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翻译后修饰调控TRPV亚家族通道功能的研究进展*

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摘要 瞬时受体势（transient receptor potential，TRP）通道广泛分布于神经和非神经系统中，响应温度、化学和机械等多种刺激，在机体对外界环境的精确感知中发挥重要功能. 根据蛋白质序列的相似性，哺乳动物中TRP通道家族的27个成员分属TRPA、TRPC、TRPM、TRPML、TRPP和TRPV 6个亚家族. 其中TRPV亚家族包含了6个成员，分别为温度敏感型的TRPV1~4通道，以及对Ca^{2+}具有高选择通透能力的TRPV5和TRPV6通道. 研究结果表明，TRPV亚家族通道参与调控细胞内的离子稳态和信号传导，在温度感知和血管扩张等生理过程中发挥作用，并与癌症、心血管等多种疾病的发生和发展密切相关. 翻译后修饰（post-translational modifications，PTMs）是翻译中或者翻译后在蛋白质特定氨基酸上添加或删减修饰官能团的过程. 越来越多的研究结果表明，TRPV亚家族通道同样可以发生翻译后修饰，并对通道功能产生重要影响. 本文综述了目前已报道的磷酸化、糖基化、泛素化、SUMO化和共价修饰等多种翻译后修饰调控TRPV亚家族成员功能的主要研究进展，以期为进一步研究翻译后修饰对TRPV通道的功能调节提供参考，丰富我们对蛋白质翻译后修饰与生理或病理活动相关性的认识.

关键词 TRPV通道，翻译后修饰，钙信号
中图分类号 Q5，Q7
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瞬时受体势（transient receptor potential，TRP）通道是一类非选择性阳离子通道，参与感知细胞内、外的多种刺激，在多条信号通路中发挥作用. 翻译后修饰作为主要的内源调节手段操控蛋白质的一生. 目前翻译后修饰已有超过200余种类型，成为生命科学领域的研究热点. 本文对翻译后修饰调控TRPV亚家族功能的研究进展进行了综述.

1 TRPV通道的表达分布及生理功能

1.1 TRPV通道表达及分布

根据序列同源性，哺乳动物TRP通道被分为6大亚家族，其中香草素受体亚家族（transient receptor potential vanilloid，TRPV）是根据首个报道的成员TRPV1可响应辣椒素的刺激而得名[1]. TRPV亚家族有6个成员组成，包含参与伤害性感受的热敏通道TRPV1~4以及主导Ca^{2+}吸收/重吸收的TRPV5和TRPV6[2]. TRPV1是目前研究最多、了解最为深入的TRP通道，广泛分布于诸如下丘脑尾侧、中脑、三叉神经节（trigeminal ganglion，TG）、背根神经节（dorsal root ganglion，DRG）等神经组织中，以及心脏、肠胃、骨骼、肌肉、皮肤等非神经组织中[3-4]. TRPV2通道蛋白主要表达于感觉神经系统例如大脑、小脑中[5]，此外在非神经系统的多个器官中也有表达，诸如膀胱、淋巴结、心脏，其中在心脏间盘中表达量较丰富[6-7]. TRPV3通道常见于皮肤、口鼻和胃肠道等各种组织器官[8]. TRPV4通道蛋白在包括大脑、心脏、皮肤、肾脏、肺、脾脏等多个组织器官中均有表

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达[9-10]. TRPV5与TRPV6最早在卵母细胞中发现[11]，与TRPV1~4的表达分布存在较大差异，TRPV5主要分布于肾脏的远曲小管（distal convoluted tubules，DCT）和连接小管（connecting tubules，CNT）中，而TRPV6多存在于胃、肠道、胰腺、前列腺、子宫以及胎盘当中[12].

1.2　TRPV通道的结构及生物物理学特性

1.2.1　TRPV通道蛋白的结构

随着蛋白质解析技术的发展与进步，利用单颗粒冷冻电镜技术（single-particle electron cryomicroscopy，cryo-EM），TRPV1通道的结构于2013年以3.4 Å近原子的分辨率成功解析[13]. 在这之后，TRPV2[14-15]、TRPV3[16-17]、TRPV4[18]、TRPV5[19]、TRPV6[20-21]的蛋白质结构相继得到解析. 纳米碟技术（nano disc）与单颗粒冷冻电镜技术的创新性结合，使得跨膜蛋白的晶体结构更加稳定，TRPV1、TRPV2、TRPV5的结构得到进一步阐明[22-24].

