·综 述·

瞬时受体电位通道在呼吸系统疾病中的作用研究进展

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摘要：瞬时受体电位（TRP）离子通道是一类非特异性的阳离子通道蛋白家族，在呼吸道感觉神经纤维和非神经细胞中广泛表达，能响应多种刺激，从而参与呼吸系统疾病的发生发展过程。其中TRPA1，TRPV1，TRPV4和TRPM8亚型在呼吸道组织损伤和炎症反应中的作用尤为重要，是近年来呼吸系统领域研究的热点。本文重点对TRPA1，TRPV1，TRPV4和TRPM8在咳嗽、哮喘和慢性阻塞性肺病等呼吸系统疾病中的作用进行综述，提示TRP通道可作为治疗呼吸道疾病的潜在药物靶点。

关键词：瞬时受体电位；咳嗽；哮喘；慢性阻塞性肺病

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瞬时受体电位（transient receptor potential，TRP）最早发现于视力受损的果蝇，因携带TRP突变基因的果蝇在接受持续光照射时光感受器只产生瞬时而非持续性的电位变化而得名[1]。TRP阳离子家族被认为是最大的离子通道家族之一，目前已发现约30个TRP基因和100多个TRP通道，按其氨基酸序列的同源性差异分为7个亚家族，包括TRPC（canonical，TRPC1～TRPC7），TRPV（vanilloid，TRPV1～TRPV6），TRPM（melastatin，TRPM1～TRPM8），TRPA（ankyrin，TRPA1），TRPP（polycystin，TRPP1～TRPP3），TRPML（mucolipin，TRPML1～TRPML3）和TRPN（Drosophila NOMPC），但TRPN蛋白仅在鱼类和果蝇中检测到，哺乳动物中尚未检测到*TRPN*基因的表达[2]。近来在酵母中发现了第8个TRP亚家族，命名为TRPY（Yeast）[2]。TRP家族的共有特征是含6个跨膜多肽（S1～S6），S5和S6之间向内嵌入形成的疏水区是转运离子的孔道区域，不同亚型跨膜多肽结构的锚蛋白重复序列数目不同。同种或异种TRP亚单位组成的同源或异源四聚体构成功能性离子通道，与K^+和Ca^{2+}的电压门控通道具有相似性，对Ca^{2+}，Mg^{2+}，Na^+和K^+等多种单价或二价阳离子具有通透性[3-5]。

TRP在心、肝、肺、肾、胰腺、前列腺、大脑和肠道等多种组织中表达，与器官纤维化、癌症、阿尔茨海默病等多种疾病的发生密切相关。TRP除响应光刺激外，还介导机械刺激、化学刺激、血管舒张、代谢应激及温度、渗透压和pH的改变等引发的反应[6]。鉴于其具有响应多种信号刺激的能力，TRP又被称为细胞传感器和信号整合器。

1 与呼吸系统疾病密切相关的TRP通道

在呼吸系统中，多种不同亚型的TRP通道对呼吸系统生理病理功能发挥重要调控作用，TRP通道已成为近十年来呼吸道疾病研究的热点，其中TRPA1，TRPV1，TRPV4和TRPM8亚型与呼吸道疾病密切相关且研究较多。

1.1 TRPA1

TRPA1主要在直径很小的感觉神经元上表达[7]，也在支气管上皮细胞、平滑肌细胞和肺成纤维细胞等非神经元细胞上表达[8]。哺乳动物的TRPA1和TRPV1在脊髓背根神经节、鼻三叉神经和迷走神经等具有细胞体的C纤维子集中共表达，激活后会促进神经激肽A（neurokinin A，NKA）、P物质和降钙素基因相关肽（calcitonin gene related peptide，CGRP）的释放[9]。温度变化、空气污染物和烟雾等外部刺激以及肉桂素、异硫氰酸烯丙酯和大蒜素等化学刺激均能以不同作用方式选择性靶向激活TRPA1；钙离子、微量金属、活性氧（reactive oxygen species，ROS）、氮、羰基物质、缓激肽和神经生长因子等均可作为TRPA1的内源性激活剂，进而调控TRPA1的表达[9-12]。

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1.2 TRPV1

TRPV1在背根神经节、三叉神经和迷走神经中高表达[13]，表达TRPV1的神经元中通常还能检测到与TRPA1和TRPV4等通道的共表达，这些共表达的通道大多与P物质、神经肽和CGRP的产生有关。在肺泡上皮细胞、气道上皮细胞（airway epithelial cells，AEC）和气道平滑肌（airway smooth muscle，ASM）细胞等非神经细胞中，TRPV1的表达可能与气道中白细胞介素（interleukin，IL）-8、IL-13和IL-33等炎症介质的释放有关[14-16]。高温（42～53℃）、细胞外低pH（pH 5～6）、一些脂质衍生物和外源性化合物等均能激活TRPV1[17-20]，缓激肽、前列腺素E2（prostaglandin E2，PGE2）和蛋白酶激活受体2激活肽等炎症介质可能通过G蛋白偶联受体激活TRPV1[21-22]。

1.3 TRPV4

TRPV4在神经元、角质形成细胞、内皮细胞、单核细胞、肺泡巨噬细胞和中性粒细胞等细胞中表达[23]，在气管、支气管和下呼吸道的上皮衬层以及肺泡隔中高表达。5，6-环氧二十碳三烯酸和4α-佛波醇-12，13-二癸酸等化学物质以及膜牵张和低渗等物理刺激均可激活TRPV4。此外，TRPV4通道是一个温度感受器，27～35℃即可激活TRPV4[24]。

1.4 TRPM8

吸入冷空气可引起气道收缩、咳嗽和血浆蛋白外渗等呼吸道反应，并可引发哮喘，而TRPM8被广泛认为是冷觉感受器，丰富表达于鼻黏膜神经纤维中[25-26]。在人支气管上皮细胞中发现了一种冷和薄荷醇激活的TRPM8截短变异体，寒冷（≤18℃）或相对较高浓度的薄荷醇可激活肺细胞中的TRPM8变异体，进而可介导IL-1α、IL-1β、IL-4、IL-6、IL-8、IL-13、粒细胞-巨噬细胞集落刺激因子（granulocyte-macrophage colony stimulating factor，GM-CSF）和肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）等一系列促炎性细胞因子的表达[27]。

