PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2021,48(12):1392~1397
www.pibb.ac.cn

温度感受器TRPV1调节疼痛*

吴一箐[1)] 童志前[1)**] 万 有[2)]
([1)] 温州医科大学老年研究院，精神医学学院，浙江省阿尔茨海默病研究重点实验室，温州 325035；
[2)] 北京大学神经科学研究所，北京 100083）

摘要 2021年诺贝尔生理学或医学奖由戴维·朱利叶斯（David Julius）和阿德姆·帕塔普蒂安（Ardem Patapoutian）共同获得，以表彰二人分别在温度感受器辣椒素受体（TRPV1）和触觉感受器PIEZO1/2方面做出的杰出贡献. 此项工作有助于阐明神经系统如何感知冷、热和机械刺激的机制，以及开发治疗疼痛的药物. 本文简介David Julius关于能被辣椒素、热(>43℃)、酸（pH<6.0）激活的TRPV1的开创性工作，以及TRPV1在外周和中枢敏化，从而增强癌症痛、慢性炎症痛、神经病理性痛等方向的最新成果.

关键词 辣椒素受体，癌症痛，炎症痛，神经病理性痛，外周敏化，中枢敏化
中图分类号 Q5，R74 **DOI**：10.16476/j.pibb.2021.0303

北京时间2021年10月4日，新一届诺贝尔生理学或医学奖揭晓，戴维·朱利叶斯（David Julius）和阿德姆·帕塔普蒂安（Ardem Patapoutian）共同获奖，以表彰二人在发现温度与触觉感受器方面所做出的贡献. 人类对热、冷和触觉的感知能力对生存至关重要. 在日常生活中，人对这些感觉习以为常. 但神经冲动是如何产生，使热可以被感知？David Julius发现了辣椒素受体（transient receptor potential vanilloid subfamily member 1，TRPV1），解决了这个问题[1]. TRPV1在人体的分布很广泛，如神经纤维、肠道、脑等，参与了外周痛觉感知、血管的血压调节、脑记忆功能等[2].

近20年来，研究发现TRPV1在急、慢性疼痛的发生、发展中都发挥重要作用[3-4]. 急性疼痛常发生于创伤或手术后，当组织损伤恢复后即减轻. 慢性疼痛指持续时间超过急性损伤或疾病的正常痊愈时间的痛，按其病因可分为癌症痛、慢性炎症痛、神经病理性疼痛等，具有持续性、顽固性和反复性的特点，临床上较难控制，严重影响患者生活质量和工作状态[5]. 本文着重介绍TRPV1在温度感知、癌症痛、慢性炎症痛、神经病理性痛、内脏痛等方面的作用.

1 TRPV1与温度感知

为什么辣椒涂抹皮肤就会觉得火辣辣地疼？Julius课题组发现的TRPV1解释了这个现象. 辣椒素是辣椒中的主要辛辣成分，19世纪中叶，首次从辣椒粉中被分离出来，并命名为辣椒素（capsaicin）. 1919年，Nelson报道了辣椒素的化学结构[6]. 1997年，Julius的团队发现了辣椒素的受体（capsaicin receptor，又名TRPV1），并发现其能被高于43℃的热刺激激活而通道开放. 这一发现揭开了温度感受的机理和外周痛觉感受的部分机制[1].

TRPV1是一种非选择性的阳离子通道，主要分布于伤害性感觉神经元. 这些神经元发出的感觉神经纤维主要是无髓鞘的C类纤维以及部分薄髓鞘的Aδ纤维. TRPV1可被一些化学物质、热刺激（如温度>43℃）、酸（pH<6.0）等激活，阳离子（主要是Ca^{2+}）从胞外进入胞内，触发神经末梢释

* 国家自然科学基金（82071214，81974166，30570566）和北京自然科学基金（M21004，7202083）资助项目.
** 通讯联系人.
Tel：0577-86699661，E-mail：tzqbeida@163.com
收稿日期：2021-10-08，接受日期：2021-10-22

放神经肽类和兴奋性氨基酸，最终引起大脑皮层痛觉形成[7-9]. 2013 年 Julius 领导的课题组解析了 TRPV1 的三维晶体结构[10-11]（图 1）.