功能性TRPV通道由同源或异源的四聚体组合而成，类似于电压门控离子通道[25]. 4个亚基围绕孔区对称排列（图1），其中每个亚基由6次跨膜α螺旋结构域（S1~S6）、胞内的N末端（N terminal domain，NTD）和C末端（C terminal domain，CTD）构成. 在C端紧邻S6跨膜区包含一段23~25个氨基酸组成的α螺旋，称为TRP结构域（TRP domain），这段短基序在TRPV家族中高度保守，与脂双层膜的内层平行延伸，并与多个区段相互作用，参与亚基的正确折叠以及组装，有助于对刺激的感应（sensing）和通道的变构偶联（coupling）. 其中，TRP结构域中的TRP盒（TRP box）在通道门控和脱敏过程中发挥重要作用[14-15]. 在TRPV亚家族的N末端含有6个锚蛋白重复序列（ankyrin repeat domain，ARD），它们由反向平行的α螺旋和1个指结构域（finger domain）构成凹面状结构，通常是TRPV通道与其他蛋白质相互作用的结合区[26-27]. 位于ARD与pre-S1螺旋之间的连接区段（linker domain）由反向平行β折叠和α螺旋构成. pre-S1螺旋中带正电荷的氨基酸（精氨酸、赖氨酸、组氨酸）在TRPV亚家族中保守存在[27]. S5和S6远离S1~S4延伸，与相邻亚基互作，通过域交换（domain-swapped）形成类似风车状的孔

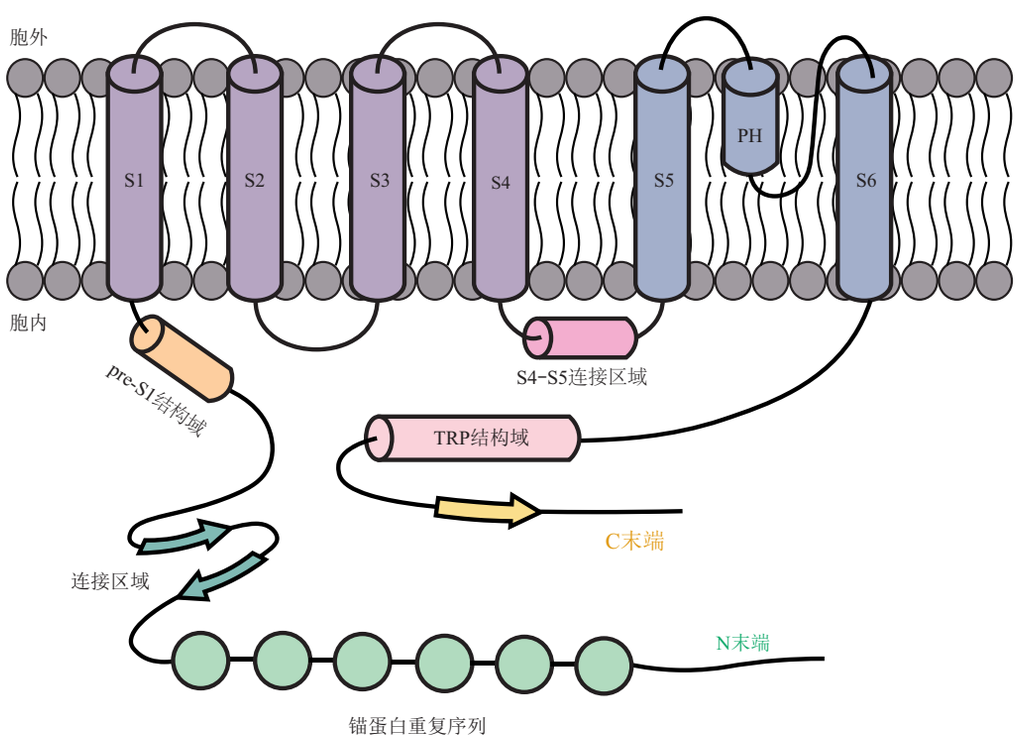

Fig. 1　The structure of single TRPV channel subunit

图1　TRPV通道单亚基结构

域[15，28]，构成中心孔和胞内的下门，在跨膜螺旋S5和S6之间包含一段短的疏水性凹环和螺旋，称为孔螺旋（pore helix，PH），形成一个选择性过滤器（selectivity filter），构成“倒置帐篷”（inverted teepee）式的离子通道孔环区（pore loop）[13]. S6螺旋在TRPV通道家族中高度保守，选择性过滤器在TRPV1~4中高度保守，而在TRPV5和TRPV6中序列同源性较高.

在TRPV通道的胞内部分，TRP结构域、S4~S5连接区与pre-S1三者互作，作为感受物理性刺激的位点[13]. 亚基N端连接区段中的两条β链与自身C端的β链共同构成三链β折叠，并与相邻亚基的ARD互作，组装并包围成胞内裙状结构域（skirt domain），调控通道与其他蛋白质的相互作用[18，28-29].

1.2.2　TRPV通道的离子选择性

TRPV通道是非选择性的阳离子通道，对Ca^{2+}具有一定的选择通透能力，TRPV1中P_{Ca}：P_{Na}=10，TRPV2中P_{Ca}：P_{Na}=2.9. TRPV5与TRPV6则对Ca^{2+}表现出了惊人的通透能力，钙钠的通透比值均大于100，表1对各TRPV通道的离子通透性进行了总结.