2 TRP通道在呼吸系统疾病中的作用

2.1 TRP通道与咳嗽

气道受迷走神经传递至中枢神经系统的感觉传入神经调控，其受体有快速适应性受体Aδ纤维、缓慢适应性拉伸受体和无髓C纤维，其中C纤维是引起咳嗽的主要纤维类型[28]，从迷走神经细胞体突出的轴突通过多条神经分支到达气道，将纤维输送至气管和支气管[29]。目前，对TRP通道亚型TRPA1，TRPV1和TRPV4在咳嗽中的作用机制研究较多，对TRPM8的报道相关较少。

支气管迷走神经能响应多种TRPA1激动剂如肉桂素和大蒜素等的激活，气道受到刺激时，会优先表达TRPA1阳离子通道，进而激活迷走性支气管肺C纤维，诱发咳嗽[20,30-31]。H_2S可通过作用于感觉神经元TRPA1 N端内部结构域中的2个半胱氨酸残基诱导其活化，进而通过TRPA1介导辣椒素敏感性肺迷走神经传入纤维的超敏反应引发哮喘等气道炎症性疾病[32]。使用TRPA1拮抗剂HC-030031或AP-18能够消除因吸入H_2S供体NaHS后对辣椒素敏感性肺迷走神经元内向电流的增强作用，而使用TRPA1激动剂则会对辣椒素敏感性肺迷走神经元介导的气道反射产生与H_2S刺激类似的增敏作用。内源性炎症介质缓激肽通过作用于二级神经元上的B2受体（bradykinin B2 receptor，B2R），刺激环氧合酶和12-脂氧合酶代谢产物的释放，进而激活二级神经元上的TRPV1和TRPA1通道，增强咳嗽反应[21]。另有研究发现，神经生长因子和聚肌胞苷酸模拟病毒处理周围神经元等效物后，可直接快速诱导激活TRPA1，可能与咳嗽反射过反应的神经炎症有关[33]。

TRPA1在非神经细胞中的表达与呼吸系统疾病关系的研究较少。有研究表明，A549肺泡Ⅱ型上皮细胞中TRPA1的激活可促进细胞钙内流的增加，进而激活细胞外信号调节激酶（extracellular signal-regulated kinases 1/2，ERK 1/2）通路，并促进一氧化氮的产生[34-35]；另外，ASM细胞上TRPA1的激活可抑制细胞增殖，同时促进血管内皮生长因子的释放[36-37]。激活豚鼠气道TRPA1诱导产生非上皮PGE2，可中和河豚毒素敏感神经因TRPA1激活所产生的支气管收缩作用，最终在气道中的综合反应表现为气道松弛，推测刺激ASM的TRPA1可介导旁分泌PGE2缓解气道收缩，但PGE2具体来源尚未明确[38]。

TRPV1特异性激动剂辣椒素可有效激活多种动物的咳嗽反射[39]，其特异性抑制剂SB705498可有效抑制辣椒素诱导的咳嗽[40]，并显著降低P物质、CGRP和NKA的浓度，减少肺组织炎性细胞浸润或支气管纤毛堆积，具有治疗慢性咳嗽的潜力。TRPV1单核苷酸多态性（single nucleotide polymorphisms，SNP）会改变通道的功能特性[41]，与工作场所暴露的咳嗽易感患者患慢性咳嗽的风险更高有关[42]，而携带TRPV1-V585突变体的人群可能对呼吸道刺激不敏感[43]。Liviero等[44]进一步在人

体试验中评估了TRPV1的6种SNP对辣椒素诱导产生咳嗽之间的关系，证实了人体对辣椒素敏感性咳嗽归因于4种SNP（I315M, I585V, T469I和P91S）的组合。目前对于SNP的变异性来源尚不清楚，对这种基因变异诱发咳嗽的原因仍有待进一步研究。其他研究发现，豚鼠气道的过敏性炎症与气管Aδ神经元的TRPV1表达有关，过敏原刺激会在气道黏膜中产生脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）和胶质细胞源性神经营养因子，BDNF诱导大多数气管Aδ神经元中TRPV1的表达，外源使用BDNF或胶质细胞源性神经营养因子可模拟变应原刺激诱导气管Aδ神经元中TRPV1表达增加及通道开放[45]。

TRPV4-ATP-P2X3相互作用是低渗诱导激活气道感觉神经反射的主要通路，TRPV4配体和低渗溶液导致小鼠、豚鼠和人迷走神经去极化并激活Aδ纤维，而TRPV4和P2X3抑制剂均能拮抗由TRPV4诱发的咳嗽[46]。相对TRPA1和TRPV1来说，对TRPV4引起咳嗽反应的研究相对较少，机制也尚不明确。

2.2 TRP通道与哮喘

哮喘是一种常见的慢性呼吸系统疾病，反复发作时出现咳嗽、呼吸困难、胸闷和喘息等症状，病理特征是出现嗜酸性粒细胞肺部浸润和肥大细胞脱粒[47]，全世界有>3亿不同年龄段的人群深受其扰[48]。由于平滑肌的收缩主要由支配肺和气道的感觉和运动神经元控制，因此普遍认为周围神经系统在哮喘中起重要作用[49]。哮喘通常与环境过敏原有关，寒冷、烟雾、尘螨以及环境中刺激性化学物质如异硫氰酸烯丙酯（allylisothiocyanate，AITC），肉桂醛和大蒜素等均可诱发哮喘的发生[9,50]。TRP通道中TRPA1，TRPV1和TRPV4参与调控哮喘的研究较多且较为深入。

ROS、脂质过氧化产物和多种炎症介质是引起哮喘气道炎症的过敏原，同时也是TRPA1通道的内源性激动剂[20]。冷空气也是哮喘发生的强力诱因。Du等[10]发现，温度变化加剧了卵白蛋白（ovalbumin，OVA）诱导小鼠哮喘模型的气道炎症，支气管肺泡灌洗液中血清总IgE和IgG1增加，且在最大温差（16℃）条件下TRPA1表达明显上调，给予TRPA1抑制剂HC030031后模型小鼠的哮喘明显减弱。但对于TRPA1是否为冷觉感受器一直存在争议[51]。

使用OVA分别刺激*TRPA1*基因敲除大鼠和野生型大鼠[52]，相对于未受刺激大鼠，接受OVA刺激的野生型大鼠支气管肺泡灌洗液中白细胞数显著增高，而*TRPA1*基因敲除大鼠白细胞浸润则明显被抑制；Caceres等[53]使用OVA刺激*TRPA1*基因敲除小鼠得到相同结论，TRPA1拮抗剂HC-030031亦能有效抑制OVA刺激引起的气道白细胞浸润、黏液产生和气道高反应性[53]。新型TRPA1拮抗剂BI01305834在豚鼠哮喘模型中能防止变应原和组胺引起的气道变窄，并逆转变应原引起的支气管收缩[54]。此外，Wang等[55]使用OVA和$PM_{2.5}$诱导的哮喘模型发现，三拗汤可通过抑制TRPA1和TRPV1通道，减少炎性细胞浸润及气道高反应性，推测其作用机制与其对Th2相关细胞因子IL-13和神经因子的调控有关。