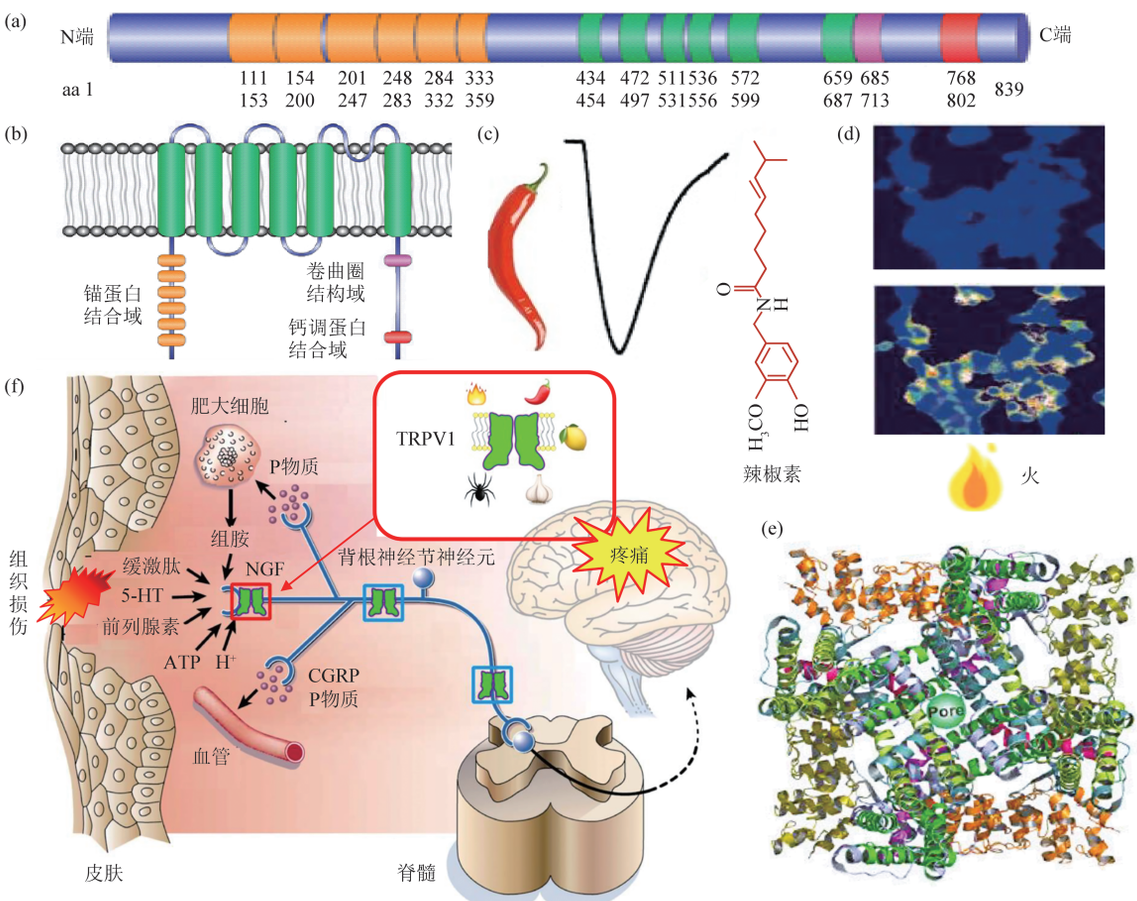

Fig. 1　Crucial role of TRPV1 in pain responses[7–11]

图1　辣椒素受体（TRPV1）在疼痛行为中的关键角色[7–11]

（a）TRPV1蛋白质序列.（b）TRPV1的跨膜结构.（c）辣椒素激活TRPV1电流.（d）TPRV1的晶体结构.（e）热刺激激活TRPV1介导的钙内流.（f）组织损伤、辣椒素、热刺激激活TRPV1诱发疼痛.

诺贝尔奖委员会对于此次获奖的官方解读认为，TRPV1 的发现回答了人类面临的最大谜团之一：“我们如何感知环境”的问题. Julius 团队发现这个能将高于 43℃以上的热、辣椒素刺激转化为生物电的感受器是 TRPV1[1]，随后又发现了其他几种对不同温度敏感的 TRP 通道家族[12-14]. 其实，TRPV1 的发现对疼痛的机制研究也具有重大意义，如辣椒的灼烧感、手碰到烧热的锅、人为什么在高烧 40℃时感到痛. 更为关键的是，TRPV1 与临床各类疼痛密切相关，这为阐明疼痛的分子机制及药物开发开辟了新的方向.

