorders [J]. Int J Mol Sci, 2019, 20(14): 3537.

[106] LIPSCOMBE D, ALLEN S E, TORO C P. Control of neuronal voltage-gated calcium ion channels from rna to protein [J]. Trends Neurosci, 2013, 36(10): 598-609.

[107] LIPSCOMBE D, ANDRADE A, ALLEN S E. Alternative splicing: functional diversity among voltage-gated calcium channels and behavioral consequences [J]. Biochim Biophys Acta, 2013, 1828: 1522-9.

[108] WILLIAM C, EDWARD P R, TERRANCE P S, et al. International union of pharmacology. Nomenclature and structure-function relationships of voltage-gated calcium channels [J]. Pharmacol Rev, 2005, 57(4): 411.

[109] GRAY A C, RAINGO J, LIPSCOMBE D. Neuronal calcium channels: splicing for optimal performance [J]. Cell Calcium, 2007, 42(4): 409-17.

[110] ERTEL E A, CAMPBELL K P, HARPOLD M M, et al. Nomenclature of voltage-gated calcium channels [J]. Neuron, 2000, 25(3): 533-5.

[111] TJADEN J, EICKHOFF A, STAHLKE S, et al. Expression pattern of t-type Ca^{2+} channels in cerebellar purkinje cells after VEGF treatment [J]. Cells, 2021, 10(9): 2277.

[112] HUGUENARD J R. Low-threshold calcium currents in central nervous system neurons [J]. Annu Rev Physiol, 1996, 58(1): 329-48.

[113] EDWARD P R. Molecular physiology of low-voltage-activated t-type calcium channels [J]. Physiol Rev, 2003, 83(1): 117-61.