Yap等[9]研究发现，TNF-α可上调人肺成纤维细胞*TRPA1*基因转录水平，并提高TRPA1介导的Ca^{2+}内流。虽已有大量研究表明哮喘发生与TRPA1密切相关，但也有研究发现晚期哮喘反应与TRPA1的表达无关[56]。对于TRPA1如何介导哮喘发生以及相关调控因素还有待进一步研究。

辣椒素诱导的咳嗽反应与哮喘反应早期的气流阻塞以及晚期的痰嗜酸性粒细胞增多有关[57]。研究表明，TRPV1在粉煤灰诱发的哮喘发作过程中具有调控作用[58]。此外，$PM_{2.5}$和甲醛均可作为哮喘发生的诱因，在2种因素共同作用于BALB/c小鼠后，会加剧过敏性哮喘发作，导致ROS、炎症因子和血清免疫球蛋白IgE水平升高，同时激活TRPV1通道，促进P物质和降钙素基因相关肽的表达增加，引起神经源性炎症继而诱发哮喘[59]。OVA致敏小鼠暴露于$PM_{2.5}$环境中，TRPV1与TRPA1表达均显著升高[11]，同时伴随着IL-13、P物质、前列腺素D2（prostaglandin D2，PDG2）和神经生长因子的表达升高。Schiffers等[16]研究发现，TRPV1与过敏原诱导的上皮IL-33分泌有关，它和蛋白酶激活受体2（protease-activated receptors 2，PAR2）的激活会促进ATP释放和P2YR2依赖性信号转导。使用微RNA可以有效抑制OVA诱导的哮喘模型小鼠嗜酸性气道炎症，减轻哮喘发作[60]。

虽有研究表明，TRPV1能调节$CD4^+$T细胞的激活和炎症特性，减弱晚期哮喘反应的表型[61]，但TRPV1抑制剂JNJ-17203212对OVA诱导的大鼠或小鼠晚期哮喘反应无显著抑制作用[62]。OVA刺激*TRPV1*缺失的小鼠仍会出现白细胞、巨噬细胞等炎症细胞升高，提示过敏性哮喘的发生可能与TRPV1通道无关[53]。Trankner等[63]同时敲除*TRPV1*，*TRPA1*和*MrgD*在神经元的表达，OVA诱

导的哮喘模型小鼠未出现OVA依赖性的气道高反应性，但仍出现过敏原特异性免疫球蛋白的产生和肺中白细胞的积累等免疫反应，发现1-磷酸鞘氨醇（sphingosine-1-phosphate，S1P）可能是连接免疫细胞活性与哮喘反应中感觉神经元依赖性气道高反应性的信号之一。

研究表明，TRPV4的SNP与哮喘和慢性阻塞性肺疾病（chronic obstructive pulmonary disease，COPD）发生有关[64-65]。此外，在ASM上，花生四烯酸衍生物或蛋白酶等内源性配体激活TRPV4促进ATP释放，通过泛连接蛋白离子孔使肥大细胞P2X4依赖性的半胱氨酰白三烯释放，从而引起ASM收缩，可能是哮喘发生的重要机制[66]。将BALB/c小鼠暴露于甲醛和湿度相对较高的环境中时，会引起肺中TRPV4-p38 MAPK通路激活，导致炎症加剧，气道黏液分泌增多，引起过敏性哮喘加重[67]。在慢性哮喘发生过程中，TRPV4还能介导KCa3.1通道调节人支气管平滑肌细胞增殖，阻断TRPV4可减弱因KCa3.1激活引起的细胞外Ca^{2+}内流。因此，TRPV4有可能成为治疗慢性哮喘的潜在靶标[68]。

2.3 TRP通道与慢性阻塞性肺病

COPD主要影响小气道和肺实质[69]，ROS或内源性抗氧化损伤等氧化应激是COPD的主要诱因，细胞内线粒体、二氢烟酰胺-腺嘌呤二核苷酸磷酸氧化酶和黄嘌呤/黄嘌呤氧化酶系统损伤导致的氧化应激也会导致COPD[70]。另外，炎症、烟雾、大气污染、粉尘、过敏、营养不良和植物神经功能紊乱等都可能导致COPD的发生。COPD和哮喘虽均以气道阻塞为特征，但气道阻塞在哮喘中是可逆的，在COPD中是进行性的且在很大程度上是不可逆的[47]。

近年有许多研究TRPA1和TRPV1参与此类疾病的相关机制报道，尤其聚焦于TRPA1在此过程中发挥的调控作用。研究表明，COPD患者AEC的*TRPA1*和*TRPV1*基因表达显著升高[71]。此外，香烟烟雾可靶向激活TRPA1诱发COPD，但具体的激活成分尚未阐明[72-73]。Xu等[74]研究发现，香烟烟雾提取物能诱导AEC（A549和Beas-2B细胞）的Ca^{2+}内流，降低抗氧化基因表达，并增强炎症相关基因表达，促进细胞内和线粒体中的ROS增加；使用TRPA1和TRPV1的抑制剂或基因敲除技术后细胞Ca^{2+}内流减少，同时细胞抗氧化基因mRNA的表达水平提高，细胞内和线粒体中ROS水平明显降低，能有效阻止线粒体损伤和下游的炎症反应。此外，香烟烟雾使A549和Beas-2B细胞中Nod样受体蛋白3（Nod-like receptor protein 3，NLRP3）表达显著升高，NLRP3介导的IL-1β和IL-18炎症介质也显著升高，敲除或抑制*TRPA1*和*TRPV1*能降低NLRP3及其介导的炎症因子的表达[75]。Yap等[76]同样发现，抑制TRPA1可以降低NLRP3/胱天蛋白酶1炎症小体复合物、以及IL-8等炎症因子的释放。Jian等[77]研究发现，黄酮可以通过调控TRPV1从而抑制香烟烟雾引起的COPD小鼠气道炎症反应和氧化应激。