1.2.3　TRPV通道的门控特性

单一的TRPV通道亚家族成员均能响应各种物理和化学刺激方式，被称为多觉感受器（polymodal receptors）. TRPV1~4通道属于温度敏感型离子通道，其中TRPV1和TRPV2感受伤害性高温，而TRPV3和TRPV4感知非伤害性温度域刺激（温度响应阈值：TRPV1>42℃；TRPV2>52℃；TRPV3为31~39℃；TRPV4为27~35℃）[7-8，30-31]. 除了响应温度刺激外，TRPV1还能够被机械张力、渗透压等多种伤害性刺激激活[7]. TRPV2则感受低渗透压和机械应力[6]. TRPV4通道对渗透压和机械压力敏感[32-33].

除物理刺激外，TRPV亚家族成员还能响应多种化学刺激. TRPV1可以被酸性pH、蜘蛛毒素（spider toxin）、辣椒素（capsaicin）等香草素类化合物激活[1，3，34-35]. 其中辣椒素作为TRPV1的专一激动剂广泛应用[36]. TRPV1通道的活性还受到炎性因子如前列腺素（prostaglandin，PG）、缓激肽（bradykinin，BK）等调节. TRPV2通道对质子和辣椒素不敏感，可被生长因子、激素和内源性大麻素[37]以及外源小分子2-aminoethoxydiphenyl borate（2-APB）[38]和丙磺舒（Probenecid）等化学物质激活[39]. 但时至今日，TRPV2通道仍缺乏专一的激动剂和抑制剂，从而极大地限制了对TRPV2的进一步深入研究[40]. TRPV3通道感受诸如樟脑（camphor）、香芹酚（carvacrol）、2-APB、薄荷醇（menthol）和百里酚（thymol）[41]等化合物的刺激. TRPV4通道感受花生四烯酸（arachidonic acid）[42]、佛波酯衍生物（phorbol ester，4α-PDD）、GSK1016790A（也称GSK101）的刺激被激活[43-44]，其中GSK101是TRPV4的特异性激动剂. TRPV5和TRPV6在酸性pH环境下活性降低，在碱性pH下活性则上调[45]. 此外，TRPV5和TRPV6还受雌激素调节，雌激素抑制剂他莫昔芬（tamoxifen）能够降低TRPV6的表达从而抑制Ca^{2+}的转运[46-47]（表1）.

1.3　TRPV的生理功能

TRPV1通道参与温度感受、钙稳态、细胞增殖、分化和凋亡等过程[48]. 此外，TRPV1通道响应多种伤害性刺激而参与痛觉感知，由于TRPV1具有Ca^{2+}依赖的脱敏特性，脱敏后的TRPV1通道能降低对疼痛的持续感知，因此可作为慢性疼痛的治疗靶点. TRPV1与心血管疾病、高血压、癌症、消化系统疾病息息相关[31，48]. TRPV2在维持心脏的结构与功能中意义重大，TRPV2基因敲除小鼠的心脏泵功能下降、间盘结构紊乱、导致心肌纤维化与心力衰竭[6-7]. 在正常细胞中，TRPV2通道被激活后可通过膜泡靶向质膜运输，并通过诱导细胞凋亡对异常增殖进行负向调控. TRPV2的表达功能异常是引起诸如肌营养不良、心肌病、糖尿病、前列腺癌、成胶质细胞瘤等疾病的重要原因之一. 在多种肿瘤组织中TRPV2通道的表达量有所上调，如TRPV2的表达水平随尿路上皮膀胱癌细胞的级别和恶化程度而逐渐增加. TRPV3与皮肤的生理病理密切相关，介导皮肤疼痛、瘙痒等感觉的信号传导，影响角质细胞的增殖分化和毛囊发育的生理过程[49-51]，参与维护皮肤健康. TRPV3的获得性功能突变引起人类的Olmsted综合征（Olmsted syndrome），这是一种罕见的角化性皮肤病，为常染色体显性遗传[52-53]. TRPV4参与骨骼生长过程中的机械传导、血管舒张和血压调节过程. TRPV5主要负责对尿钙的重吸收，妇女绝经后TRPV5缺乏

雌激素的调节，Ca^{2+}的重吸收水平下降，导致患骨质疏松症的风险增加[47]. 在TRPV5基因敲除小鼠中，表现出高钙尿症和骨骼异常. TRPV6主要负责肠胃对Ca^{2+}的摄取能力， TRPV6蛋白的缺失导致骨矿物质密度降低、生育力下降并引发低钙血症. TRPV6在前列腺癌、乳腺癌、甲状腺癌、结肠癌、卵巢癌和胰腺肿瘤的组织样本中蛋白质和mRNA表达水平均上调[46]. 其异常表达被认为与多类癌症的发生相关.