2　TRPV1与转移性骨癌痛

癌症痛（cancer pain）是由肿瘤压迫或浸润直接或间接引起的持续的、不可忍受的疼痛. 临床研究显示，30%～50% 的癌症病人和 75%～95% 的晚期癌和转移癌病人都伴有癌症痛发生，癌症痛临床治疗困难，受到广泛关注[15]. 转移性骨癌痛的发生机制包括：a. 外周敏化，即初级感觉神经元和神经纤维的兴奋性异常增强；b. 中枢敏化，主要表现为感觉神经元在脊髓背角换元时的突触传递增强. 而 TRPV1 参与了外周及中枢的敏化，加快癌症痛的发生和发展[16-17].

万有课题组 2010 年开展 TRPV1 在骨癌痛中的作用研究. 他们发现：转移进入骨髓中的乳腺癌细胞通过丝氨酸羟甲基转移酶 1 和 2（SHMT1 和 SHMT2）及赖氨酸特异性组蛋白去甲基化酶 1（LSD1）产生内源性甲醛[18]. 而过多的甲醛在酸化

环境（肿瘤组织低H^+）协同下能激活伤害性感觉神经纤维上的TRPV1，导致骨癌痛[19]. 此外，在癌细胞骨转移的情形下，骨质破坏增加的同时激活了成骨细胞；被激活的成骨细胞释放出I型胰岛素样生长因子（IGF-1），后者可上调外周神经纤维的TRPV1蛋白表达、并增强其功能[20-21]；而巨噬细胞或单核细胞分泌的肿瘤坏死因子α（TNF-α）更敏化脊髓背角神经元的TRPV1[22]；增强外周及中枢的敏感，加剧转移性骨癌痛的发生[16-17]（图2）. 2005年Julius发现TRPV1的特异性拮抗剂可减轻癌症痛模型大鼠的痛敏反应[23].