TRPA1通道激活能调控线粒体中Ca^{2+}内流，引起线粒体内ROS升高，导致线粒体功能障碍从而引发哮喘和COPD等慢性疾病[78]。急性线粒体功能障碍中线粒体产生的大量ROS可优先作用于TRPA1，引起TRPA1的N端半胱氨酸修饰，从而激活气道感觉神经，引发哮喘等疾病[78]。超氧化物和H_2O_2均可直接激活TRPA1通道；敲除*TRPA1*后，低浓度H_2O_2（<10 mmol·L^{-1}）对线粒体无刺激作用，但高浓度H_2O_2（120 mmol·L^{-1}）对线粒体仍具有刺激作用[79]。

2.4 TRP通道与其他呼吸道疾病

2019年，新型冠状病毒肺炎（coronavirus disease 2019，COVID-19）在全球蔓延。COVID-19可引起呼吸衰竭等严重呼吸系统症状。哮喘或COPD等慢性呼吸系统疾病的患者感染COVID-19的风险较高[80]，感染后一个突出特征是细胞因子驱动的炎症级联反应被强烈激活。最新研究表明，TRPV4可能是COVID-19导致肺损伤机制的靶标之一，因为感染严重急性呼吸综合征冠状病毒2（severe acute respiratory syndrome coronavirus 2，SARS-CoV-2）后会导致肺泡毛细血管屏障功能障碍，直接后果是引发肺水肿。而对心源性肺水肿和慢性咳嗽患者的临床研究表明，抑制TRPV4通道可保护肺泡毛细血管屏障。因此，可考虑将靶向抑制TRPV4作为治疗COVID-19的辅助疗法[81-82]。同样，基于TRPV1在呼吸系统炎症反应中的作用，阻断TRPV1也可能改善COVID-19患者呼吸系统症状[83]。

研究发现，在豚鼠肺纤维化模型中，TRPA1和TRPV1表达均上调[31]；在肺纤维化过程中，激活TRPV4可强化转化生长因子β1（transforming growth factor-β1，TGF-β_1）诱导的肺纤维化中肌动蛋白重塑，并增加α平滑肌肌动蛋白转录共激活因子的核易位，加快肺纤维化过程[84]。

TRPM8通常被认为是冷觉感受器[85]，丰富表达于鼻黏膜神经纤维中[25-26]，冷或薄荷醇激活人支气管上皮细胞中TRPM8截短变异体，引起一系列促炎性细胞因子的表达增强，通过使用TRPM8拮

抗剂BCTC或小干扰RNA技术可抑制这种激活作用[86]。近来也有研究发现,冷空气可通过TRPM8介导的哮喘小鼠AEC中的PKC/NF-κB信号途径诱导炎症反应[87]。虽然对TRPM8在呼吸系统疾病中的作用虽知之甚少,但已有研究表明,外界冷空气的刺激很可能通过激活TRPM8来诱发机体呼吸系统疾病。因此,TRPM8可能是治疗鼻炎等呼吸道炎症的潜在靶标。

3 TRP通道靶向治疗药物

近年来越来越多的研究揭示了TRP在结构和功能上的多样性,也开展了很多靶向TRP通道的药物研究临床试验。但由于在神经元细胞和多种非神经元细胞中激活TRP通道所引起的机体反应复杂性,加之TRP通道参与的调控机制尚未完全阐明,使靶向TRP通道的药物研发充满挑战。

TRPA1拮抗剂GRC-17536能有效抑制香烟烟雾提取物、巴豆醛、丙烯醛以及AITC诱导的Ca^{2+}内流,也可抑制AITC引起人肺成纤维细胞如CCD19-LU细胞和人肺泡上皮细胞如A549细胞中IL-8的释放,对柠檬酸引起的豚鼠咳嗽起到很好的抑制效果,目前GRC-17536已进入治疗慢性咳嗽的Ⅱ期临床试验。TRPA1抑制剂甘草苷(liquiritin)可通过双重抑制TRPV1和TRPA1通道抑制LPS引起的肺损伤[20]。

TRPV1拮抗剂大多为镇痛药,辣椒平(capsazepin)是最先发现的可以阻断由辣椒素引起TRPV1通道开放的化合物,但无法拮抗其他激动剂作用于辣椒素敏感的神经元引起的生物学反应,且具有物种选择性和非特异性。氨基化合物BCTC[88]、甘氨酰氨类复合物H-Arg-15-15C[89]均可通过阻断TRPV1发挥镇痛作用,其中BCTC浓度依赖性地抑制辣椒素诱导的Ca^{2+}内流,是强效的选择性TRPV1阻断剂。AMG-517也是高度选择性的TRPV1拮抗剂,可阻断所有TRPV1激活模式。JNJ-39729209对辣椒素诱导产生咳嗽的豚鼠模型表现出明显的镇咳活性,已进入Ⅰ期临床试验[27]。另一种TRPV1拮抗剂GRC-6211(口服)已在骨关节炎和神经性疼痛的治疗方面开展了Ⅱ期临床试验,但其临床开发已被暂停,并且未提供详细信息[27,90]。

目前尚无TRPV4阻断剂在呼吸系统疾病中作用的相关临床试验报道。GSK2798745是一种治疗心力衰竭的TRPV4拮抗剂,已进入Ⅱ期临床试验,在健康志愿者和稳定心力衰竭患者中耐受良好[91]。TRPV4特异性抑制剂HC-067047可降低5-羟色胺诱导的慢性低氧肺血管收缩的敏感性[92]。TRPM8通道拮抗剂BCTC及其衍生物硫代BCTC,均可抑制薄荷醇诱导的Ca^{2+}内流;另一种TRPM8拮抗剂2-APB,可非特异性、快速可逆地阻断薄荷醇诱导的TRPM8电流。针对实体瘤患者的TRPM8激动剂D-3263可减少大鼠良性前列腺增生,且不出现限制其耐受性的急性不良反应,已完成Ⅰ期临床试验,但后续无相关报道[93]。AMG 333是一种有效且高度选择性的TRPM8拮抗剂,可作为治疗偏头痛的候选药物,已进入临床试验[94]。