2　多种翻译后修饰调节TRPV通道功能

蛋白质翻译后修饰能够发生在蛋白质“生命周期”的任何时期，通过各种信号通路激活不同的酶，相应的酶诱导蛋白质一个或多个氨基酸侧链与功能性化学基团共价结合，在调节蛋白质的活性、稳定性、定位、相互作用或折叠中起关键作用[54]. 目前发现TRPV亚家族可以发生如磷酸化（phosphorylation）、糖基化（glycosylation）、泛素化（ubiquitination）、SUMO化（small ubiquitin-like modifier， SUMO）、共价修饰（covalent modification）等多种类型的翻译后修饰，证实了TRPV通道的翻译后修饰在调控通道表达量、活性、功能等方面具有重要作用（表2）. 以TRPV1为例，图2对多种翻译后修饰对TRPV1通道功能的调节进行了总结.

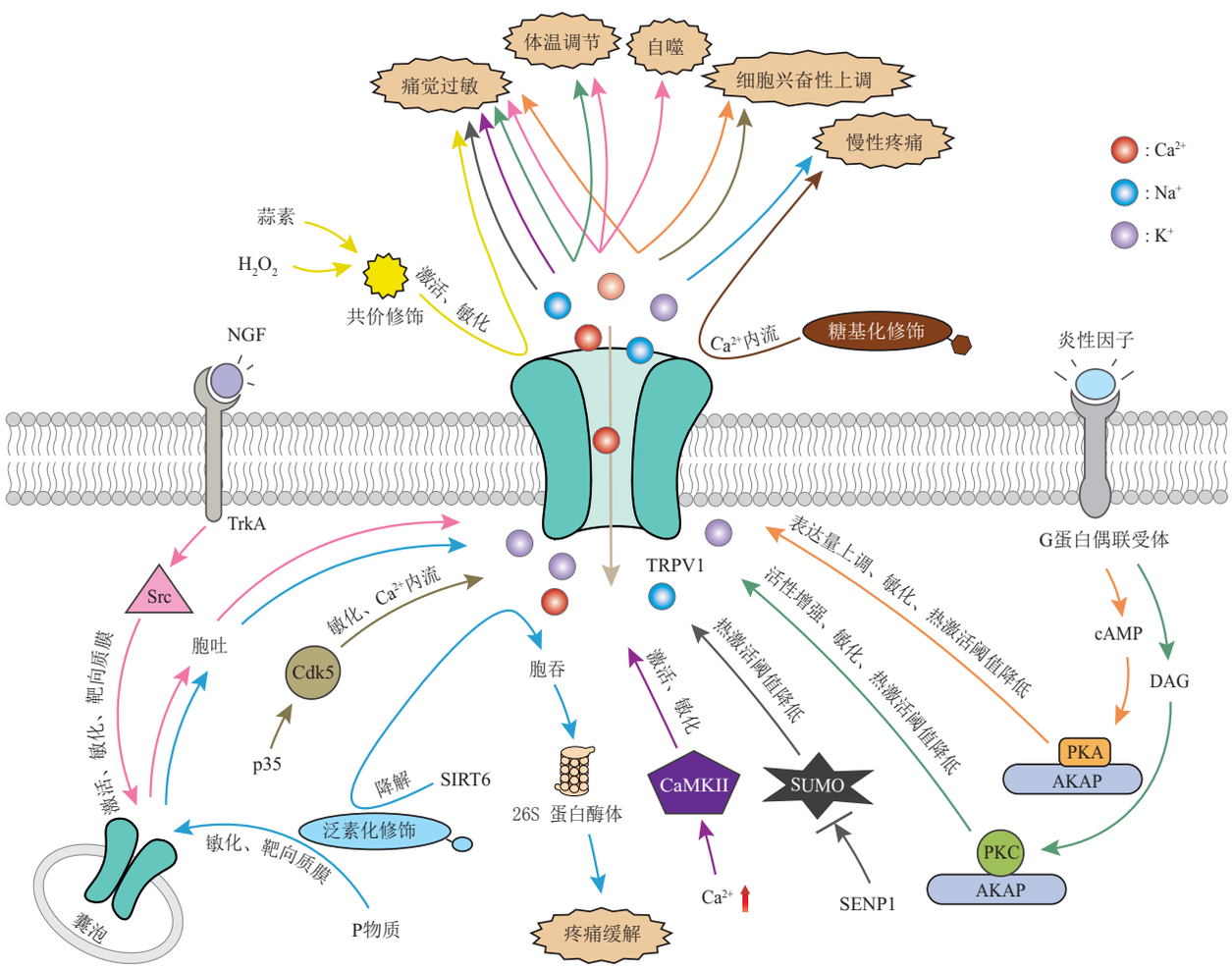

Fig. 2　Post-translational modifications regulate the function of TRPV1 channel

图2　翻译后修饰调控TRPV1通道功能

2.1　磷酸化修饰

磷酸化修饰通过蛋白激酶将磷酸基团添加在丝氨酸、苏氨酸或酪氨酸残基上，达到调控蛋白质的目的[55]. 目前发现的蛋白激酶有上百种，蛋白激酶大多通过磷酸化离子通道从而促进通道的激活、敏化或高表达，进而对刺激产生应答.