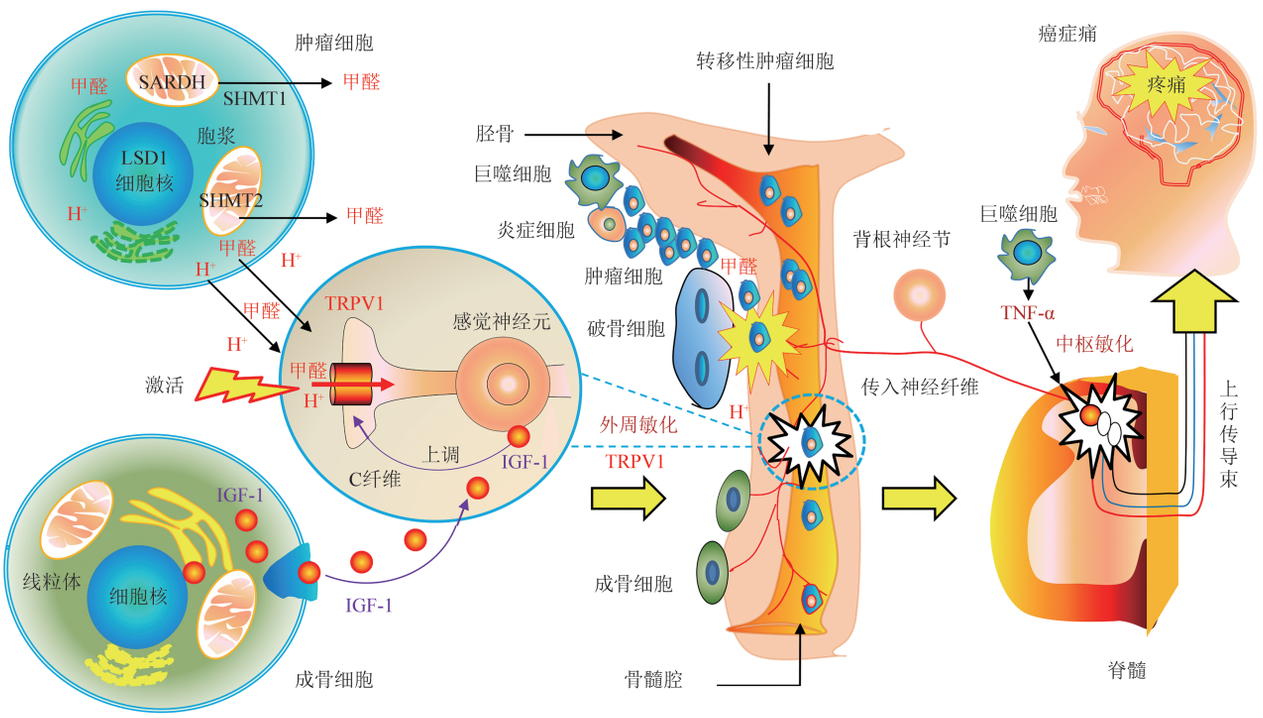

Fig. 2　Mechanisms of metastatic bone cancer pain

图2　转移性骨癌痛机制

肿瘤破坏骨质激活成骨细胞，成骨细胞分泌的IGF-1上调外周TRPV1；巨噬细胞分泌的TNF-α敏化脊髓中枢TRPV1；肿瘤细胞释放甲醛和氢离子，协同激活TRPV1诱发转移性骨癌痛[18-22].

3　TRPV1与慢性炎症痛

炎症性疼痛（inflammatory pain）是由病菌感染引起的伤口和组织疾病所致的慢性疼痛. 2004年万有课题组发现，在炎症痛模型大鼠中TRPV1在背根神经节和脊髓背角中表达显著升高，导致机械痛敏及热痛敏[24-25]，而下调TRPV1的表达或阻断TRPV1则减轻痛敏程度[26]. 第四军医大学陈军课题组也发现TRPV1能被外周局部炎症敏化[27-28].

TRPV1能够被许多前原炎症物质或介质如H^+、缓激肽（bradykinin，BK）、前列腺素（prostaglandin，PG）、神经生长因子（nerve growth factor，NGF）等直接或间接敏化或激活. 这个过程涉及G蛋白偶联受体、酪氨酸激酶（tyrosine kinase，Trk）以及多条炎症介质介导的信号转导途径，如PKC（protein kinase C）途径、丝裂源活化的蛋白激酶途径等. TRPV1敏化主要是通过胞外位点质子化和胞内位点磷酸化来实现的，另外PIP2等膜磷脂分解去抑制在敏化过程中也起到一定作用[29-30].

4　TRPV1与神经病理性痛

神经病理性痛（neuropathic pain）是由躯体感觉神经的损伤或功能紊乱而造成的疼痛综合征. 其主要表现为痛觉敏化，如自发性疼痛、痛觉过敏和痛觉超敏. 迄今为止，其发病机制尚不明确，超过2/3的病人未能得到有效的治疗. 而中枢敏化被认为是神经病理性疼痛发生、维持的关键原因[31-32].

2005年万有课题组制备了大鼠背根神经结扎（spinal nerve ligation，SNL）的神经病理性痛大鼠模型，发现外周的背根神经节神经元、脊髓背角神经元、基底外侧杏仁核都参与神经病理性痛[33-37]. 而辣椒素敏感的传入神经纤维末梢、背根神经节及脊髓背角的神经元表达的TRPV1，参与了该疼痛模型的外周和中枢的敏化[38-40]，即TRPV1的敏化可以导致更大的膜去极化，使低阈值神经元激活以及整体兴奋性增加，疼痛加剧[41]，而TRPV1的拮抗剂可减缓神经病理性痛[42-43].

5　TRPV1与内脏痛

内脏痛（visceral pain）是临床上常见的症状，可由机械性牵拉、痉挛、缺血和炎症等刺激所致. 主要特点有：a. 定位不准确，如腹痛患者常不能说出所发生疼痛的明确位置，因为痛觉感受器在内脏的分布要比在躯体稀疏得多，而且内脏感觉的传入途径比较分散；b. 发生缓慢，持续时间较长，主要表现为慢痛，常呈渐进性增强，但有时也可迅速转为剧烈疼痛[44-45]. 肠道、胃部表达的TRPV1参与了内脏痛的发生[46-47]，而注射TRPV1拮抗剂或减少其表达，则减缓内脏痛程度[48-49].

6　TRPV1与药物开发

自从1997年揭示了TRPV1在温度感知、疼痛方面发挥的关键作用，TRPV1其他的生物学作用及其作为药物靶点的研究进展很快[50]. 但该新型离子通道具有分布广泛、生物学作用复杂的特点，限制了其激动剂和拮抗剂的开发，对针对该靶点的药物的有效性、安全性的研发具有一定的挑战性[51]. 到目前为止还没有针对疼痛的临床药物成功上市[52-53]，不能不说这是TRPV1获得诺贝尔奖的一个小小的遗憾.