4 结语

近几十年,慢性咳嗽、哮喘和COPD等呼吸系统疾病呈上升趋势,阐明这类疾病的具体发病机制以及开发相应治疗药物迫在眉睫。TRP通道能广泛响应呼吸道感觉神经元、支气管上皮细胞和肺泡上皮细胞等受到刺激时所释放的信号,引起细胞外Ca^{2+}内流和组织炎症等反应,参与调控咳嗽、哮喘及COPD等呼吸系统疾病的发生过程,是呼吸系统疾病治疗药物研发的潜在靶点,近年来靶向TRP通道的药物开发已进入临床试验研究。但由于目前TRP通道在呼吸系统中的具体作用机制尚未完全明确,其靶向治疗药物不可避免地会出现一些不良反应,如Ⅰ期临床试验发现,TRPV1抑制剂AMG-517及JNJ-39729209会剂量依赖性地引起健康受试者核心体温升高[90,95]。对另一种TRPV1拮抗剂ABT-102的3个Ⅰ期临床试验的药代动力学/药效学分析研究中也发现该药会引起体温升高[96]。具有快速持久镇痛作用的AZD1386应用于受试者同样会影响受试者体温[97]。因此,TRP各亚型通道在呼吸系统疾病中的调控机制复杂性、在不同种类细胞中的调控方式多样性、在动物模型与人体中的表达差异性以及在靶向抑制TRP通道后对各组织的影响程度不可控性等均是未来TRP靶向药物研发应重点考虑的关键科学问题,需要该领域研究人员进一步深入研究。

参考文献:

[1] Cosens DJ, Manning A. Abnormal electroretinogram from a *Drosophila* mutant [J]. *Nature*, 1969, 224 (5216): 285-287.

[2] Li H. TRP channel classification [J]. *Adv Exp Med Biol*, 2017, 976:1-8.

[3] Latorre R, Zaelzer C, Brauchi S. Structure-functional intimacies of transient receptor potential channels [J]. *Q Rev Biophys*, 2009, 42(3): 201-246.

[4] Gaudet R. TRP channels entering the structural era [J]. *J Physiol* (Lond), 2008, 586(15): 3565-3575.

[5] Runnels LW, Komiya Y. TRPM6 and TRPM7: novel players in cell intercalation during vertebrate embryonic development [J]. *Dev Dyn*, 2020, 249(8): 912-923.

[6] Pan Z, Yang H, Reinach PS. Transient receptor potential (TRP) gene superfamily encoding cation channels [J]. *Hum Genomics*, 2011, 5(2): 108-116.

[7] Yang H, Li S. Transient receptor potential ankyrin 1 (TRPA1) channel and neurogenic inflammation in pathogenesis of asthma [J]. *Med Sci Monit*, 2016, 22: 2917-2923.

[8] Nassini R, Pedretti P, Moretto N, *et al*. Transient receptor potential ankyrin 1 channel localized to non-neuronal airway cells promotes non-neurogenic inflammation [J/OL]. *PLoS One*, 2012, 7(8): e42454 [2021-03-05]. https://doi.org/10.1371/journal.pone.0042454.

[9] Yap JMG, Ueda T, Takeda N, *et al*. An inflammatory stimulus sensitizes TRPA1 channel to increase cytokine release in human lung fibroblasts [J/OL]. *Cytokine*, 2020, 129:155027 [2021-03-05]. https://doi.org/10.1016/j.cyto.2020.155027.

[10] Du C, Kang J, Yu W, *et al*. Repeated exposure to temperature variation exacerbates airway inflammation through TRPA1 in a mouse model of asthma [J]. *Respirology* (Carlton, Vic), 2019, 24(3): 238-245.

[11] Liu H, Fan X, Wang N, *et al*. Exacerbating effects of $PM_{2.5}$ in OVA-sensitized and challenged mice and the expression of TRPA1 and TRPV1 proteins in lungs [J]. *J Asthma*, 2017, 54(8): 807-817.

[12] Lieder B, Hoi J, Burian N, *et al*. Correction to structure-dependent effects of cinnamaldehyde derivatives on TRPA1-induced serotonin release in human intestinal cell models [J/OL]. *J Agric Food Chem*, 2020, 68(17): 5018 [2021-03-05]. https://pubs.acs.org/doi/10.1021/acs.jafc.0c02180.

[13] Ahluwalia J, Urban L, Capogna M, *et al*. Cannabinoid 1 receptors are expressed in nociceptive primary sensory neurons [J]. *Neuroscience*, 2000, 100(4): 685-688.

[14] McGarvey LP, Butler C A, Stokesberry S, *et al*. Increased expression of bronchial epithelial transient receptor potential vanilloid 1 channels in patients with severe asthma [J]. *J Allergy Clin Immunol*, 2014, 133(3): 704-712.

[15] Rehman R, Bhat YA, Panda L, *et al*. TRPV1 inhibition attenuates IL-13 mediated asthma features in mice by reducing airway epithelial injury [J]. *Intern Immunopharmacol*, 2013, 15(3): 597-605.

[16] Schiffers C, Hristova M, Habibovic A, *et al*. The transient receptor potential channel vanilloid 1 (TRPV1) is critical in innate airway epithelial responses to protease allergens [J]. *Am J Respir Cell Mol Biol*, 2020, 63(2):198-208.

[17] Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms [J]. *Pharmacol Rev*, 1999, 51(2): 159-212.

[18] Hwang SW, Cho H, Kwak J, *et al*. Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances [J]. *Proc Natl Acad Sci USA*, 2000, 97(11): 6155-6160.

[19] Zholos AV. TRP channels in respiratory pathophysiology: the role of oxidative, chemical irritant and temperature stimuli [J]. *Curr Neuropharmacol*, 2015, 13(2): 279-291.

[20] Liu Z, Wang P, Lu S, *et al*. Liquiritin, a novel inhibitor of TRPV1 and TRPA1, protects against LPS-induced acute lung injury [J/OL]. *Cell Calcium*, 2020, 88: 102198 [2021-03-05]. https://doi.org/10.1016/j.ceca.2020.102198.

[21] Al-Shamlan F, El-Hashim AZ. Bradykinin sensitizes the cough reflex via a B receptor dependent activation of TRPV1 and TRPA1 channels through metabolites of cyclooxygenase and 12-lipoxygenase [J/OL]. *Respir Res*, 2019, 20(1): 110 [2021-03-05]. https://doi.org/10.1186/s12931-019-1060-8.

[22] Grace M, Birrell MA, Dubuis E, *et al*. Transient receptor potential channels mediate the tussive response to prostaglandin E2 and bradykinin [J]. *Thorax*, 2012, 67(10): 891-900.

[23] Grace MS, Baxter M, Dubuis E, *et al*. Transient receptor potential (TRP) channels in the airway: role in airway disease [J]. *Br J Pharmacol*, 2014, 171(10): 2593-2607.

[24] Scheraga RG, Southern BD, Grove LM, *et al*. The role of transient receptor potential vanilloid 4 in pulmonary inflammatory diseases [J/OL]. *Front Immunol*, 2017, 8:503 [2021-03-05]. https://doi.org/10.3389/fimmu.2017.00503.