在组织损伤、热应激、渗透压刺激过程中，蛋白激酶A（protein kinase A，PKA）通过A激酶锚定蛋白79（A-kinase anchoring proteins 79，AKAP79）磷酸化TRPV1的S116、S502、T144和T370位点来维持TRPV1的功能，调节TRPV1通道的活性和定位，防止通道脱敏，从而响应各种促炎性介质对细胞兴奋性的调节[56-58]. 其中，T144、T370和S502三个位点中的任何一个突变都会阻止通道的敏化，S502是调控通道激活与敏化的关键位点[59]. 在NaCl诱导的高渗应激条件下，视网膜神经节细胞（retinal ganglion cells，RGCs）中PKA介导TRPV1蛋白表达量上调并激活离子通道，导致高渗压力下RGC的兴奋性上调并凋亡，从而介导视神经病变过程[60-61]. 在脂多糖（lipopolysaccharides，LPS）诱导的发烧模型中，PKA与蛋白激酶C（protein kinase C，PKC）介导TRPV1的磷酸化，导致TRPV1表达量上升并使其敏化，拮抗LPS诱导的高温状态，从而在体温调节中发挥作用[62]. 在痛觉过敏过程中，损伤部位释放的炎症介质通过G蛋白偶联受体的作用，激活PKA进而磷酸化TRPV1，导致TRPV1的热激活阈值降低，从而诱发炎症介导的痛觉过敏[57]. 另外，肥大细胞在响应物理刺激时，酰基辅酶A结合蛋白3（acyl CoA binding domain containing protein 3，ACBD3）能够与TRPV2相互作用，募集PKA，促进TRPV2的磷酸化，激活通道，引起肥大细胞脱颗粒作用[63]. 在烧伤皮肤的恢复过程，角质形成细胞中的PKA与PKC磷酸化TRPV3使其致敏，导致烧伤后的炎症反应与皮肤瘙痒[64]. 在冠状动脉内皮细胞中，H_2O_2介导TRPV4通道C末端的Ser824位点被PKA磷酸化，调控TRPV4通道的开启，并导致通道在低渗条件下敏化，进而诱导冠状小动脉扩张[65]. 在Ca^{2+}浓度降低时，甲状旁腺激素（parathyroid hormone，PTH）促使PKA磷酸化TRPV5通道T709位点，导致TRPV5单通道开放几率（open probability）增加，活化后的TRPV5通道增加了机体对尿液中Ca^{2+}的重吸收[66].

PKC可磷酸化鼠源TRPV1的S502、T704和S800位点，使得TRPV1通道敏化，热激活阈值降低，导致痛觉过敏和异常性疼痛[67]. 肌肉损伤或炎症反应释放的多种炎症介质（如缓激肽），能促进PKC介导的TRPV1 S800位点磷酸化，增强TRPV1的活性，导致肌肉组织出现机械性痛觉过敏[68]. 周围受损、发炎或缺血组织引起炎性介质（如缓激肽）的释放，触发PKC-ε磷酸化TRPV1的S505与S800位点，导致TRPV1对辣椒素的响应电流增大，引起炎性疼痛[69]. 在结肠炎模型中，PKC对TRPV1的磷酸化可降低通道的激活阈值并促进其靶向细胞膜转运，导致TRPV1活性增强，激活阈值降低，引起急性结肠炎后的慢性疼痛[70]. 总之，PKC诱导的TRPV1致敏与诸如慢性疼痛、膀胱炎和糖尿病性神经病变等疾病密切相关[71]. 在低渗溶液中，细胞膨胀致使PKC磷酸化TRPV4通道的S162、T175和S189三个位点，导致通道敏化[72]. 内皮细胞在感受机械刺激中，PKC-α介导TRPV4的磷酸化，导致内皮细胞血管舒张[73]. 在Ca^{2+}浓度降低时PTH还可促使PKC磷酸化TRPV5的S299和S654位点，抑制通道的内吞作用，导致细胞膜上通道表达量升高，且活性增加[74]. 肾病综合征（nephrotic syndrome，NS）患者尿纤溶酶（urinary plasmin）促使PKC磷酸化TRPV5的S144位点，导致Ca^{2+}重吸收受损[75]. 在胎盘中，当Ca^{2+}超载时，PKC-β促使TRPV6中S114和T688位点磷酸化，磷酸化将阻碍通道与ATP的结合，减少Ca^{2+}的流入[76].