参　考　文　献

[1] Caterina M J, Schumacher M A, Tominaga M, *et al*. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature, 1997, **389**(6653):816-824

[2] 陈敏, 张陆勇, 严明. 辣椒素受体研究进展. 中国临床药理学与治疗学, 2006, **11**(2):126-130
Chen M, Zhang L Y, Yan M. Chin J Clin Pharmacol Ther. 2006, **11**(2):126-130

[3] Conway S J. TRPing the switch on pain: an introduction to the chemistry and biology of capsaicin and TRPV1. Chem Soc Rev, 2008, **37**(8):1530-1545

[4] Jara-Oseguera A, Simon S A, Rosenbaum T. TRPV1: on the road to pain relief. Curr Mol Pharmacol, 2008, **1**(3):255-269

[5] Lei Y, Liu H, Xia F, *et al*. Effects of esketamine on acute and chronic pain after thoracoscopy pulmonary surgery under general anesthesia: a multicenter-prospective, randomized, double-blind, and controlled trial. Front Med (Lausanne), 2021, **8**:693594

[6] Nelson E K. The constitution of capsaicin, the pungent principle of capsicum. J Am Chem Soc, 1919. **41**(7):1115-1121

[7] Cao E, Cordero-Morales J F, Liu B, *et al*. TRPV1 channels are intrinsically heat sensitive and negatively regulated by phosphoinositide lipids. Neuron, 2013, **77**(4):667-679

[8] Zhang K, Julius D, Cheng Y. Structural snapshots of TRPV1 reveal mechanism of polymodal functionality. Cell, 2021, **184**(20): 5138-5150

[9] Chuang H H, Prescott E D, Kong H, *et al*. Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4, 5)P2-mediated inhibition. Nature, 2001, **411**(6840):957-962

[10] Liao M, Cao E, Julius D, *et al*. Structure of the TRPV1 ion channel determined by electron cryo-microscopy. Nature, 2013, **504**(7478):107-112

[11] Cao E, Liao M, Cheng Y, *et al*. TRPV1 structures in distinct conformations reveal activation mechanisms. Nature, 2013, **504**(7478):113-118

[12] Montell C, Birnbaumer L, Flockerzi V, *et al*. A unified nomenclature for the superfamily of TRP cation channels. Mol Cell, 2002, **9**(2):229-231

[13] McKemy D D, Neuhausser W M, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature, 2002, **416**(6876):52-58

[14] Julius D. TRP channels and pain. Annu Rev Cell Dev Biol, 2013, **29**:355-384

[15] Farquhar-Smith P. Clinical practice guidelines for cancer pain: problems and solutions. Curr Opin Support Palliat Care, 2021, **15**(2):84-90

[16] Wan Y. New mechanism of bone cancer pain: tumor tissue-derived endogenous formaldehyde induced bone cancer pain *via* TRPV1 activation. Adv Exp Med Biol, 2016, **904**:41-58

[17] Chou P R, Lu C Y, Kan J Y, *et al*. Simultaneous hyperbaric oxygen therapy during systemic chemotherapy reverses chemotherapy-induced peripheral neuropathy by inhibiting TLR4 and TRPV1 activation in the central and peripheral nervous system. Support Care Cancer, 2021, **29**(11):6841-6850

[18] Liu J, Liu F Y, Tong Z Q, *et al*. Lysine-specific demethylase 1 in breast cancer cells contributes to the production of endogenous formaldehyde in the metastatic bone cancer pain model of rats. PLoS One, 2013, **8**(3):e58957

[19] Tong Z, Luo W, Wang Y, *et al*. Tumor tissue-derived formaldehyde and acidic microenvironment synergistically induce bone cancer pain. PLoS One, 2010, **5**(4):e10234

[20] Han Y, Li Y, Xiao X, *et al*. Formaldehyde up-regulates TRPV1 through MAPK and PI3K signaling pathways in a rat model of bone cancer pain. Neurosci Bull, 2012, **28**(2):165-172

[21] Li Y, Cai J, Han Y, *et al*. Enhanced function of TRPV1 *via* up-regulation by insulin-like growth factor-1 in a rat model of bone cancer pain. Eur J Pain, 2014, **18**(6):774-784