[25] Liu SC, Lu HH, Cheng LH, *et al*. Identification of the cold receptor TRPM8 in the nasal mucosa [J/OL].

Am J Rhinol Allergy, 2015, 29(4): e112-e116 [2021-03-05]. https://doi.org/10.2500/ajra.2015.29.4202.

[26] Keh SM, Facer P, Yehia A, *et al*. The menthol and cold sensation receptor TRPM8 in normal human nasal mucosa and rhinitis [J]. *Rhinology*, 2011, 49 (4): 453-457.

[27] Preti D, Szallasi A, Patacchini R. TRP channels as therapeutic targets in airway disorders: a patent review [J]. *Expert Opin Ther Pat*, 2012, 22(6): 663-695.

[28] Taylor-Clark TE, McAlexander MA, Nassenstein C, *et al*. Relative contributions of TRPA1 and TRPV1 channels in the activation of vagal bronchopulmonary C-fibres by the endogenous autacoid 4-oxononenal [J]. *J Physiol* (Lond), 2008, 586(14): 3447-3459.

[29] Talavera K, Startek JB, Alvarez-Collazo J, *et al*. Mammalian transient receptor potential TRPA1 channels: from structure to disease [J]. *Physiol Rev*, 2020, 100(2): 725-803.

[30] Birrell MA, Belvisi MG, Grace M, *et al*. TRPA1 agonists evoke coughing in guinea pig and human volunteers [J]. *Am J Respir Crit Care Med*, 2009, 180(11): 1042-1047.

[31] Guo Y, Ying S, Zhao X, *et al*. Increased expression of lung TRPV1/TRPA1 in a cough model of bleomycin-induced pulmonary fibrosis in Guinea pigs [J / OL]. *BMC Pulm Med*, 2019, 19(1): 27 [2021-03-05]. https://doi.org/10.1186/s12890-019-0792-z.

[32] Chung CL, Lin YS, Chan NJ, *et al*. Hypersensitivity of airway reflexes induced by hydrogen sulfide: role of TRPA1 receptors [J/OL]. *Intern J Mol Sci*, 2020, 21(11): 3929 [2021-03-05]. https://www.ncbi.nlm.nih.gov / pmc / articles / PMC7312894. DOI: 10.3390 / ijms21113929.

[33] Clarke R, Monaghan K, About I, *et al*. TRPA1 activation in a human sensory neuronal model: relevance to cough hypersensitivity? [J / OL]. *Eur Respir J*, 2017, 50(3): 1700995 [2021-03-05]. https://journals.sagepub. com / doi / 10.2500 / ajra. 2015.29.4202?url_ver=Z39.88−2003&rfr_id=ori: rid: crossref. org&rfr_dat=cr_pub%20%200pubmed. DOI: 10.1016/j.pupt.2020.101889.

[34] Büch TR, Schäfer EA, Demmel MT, *et al*. Functional expression of the transient receptor potential channel TRPA1, a sensor for toxic lung inhalants, in pulmonary epithelial cells [J]. *Chem Biol Interact*, 2013, 206(3): 462-471.

[35] Sun W, Wang Z, Cao J, *et al*. Enhanced production of nitric oxide in A549 cells through activation of TRPA1 ion channel by cold stress [J]. *Nitric Oxide*, 2014, 40:31-35.

[36] Volpi G, Facchinetti F, Moretto N, *et al*. Cigarette smoke and α,β-unsaturated aldehydes elicit VEGF release through the p38 MAPK pathway in human airway smooth muscle cells and lung fibroblasts [J]. *Br J Pharmacol*, 2011, 163(3): 649-661.

[37] Zhang L, An X, Wang Q, *et al*. Activation of cold-sensitive channels TRPM8 and TRPA1 inhibits the proliferative airway smooth muscle cell phenotype [J]. *Lung*, 2016, 194(4): 595-603.

[38] Marsh BJ, Fryer AD, Jacoby DB, *et al*. Transient receptor potential ankyrin-1 causes rapid bronchodilation via nonepithelial PGE [J]. *Am J Physiol Lung Cell Mol Physiol*, 2020, 318(5): L943-L952.

[39] Khalid S, Murdoch R, Newlands A, *et al*. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial [J]. *J Allergy Clin Immunol*, 2014, 134(1): 56-62.

[40] Zhang L, Sun T, Liu L, *et al*. The research of the possible mechanism and the treatment for capsaicin-induced cough [J]. *Pulm Pharmacol Ther*, 2018, 49:1-9.

[41] Xu GY, Winston JH, Shenoy M, *et al*. Transient receptor potential vanilloid 1 mediates hyperalgesia and is up-regulated in rats with chronic pancreatitis [J]. *Gastroenterology*, 2007, 133(4): 1282-1292.

[42] Smit LAM, Kogevinas M, Antó JM, *et al*. Transient receptor potential genes, smoking, occupational exposures and cough in adults [J/OL]. *Respir Res*, 2012, 13:26 [2021-03-05]. https://pubmed.ncbi.nlm.nih.gov/22443337. DOI: 10.1186/1465-9921-13-26.

[43] Sadofsky LR, Cantero-Recasens G, Wright C, *et al*. TRPV1 polymorphisms influence capsaicin cough sensitivity in men [J]. *J Thorac Dis*, 2017, 9(3): 839-840.

[44] Liviero F, Campisi M, Scarpa MC, *et al*. Multiple single nucleotide polymorphisms of the transient receptor potential vanilloid 1 (TRPV1) genes associate with cough sensitivity to capsaicin in healthy subjects [J/OL]. *Pulm Pharmacol Ther*, 2020, 61:101889 [2021-03-05]. https://doi.org/10.1016/j.pupt. 2020.101889.

[45] Lieu TM, Myers AC, Meeker S, *et al*. TRPV1 induction in airway vagal low-threshold mechanosensory neurons by allergen challenge and neurotrophic factors [J]. *Am J Physiol Lung Cell Mol Physiol*, 2012, 302 (9): L941-L948.

[46] Bonvini SJ, Birrell MA, Grace MS, *et al*. Transient

receptor potential cation channel, subfamily V, member 4 and airway sensory afferent activation: role of adenosine triphosphate [J]. *J Allergy Clin Immunol*, 2016, 138(1): 249-261.

[47] Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease [J]. *Nat Rev Immunol*, 2008, 8(3): 183-192.

[48] GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015 [J]. *Lancet Respir Med*, 2017, 5(9): 691-706.