除PKA和PKC之外，神经生长因子（nerve growth factor，NGF）促使Src酪氨酸激酶磷酸化TRPV1的Y200位点，致使通道快速敏化，导致组织损伤或细胞外炎性介质的释放后，痛觉感受神经元热痛觉感受阈值降低. 并且这一位点在TRPV1~4通道中保守存在，暗示Src酪氨酸激酶可磷酸化TRPV亚家族进而调节通道的功能[77]. 胸腺细胞在应激条件下（如营养因子缺乏、氧化应激过程），TRPV1被Lck酪氨酸激酶磷酸化，激活TRPV1通道，诱导细胞发生自噬[78]. 在低渗压力下，Src酪氨酸激酶Lyn可使TRPV4通道Y253位点磷酸化，

激活通道，且Lyn对TRPV4通道Y253处的磷酸化是低渗压力激活TRPV4所必需的[79]. 在外源表达体系中，发现Src磷酸化TRPV6的Y161/Y162位点，激活通道，促使细胞吸收Ca^{2+}[80]. 在对辣椒素的响应过程中，细胞周期依赖性蛋白激酶5（cyclin-dependent kinase 5，Cdk5）磷酸化小鼠TRPV1的T407位点，导致TRPV1敏化，Ca^{2+}内流，机体对疼痛的耐受性降低，此位点被视为调节疼痛敏感性的重要分子开关[81-82]. 在胚胎背根神经元（mouse dorsal root ganglion，DRG）发育过程中，信号调节激酶（signal-regulated kinase，ERK）通过对TRPV2中S6和S760位点的磷酸化，增加胞内Ca^{2+}水平并激活MAPK信号通路，促进神经突的生长[40]. 在表皮细胞中，表皮生长因子受体（epidermal growth factor receptor，EGFR）介导磷脂酶C（phospholipase C，PLC）和ERK磷酸化TRPV3上T264位点，导致通道敏化，促进毛发形态正常生长[83]. 在辣椒素激活TRPV1的过程中，钙调蛋白依赖性激酶II（Ca^{2+}-calmodulin dependent kinase II，CaMKII）磷酸化TRPV1的S502、T704位点，致使配体结合，通道激活并敏化，进而介导感觉神经元在炎性疼痛中的兴奋性[59].

2.2　糖基化修饰

糖基化修饰通常是利用酶促反应将糖链添加到脂质或蛋白质上. 糖基化修饰主要包括N-糖基化和O-糖基化修饰. 目前在TRPV家族中发现的糖基化修饰主要为N-糖基化修饰.

在慢性疼痛中，TRPV1的N604位点发生N-糖基化修饰可阻碍Ca^{2+}介导的脱敏作用，导致神经元对疼痛刺激的敏感性升高，可能发展为慢性疼痛[84-85]. 在大鼠的肥大细胞中，TRPV2的糖基化修饰有助于其与重组激活基因产生的蛋白质RAG（recombinase gene activator）互作，可能在TRPV2的成熟或运输中发挥作用[86]. 在鼠源TRPV2中发现了糖基化位点N567（兔源的糖基化位点有N571、N572），糖基化的蛋白质能够定位于细胞质膜上，而非糖基化的蛋白质则定位于胞质内[87]. TRPV4的Asn651位点发生的糖基化修饰会抑制TRPV4向质膜的转移，降低TRPV4对渗透压的敏感性[88]. β葡糖醛酸糖苷酶Klotho通过水解打断TRPV5的N358位点N-糖基化修饰，稳定TRPV5通道的活性和膜上表达量，将血钙浓度维持在合适的范围内[89-90]. 在TRPV6通道中，TRPV5上N358的同源位点N357同样存在由Klotho调控的N-糖基化修饰[90].

2.3　泛素化修饰

泛素化修饰是指泛素分子在泛素激活酶（E1）、泛素结合酶（E2）和泛素连接酶（E3）的接力作用下与靶蛋白相结合，进行特异性修饰的过程.

在结肠炎模型恢复过程中，结肠中P物质（substance P）表达量升高导致TRPV1通道敏化且泛素化水平增加，导致TRPV1致敏并聚集于细胞膜上，从而建立急性炎症后的持续性腹痛过程[91]. 脂多糖引起的牙髓炎中，烟酰胺腺嘌呤二核苷酸依赖的去乙酰化酶（NAD-dependent protein deacetylase）SIRT6的表达量下调，抑制了SIRT6诱导的TRPV1泛素化与降解，引起疼痛，表明SIRT6可作为牙髓炎的治疗靶标[92]. 在TRPV4的翻译和装配过程中，内质网结合蛋白OS-9通过与泛素连接酶竞争性结合TRPV4，抑制TRPV4的多聚泛素化，从而阻止了正确组装折叠的TRPV4蛋白被逆向转运至蛋白酶体中并降解[93]. β抑制蛋白（β-arrestin1）可以被招募到血管紧张素（angiotensin）AT1aR和TRPV4形成的复合体上，影响泛素连接酶AIP4与TRPV4相互作用，促进TRPV4发生泛素化修饰并被降解，导致血管收缩[94]. 在结肠炎模型中，小鼠肾上皮细胞中肿瘤坏死因子（tumor necrosis factor，TNF）等刺激因子降低Klotho的活性，这一过程促进TRPV5与泛素连接酶UBR4的相互作用，导致TRPV5泛素化修饰水平提高，促进TRPV5的内吞过程，导致肾脏中本该吸收的Ca^{2+}大量流失，尿钙浓度升高. 说明Klotho介导的N-糖基化修饰可以拮抗由泛素化引起的TRPV5蛋白表达水平的降低[95]. 在卵母细胞中共表达发育抑制蛋白Nedd4-2（neuronal precursor cell-expressed developmentally down-regulated 4-2）与TRPV6，发现TRPV6泛素化水平升高. 之后研究发现TRPV6通道的D204H和D376H位点作为分子开关调控TRPV6的表达水平[96].