[22] Spicarova D, Palecek J. Tumor necrosis factor alpha sensitizes

spinal cord TRPV1 receptors to the endogenous agonist N-oleoyldopamine. J Neuroinflammation, 2010, **7**:49

[23] Ghilardi J R, Röhrich H, Lindsay T H, *et al*. Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. J Neurosci, 2005,**25**(12):3126-3131

[24] Luo H, Cheng J, Han J S, *et al*. Change of vanilloid receptor 1 expression in dorsal root ganglion and spinal dorsal horn during inflammatory nociception induced by complete Freund's adjuvant in rats. Neuroreport, 2004, **15**(4):655-658

[25] Yu L, Yang F, Luo H, *et al*. The role of TRPV1 in different subtypes of dorsal root ganglion neurons in rat chronic inflammatory nociception induced by complete Freund's adjuvant. Mol Pain, 2008, **4**:61

[26] Xiao X, Zhao X T, Xu L C, *et al*. Shp-1 dephosphorylates TRPV1 in dorsal root ganglion neurons and alleviates CFA-induced inflammatory pain in rats. Pain, 2015, **156**(4):597-608

[27] 衡立君, 高国栋, 陈军. 辣椒素受体VR1在局部炎症状态下的敏化机制. 神经解剖学杂志, 2004, **20**(3):315-318
Heng L J, Gao G D, Chen J. Chinese Journal of Neuroanatomy, 2004, **20**(3):315-318

[28] 田丽娟, 杜意如, 萧勇, 等. TRPV1介导甲醛激活初级传入伤害性感受器细胞的作用. 生理学报, 2009, **61**(5):404-416
Tian L J, Du Y R, Xiao Y, *et al*. Acta Physiologica Sinica, 2009, **61**(5):404-416

[29] 程阔菊, 景胜, 杨天德. 辣椒素受体与慢性疼痛. 重庆医学, 2012,**41**(2):199-201
Cheng K J, Jing S, Yang T D. Chongqing Medicine, 2012, **41**(2):199-201

[30] 梁凯, 张宏伟. 辣椒素受体在炎性疼痛中的作用. 医药论坛杂志, 2009, **30**(23):121-123
Liang K, Zhang H W. Journal of Medical Forum, 2009, **30**(23):121-123

[31] Koltzenburg M, Torebjörk H E, Wahren L K. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain, 1994, **117**(Pt 3):579-591

[32] Devor M. Centralization, central sensitization and neuropathic pain. Focus on "sciatic chronic constriction injury produces cell-type-specific changes in the electrophysiological properties of rat substantia gelatinosa neurons". J Neurophysiol, 2006, **96**(2):522-523

[33] Sun Q, Xing G G, Tu H Y, *et al*. Inhibition of hyperpolarization-activated current by ZD7288 suppresses ectopic discharges of injured dorsal root ganglion neurons in a rat model of neuropathic pain. Brain Res, 2005, **1032**(1-2):63-69

[34] Xing G G, Liu F Y, Qu X X, *et al*. Long-term synaptic plasticity in the spinal dorsal horn and its modulation by electroacupuncture in rats with neuropathic pain. Exp Neurol, 2007, **208**(2):323-332

[35] Wan Y. Involvement of hyperpolarization-activated, cyclic nucleotide-gated cation channels in dorsal root ganglion in neuropathic pain. Acta Physiologica Sinica, 2008, **60**(5):579-580

[36] Liu F Y, Qu X X, Cai J, *et al*. Electrophysiological properties of spinal wide dynamic range neurons in neuropathic pain rats following spinal nerve ligation. Neurosci Bull, 2011, **27**(1):1-8

[37] Li Z, Wang J, Chen L, *et al*. Basolateral amygdala lesion inhibits the development of pain chronicity in neuropathic pain rats. PLoS One, 2013, **8**(8):e70921

[38] Nakao A, Takahashi Y, Nagase M, *et al*. Role of capsaicin-sensitive C-fiber afferents in neuropathic pain-induced synaptic potentiation in the nociceptive amygdala. Mol Pain, 2012, **8**:51

[39] Obata K, Noguchi K. Contribution of primary sensory neurons and spinal glial cells to pathomechanisms of neuropathic pain. Brain Nerve, 2008, **60**(5):483-492