[49] Sharifi L, Dashti R, Pouprak Z, *et al*. Economic burden of pediatric asthma: annual cost of disease in Iran [J]. *Iran J Public Health*, 2018, 47(2): 256-263.

[50] Milián E, Díaz AM. Allergy to house dust mites and asthma [J]. *P R Health Sci J*, 2004, 23(1): 47-57.

[51] Chen J, Kang D, Xu J, *et al*. Species differences and molecular determinant of TRPA1 cold sensitivity [J/OL]. *Nat Commun*, 2013, 4: 2501 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC379-1479. DOI: 10.1038/ncomms3501.

[52] Reese RM, Dourado M, Anderson K, *et al*. Behavioral characterization of a CRISPR-generated TRPA1 knockout rat in models of pain, itch, and asthma [J/OL]. *Sci Rep*, 2020, 10(1): 979 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6976688. DOI: 10.1038/s41598-020-57936-5.

[53] Caceres AI, Brackmann M, Elia MD, *et al*. A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma [J]. *Proc Natl Acad Sci USA*, 2009, 106(22): 9099-9104.

[54] van den Berg MPM, Nijboer-Brinksma S, Bos IST, *et al*. The novel TRPA1 antagonist BI01305834 inhibits ovalbumin-induced bronchoconstriction in Guinea pigs [J/OL]. *Br J Pharmacol*, 2020, 22(1):48 [2021-03-05]. https://doi.org/10.1186/s12931-021-01638-7.

[55] Wang P, Liu H, Fan X, *et al*. Effect of San´ao decoction on aggravated asthma mice model induced by $PM_{2.5}$ and TRPA1/TRPV1 expressions [J]. *J Ethnopharmacol*, 2019, 236:82-90.

[56] Baker K, Raemdonck K, Snelgrove RJ, *et al*. Characterisation of a murine model of the late asthmatic response [J/OL]. *Respir Res*, 2017, 18(1): 55 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5387391. DOI: 10.1186/s12931-017-0541-x.

[57] Puebla-Neira D, Calhoun WJ. Why do asthma patients cough? New insights into cough in allergic asthma [J]. *J Allergy Clin Immunol*, 2019, 144(3): 656-657.

[58] Deering-Rice CE, Stockmann C, Romero EG, *et al*. Characterization of transient receptor potential vanilloid-1 (TRPV1) variant activation by coal fly ash particles and associations with altered transient receptor potential ankyrin-1 (TRPA1) expression and asthma [J]. *J Biol Chem*, 2016, 291(48): 24866-24879.

[59] Song J, Kang J, Lin B, *et al*. Mediating role of TRPV1 ion channels in the co-exposure to $PM_{2.5}$ and formaldehyde of BALB/c mice asthma model [J/OL]. *Sci Rep*, 2017, 7(1): 11926 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5607312. DOI: 10.1038/s41598-017-11833-6.

[60] Choi JY, Lee HY, Hur J, *et al*. TRPV1 blocking alleviates airway inflammation and remodeling in a chronic asthma murine model [J]. *Allergy Asthma Immunol Res*, 2018, 10(3): 216-224.

[61] Baker K, Raemdonck K, Dekkak B, *et al*. Role of the ion channel, transient receptor potential cation channel subfamily V member 1 (TRPV1), in allergic asthma [J/OL]. *Respir Res*, 2016, 17(1): 67 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4890475. DOI: 10.1186/s12931-016-0384-x.

[62] Raemdonck K, De Alba J, Birrell MA, *et al*. A role for sensory nerves in the late asthmatic response [J]. *Thorax*, 2012, 67(1): 19-25.

[63] Tränkner D, Hahne N, Sugino K, *et al*. Population of sensory neurons essential for asthmatic hyperreactivity of inflamed airways [J]. *Proc Natl Acad Sci USA*, 2014, 111(31): 11515-11520.

[64] Zhu G, Gulsvik A, Bakke P, *et al*. Association of TRPV4 gene polymorphisms with chronic obstructive pulmonary disease [J]. *Human Mol Genet*, 2009, 18(11): 2053-2062.

[65] Naumov DE, Kolosov VP, Perelman JM, *et al*. Influence of TRPV4 gene polymorphisms on the development of osmotic airway hyperresponsiveness in patients with bronchial asthma [J]. *Dokl Biochem Biophys*, 2016, 469(1): 260-263.

[66] Bonvini SJ, Birrell MA, Dubuis E, *et al*. Novel airway smooth muscle-mast cell interactions and a role for the TRPV4-ATP axis in non-atopic asthma [J/OL]. *Eur Respir J*, 2020, 56(1): 1901458 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7330131. DOI: 10.1183/13993003.01458-2019.

[67] Duan J, Xie J, Deng T, *et al*. Exposure to both form-

aldehyde and high relative humidity exacerbates allergic asthma by activating the TRPV4-p38 MAPK pathway in BALB/c mice [J/OL]. *Environ Pollut*, 2020, 256:113375 [2021-03-05]. https://doi.org/10.1016/j.envpol.2019.113375.

[68] Yu Z, Wang Y, Qin L, *et al*. Functional cooperation between KCa3.1 and TRPV4 channels in bronchial smooth muscle cell proliferation associated with chronic asthma [J/OL]. *Front Pharmacol*, 2017, 8: 559 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5609593. DOI: 10.3389/fphar.2017.00559.

[69] Alobaidi NY, Stockley JA, Stockley RA, *et al*. An overview of exacerbations of chronic obstructive pulmonary disease: can tests of small airways′ function guide diagnosis and management? [J]. *Ann Thorac Med*, 2020, 15(2): 54-63.

[70] Barnes PJ. Oxidative stress-based therapeutics in COPD [J/OL]. *Redox Biol*, 2020, 33:101544 [2021-03-05]. https://doi.org/10.1016/j.redox.2020.101544.

[71] Bonvini SJ, Belvisi MG. Cough and airway disease: the role of ion channels [J]. *Pulm Pharmacol Ther*, 2017, 47:21-28.

[72] Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD-implications and relevance for treatment [J]. *Int J Chron Obstruct Pulmon Dis*, 2014, 9:1207-1224.

[73] De Logu F, Patacchini R, Fontana G, *et al*. TRP functions in the broncho-pulmonary system [J]. *Semin Immunopathol*, 2016, 38(3): 321-329.

[74] Xu M, Zhang Y, Wang M, *et al*. TRPV1 and TRPA1 in lung inflammation and airway hyperresponsiveness induced by fine particulate matter (PM) [J/OL]. *Oxid Med Cell Longevity*, 2019, 2019:7450151 [2021-03-05]. https://doi.org/10.1155/2019/7450151.