2.4　SUMO化修饰

SUMO化修饰又被称为类泛素化修饰，与泛素化循环相似. Wang等[97]研究者近期发现，在小鼠背根神经节细胞中敲除去SUMO化酶SENP1后，加剧了弗氏完全佐剂（complete Freund's adjuvant，CFA）诱导的炎症模型中热痛觉过敏，进一步在炎症小鼠模型中研究发现TRPV1蛋白C端K822发生SUMO化修饰，能够特异地降低TRPV1通道的温度响应阈值（从约42℃降到36℃），导致热痛觉过敏，但却不影响通道对诸如辣椒素、H^+和电压的响应，该研究结果为镇痛药物的开发提供了新思路.

2.5　共价修饰

共价修饰是指在酶促作用下对蛋白质的单个或多个氨基酸通过共价连接或去除化学基团的修饰方式[98].

在DRG神经元细胞中，洋葱和大蒜的提取物蒜素对TRPV1通道N端的半胱氨酸（人源C158位点）进行共价修饰，激活通道，引起痛觉响应[99]. 在氧化应激过程中，TRPV1的4个位点（C158、C387、C391和C767）发生共价修饰，引起TRPV1有效而持久的敏化作用，导致疼痛感增强，进而发展为慢性疼痛[100].

Table 1　Biophysical characters of mammalian TRPV channels

表1　哺乳动物TRPV通道的生物物理特性

	TRPV亚家族成员					
	TRPV1	TRPV2	TRPV3	TRPV4	TRPV5	TRPV6
离子选择性	Ca^{2+}>Na^+≈K^+≈Cs^+≈Li^+≈Rb^+［1，101-102］	Ca^{2+}>Mg^{2+}>Na^+≈Cs^+>K^+［7］	Ca^{2+}>Na^+=K^+=Cs^+［49］	K^+>Cs^+>Rb^+>Na^+>Li^+［104］	Ca^{2+}>Mn^{2+}>Ba^{2+}>Sr^{2+}［105］	Ca^{2+}>Sr^{2+}≈Ba^{2+}>Mn^{2+}［106］
门控调节方式	前列腺素［103］ 缓激肽［30］ 蜘蛛毒素［35］ 辣椒素［1］ （>42℃）［7］ 酸性pH［1］ 渗透压［7］ 瘙痒［34］	内源性大麻素［37］ 2-APB［38］ 丙磺舒［39］ 生长因子［40］ 低渗透压［6］ 机械应力［6］ （>52℃）［8］	樟脑［41］ 香芹酚［41］ 2-APB［41］ 丁香酚［41］ 百里酚［41］ （31-39℃）［30］	花生四烯酸［42］ 佛波酯衍生物［44］ GSK1016790A［43］ （27-35℃）［31］ 渗透压［32］	雌激素［47］ 维生素D［35］ pH［45］	雌激素［46］ 维生素D［35］
主要表达分布	下丘脑尾侧［3］ 中脑［3］ 三叉神经节［3］ 背根神经节［3］ 心脏［3，4］ 膀胱［3］ 骨骼［4］ 肌肉［3］ 皮肤［3，4］	大脑［5］ 小脑［5］ 膀胱［6］ 淋巴结［6］ 心脏［6，7］ 肌肉［7］	皮肤［8］ 口鼻［8］ 肠胃［8］	大脑［9］ 心脏［10］ 皮肤［9，10］ 肾脏［10］ 肺［10］ 脾脏［10］	肾脏［12］	前列腺［12］ 子宫［12］ 肠胃［12］ 胎盘［12］ 胰腺［12］