[40] Huang Y K, Lu Y G, Zhao X, *et al*. Cytokine activin C ameliorates chronic neuropathic pain in peripheral nerve injury rodents by modulating the TRPV1 channel. Br J Pharmacol, 2020, **177**(24):5642-5657

[41] Zhang X F, Han P, Neelands T R, *et al*. Coexpression and activation of TRPV1 suppress the activity of the KCNQ2/3 channel. J Gen Physiol, 2011, **138**(3):341-352

[42] Watabiki T, Kiso T, Tsukamoto M, *et al*. Intrathecal administration of AS1928370, a transient receptor potential vanilloid 1 antagonist, attenuates mechanical allodynia in a mouse model of neuropathic pain. Biol Pharm Bull, 2011, **34**(7):1105-1108

[43] Watabiki T, Kiso T, Kuramochi T, *et al*. Amelioration of neuropathic pain by novel transient receptor potential vanilloid 1 antagonist AS1928370 in rats without hyperthermic effect. J Pharmacol Exp Ther, 2011, **336**(3):743-750

[44] Grundy L, Erickson A, Brierley S M. Visceral pain. Annu Rev Physiol, 2019, **81**:261-284

[45] Gebhart G F, Bielefeldt K. Physiology of visceral pain. Compr Physiol, 2016, **6**(4):1609-1633

[46] Lapointe T K, Basso L, Iftinca M C, *et al*. TRPV1 sensitization mediates postinflammatory visceral pain following acute colitis. Am J Physiol Gastrointest Liver Physiol, 2015, **309**(2):G87-G99

[47] Holzer P. TRPV1: a new target for treatment of visceral pain in IBS. Gut, 2008, **57**(7):882-884

[48] Zhou Q, Yang L, Larson S, *et al*. Decreased miR-199 augments visceral pain in patients with IBS through translational upregulation of TRPV1. Gut, 2016, **65**(5):797-805

[49] Ji W, Cui C, Zhang Z, *et al*. Paradoxic effects of propofol on visceral pain induced by various TRPV1 agonists. Exp Ther Med, 2013, **5**(4):1259-1263

[50] Iftinca M, Defaye M, Altier C. TRPV1-targeted drugs in development for human pain conditions. Drugs, 2021, **81**(1):7-27

[51] 李魁君, 李春刚, 刘兴君. 辣椒素受体(TRPV1)的生物学作用及其作为药物靶点的研究进展. 沈阳药科大学学报, 2011, **28**(11):917-927
Li K J, Li C G, Liu X J. Journal of Shenyang Pharmaceutical University. 2011, **28**(11):917-927

[52] Abbas M A. Modulation of TRPV1 channel function by natural products in the treatment of pain. Chem Biol Interact, 2020, **330**:109178

[53] Szallasi A, Sheta M. Targeting TRPV1 for pain relief: limits, losers and laurels. Expert Opin Investig Drugs, 2012, **21**(9):1351-1369

Temperature Sensor TRPV1 Regulates Pain*

WU Yi-Qing[1)], TONG Zhi-Qian[1)**], WAN You[2)]

([1)]*Key Laboratory of Alzheimer's Disease of Zhejiang Province, School of Mental Health, Institute of Aging, Wenzhou Medical University, Wenzhou* 325035, China;

[2)]*Neuroscience Research Institute, Peking University, Beijing* 100083, China)

Abstract　The 2021 Nobel Prize in physiology or medicine was awarded to David Julius and Ardem Patapoutian, based on the outstanding contributions in temperature receptors TRPV1 and tactile receptors PIEZO1/PIEZO2, respectively. They elucidated the mechanisms underlying how the human nervous system senses cold/heat and mechanical stimulation, which contributes to the development of drugs for long-term pain. This article reviews David Julius' pioneering work on TRPV1 which can be activated by capsaicin, heat (>43℃), H^+ (pH<6.0), and the critical roles of TRPV1 participating in cancer pain, chronic inflammatory pain, neuropathic pain, and visceral pain by inducing peripheral and/or central sensitization.

Key words　TRPV1, cancer pain, inflammation pain, neuropathic pain, peripheral sensitization, central sensitization

DOI：10.16476/j.pibb.2021.0303

* This work was supported by grants from The National Natural Science Foundation of China (82071214, 81974166, 30570566), and Beijing Natural Science Foundation (M21004, 7202083).

** Corresponding author.

Tel：86-577-86699661，E-mail：tzqbeida@163.com

Received：October 8，2021　Accepted：October 22，2021