Table 2　Post-translational modification regulate the function of TRPV channels

表 2　翻译后修饰调控TRPV通道功能

TRPV亚家族成员	修饰类型	酶	修饰位点	功能	参考文献
TRPV1	磷酸化	PKA	S116，S502，T144，T370	防止通道脱敏，介导痛觉过敏，调节细胞兴奋性，导致凋亡或自噬	［56-61］
		PKC	S502，T704，S800	通道敏化，热激活阈值降低，靶向细胞膜，导致痛觉过敏或慢性疼痛	［67-71］
		Src	Y200	通道快速敏化并靶向细胞膜，热痛觉阈值降低，导致痛觉过敏或诱导细胞自噬	［77-78］
		Cdk5	T407	通道敏化，Ca^{2+}内流，导致痛觉过敏	［81-82］
		CaMKII	S502，T704	通道激活并敏化，导致炎性疼痛	［59］
	糖基化		N604	防止通道脱敏，可发展为慢性疼痛	［84-85］
	泛素化			靶向质膜，导致炎症后的慢性疼痛；导致通道降解，缓解疼痛	［91-92］
	SUMO化		K822	降低通道的温度响应阈值，导致热痛觉过敏	［97］
	共价修饰		C158，C378，C291，C767	通道敏化，导致慢性疼痛	［99-100］
TRPV2	磷酸化	PKA		激活通道，引起肥大细胞脱颗粒作用	［63］
		ERK	S6，S760	胞内Ca^{2+}水平升高并激活MAPK信号通路，促进神经突的生长	［40］
	糖基化		N567	可能在TRPV2的成熟或运输中发挥作用	［86-87］
TRPV3	磷酸化	PKA		通道敏化，介导烧伤后的炎症反应与皮肤瘙痒	［64］
		PKC		通道敏化，介导烧伤后的炎症反应与皮肤瘙痒	［64］
		ERK	T264	通道致敏，促进毛发形态生长正常	［83］
TRPV4	磷酸化	PKA	S824	通道敏化，从而诱导冠状小动脉扩张	［65］
		PKC	S162，T175，S189	通道敏化，导致内皮细胞血管舒张	［72-73］
		Src（Lyn）	Y253	激活通道	［79］
	糖基化		N651	抑制TRPV4向质膜的转移，降低TRPV4对渗透压的敏感性	［88］
	泛素化	AIP4		通道降解，血管收缩	［94］
TRPV5	磷酸化	PKA	T709	单通道开放概率增加，增加对尿液中Ca^{2+}重吸收	［66］
		PKC	S144，S229，S654	S299，S654：抑制通道的内吞作用，膜上表达量升高，活性增加	［74］
				S144：导致Ca^{2+}重吸收受损	［75］
	糖基化		N358	稳定TRPV5通道的活性和膜上表达量，将血钙浓度维持在合适的范围内	［89-90］
	泛素化	UBR4		促进TRPV5的内吞过程，尿钙浓度升高	［95］
TRPV6	磷酸化	PKC	S144，T688	阻碍通道与ATP的结合，减少Ca^{2+}的流入	［76］
		Src	Y161，Y162	激活通道，促使细胞吸收Ca^{2+}	［80］
	糖基化		N357（90）		
	泛素化	Nedd4-2	D204，D367	调控TRPV6的表达水平	［96］

3　小　　结

TRPV亚家族进化上高度保守，参与从酵母到哺乳动物等生物的多个重要生理过程，受到各种内源性物质和外源化合物等化学刺激的调控，也可感受物理刺激（如温度、渗透压、机械应力等）. 研

究结果表明，TRPV亚家族成员是翻译后修饰的重要靶标，这些修饰极大地丰富了通道功能的调控方式，通过单独作用甚至是相互拮抗或者共同作用来调节TRPV通道的生物学特性如通道的敏感性、表达量、运输、定位、门控等. 对于TRPV亚家族翻译后修饰的研究有助于对通道调控机制的认识，并为相关靶向药物的研发提供新策略.

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Research Progress on Post−translational Modification Regulate The Function of TRPV Channel*

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Abstract　Transient receptor potential (TRP) channels are widely distributed in nervous and non-nervous systems, responding to thermal, chemical, mechanical and other stimuli. They are emerging as essential sensory molecules that allow animals to respond to environmental changes. The 27 members of the mammalian TRP superfamily are grouped into six subfamilies, the TRPA (ankyrin) family, the TRPC (canonical) family, the TRPM (melastatin) family, the TRPML (mucolipin) family, the TRPP (polycystin) family, and the TRPV (vanilloid) family on the basis of amino acid sequence homology. The TRPV subfamily is composed of six members, TRPV1−6. They can be further divided into two groups, TRPV1−4 subgroup which is weakly Ca^{2+}-selective and highly sensitive to heat, and TRPV5, TRPV6 subgroup which is highly Ca^{2+}-selective and not heat-sensitive. Mounting evidences suggest that TRPV channels are responsible for membrane potential regulation and intracellular Ca^{2+} signaling, and thus regulate a large number of cellular functions, such as temperature sensation and vasodilation. Dysfunction in channel expression and/or activity has been linked to human disease like cancer and cardiovascular disease. Post-translational modifications (PTMs) involving a functional group being added to a protein, a chemical change in amino acids, and a structural change in the protein have been implicated in regulating activity, localization and interaction with other cellular molecules, thereby increasing the functional diversity of the proteome. Many studies show that TRPV subfamily channels can also undergo post-translational modifications and PTMs have an important impact on channel function. The aim of this review is to address the major advances regarding the various post-translational modifications such as phosphorylation, glycosylation, ubiquitination, SUMOylation, and covalent modification that have been reported to regulate the functions of TRPV channels. Furthermore, we also discussed the possible functions of TRPV channels before and after PTMs in physiological or pathological activities, for a better understanding of the relationship between PTM and physiological or pathological activities.

Key words　TRPV channel, post-translational modification, calcium signaling

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