[75] Wang M, Zhang Y, Xu M, *et al*. Roles of TRPA1 and TRPV1 in cigarette smoke-induced airway epithelial cell injury model [J]. *Free Radic Biol Med*, 2019, 134:229-238.

[76] Yap JMG, Ueda T, Takeda N, *et al*. An inflammatory stimulus sensitizes TRPA1 channel to increase cytokine release in human lung fibroblasts [J/OL]. *Cytokine*, 2020, 129:155027 [2021-03-05]. https://doi.org/10.1016/j.cyto.2020.155027.

[77] Jian T, Chen J, Ding X, *et al*. Flavonoids isolated from loquat (*Eriobotrya japonica*) leaves inhibit oxidative stress and inflammation induced by cigarette smoke in COPD mice: the role of TRPV1 signaling pathways [J]. *Food Funct*, 2020, 11(4): 3516-3526.

[78] Nesuashvili L, Hadley SH, Bahia PK, *et al*. Sensory nerve terminal mitochondrial dysfunction activates airway sensory nerves via transient receptor potential (TRP) channels [J]. *Mol Pharmacol*, 2013, 83(5): 1007-1019.

[79] Andersson DA, Gentry C, Moss S, *et al*. Transient receptor potential A1 is a sensory receptor for multiple products of oxidative stress [J]. *J Neurosci*, 2008, 28(10): 2485-2494.

[80] Sockrider M, Tal-Singer R. Managing your chronic lung disease during the COVID-19 pandemic [J]. *Am J Respir Crit Care Med*, 2020, 202(2):P5-P6.

[81] Brooks CA, Barton LS, Behm DJ, *et al*. Discovery of GSK2798745: a clinical candidate for inhibition of transient receptor potential vanilloid 4 (TRPV4) [J]. *ACS Med Chem Lett*, 2019, 10(8): 1228-1233.

[82] Kuebler WM, Jordt SE, Liedtke WB. Urgent reconsideration of lung edema as a preventable outcome in COVID-19: inhibition of TRPV4 represents a promising and feasible approach [J]. *Am J Physiol Lung Cell Mol Physiol*, 2020, 318(6): L1239-L1243.

[83] Janda KD, Iadarola MJ. Standing out from the crowd in treating COVID-19 [J/OL]. *Med Drug Discov*, 2020, 100034 [2021-03-05]. http://dx.doi.org/10.1016/j.medidd.2020.100034.

[84] Rahaman SO, Grove LM, Paruchuri S, *et al*. TRPV4 Mediates myofibroblast differentiation and pulmonary fibrosis in mice [J]. *J Clin Invest*, 2014, 124 (12): 5225-5238.

[85] Liu SC, Lu HH, Fan HC, *et al*. The identification of the TRPM8 channel on primary culture of human nasal epithelial cells and its response to cooling [J/OL]. *Medicine* (Baltimore), 2017, 96(31): e7640 [2021-03-05]. http://dx.doi.org/10.1097/MD.0000000000007640.

[86] Sabnis AS, Reilly CA, Veranth JM, *et al*. Increased transcription of cytokine genes in human lung epithelial cells through activation of a TRPM8 variant by cold temperatures [J]. *Am J Physiol Lung Cell Mol Physiol,* 2008, 295(1): L194-L200.

[87] Liu H, Hua L, Liu Q, *et al*. Cold stimuli facilitate inflammatory responses through transient receptor potential melastatin 8 (TRPM8) in primary airway epithelial cells of asthmatic mice [J]. *Inflammation*, 2018, 41(4): 1266-1275.

[88] Heber S, Ciotu CI, Hartener G, *et al*. TRPV1 antagonist BCTC inhibits pH6.0-induced pain in human skin [J]. *Pain*, 2020, 161(7): 1532-1541.

[89] García-Martínez C, Fernández-Carvajal A, Valenzuela

B, *et al*. Design and characterization of a noncompetitive antagonist of the transient receptor potential vanilloid subunit 1 channel with *in vivo* analgesic and anti-inflammatory activity [J]. *J Pain*, 2006, 7(10): 735-746.

[90] Bamps D, Vriens J, de Hoon J, *et al*. TRP channel cooperation for nociception: therapeutic opportunities [J/ OL]. *Annu Rev Pharmacol Toxicol*, 2021, 61: 655-677 [2021-03-05]. https://doi.org/10.1146/annurev-pharmtox-010919-023238.

[91] Goyal N, Skrdla P, Schroyer R, *et al*. Clinical pharmacokinetics, safety, and tolerability of a novel, first-in-class TRPV4 ion channel inhibitor, GSK2798745, in healthy and heart failure subjects [J]. *Am J Cardiovasc Drugs*, 2019, 19(3): 335-342.

[92] Xia Y, Xia L, Jin Z, *et al*. Cytochrome P450 epoxygenase-dependent activation of TRPV4 channel participates in enhanced serotonin-induced pulmonary vasoconstriction in chronic hypoxic pulmonary hypertension [J/OL]. *Anal Cell Pathol* (Amst), 2020, 2020: 8927381 [2021-03-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7204149. DOI: 10.1155/2020/8927381.

[93] Moran MM, McAlexander MA, Bíró T, *et al*. Transient receptor potential channels as therapeutic targets [J]. *Nat Rev Drug Discov*, 2011, 10(8): 601-620.

[94] Horne DB, Biswas K, Brown J, *et al*. Discovery of TRPM8 antagonist (*S*)-6-(3-fluoro-4-(trifluoromethoxy) phenyl)(3-fluoropyridin-2-yl) methyl) carbamoyl) nicotinic acid (AMG 333), a clinical candidate for the treatment of migraine [J]. *J Med Chem*, 2018, 61 (18): 8186-8201.

[95] Kort ME, Kym PR. TRPV1 antagonists: clinical setbacks and prospects for future development [J]. *Prog Med Chem*, 2012, 51:57-70.

[96] Othman AA, Nothaft W, Awni WM, *et al*. Effects of the TRPV1 antagonist ABT-102 on body temperature in healthy volunteers: pharmacokinetic/ pharmacodynamic analysis of three phase 1 trials [J]. *Br J Clin Pharmacol*, 2013, 75(4): 1029-1040.

[97] Quiding H, Jonzon B, Svensson O, *et al*. TRPV1 antagonistic analgesic effect: a randomized study of AZD1386 in pain after third molar extraction [J]. *Pain*, 2013, 154(6): 808-812.

Research progress in role of transient receptor potential channels in respiratory diseases

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Abstract: Transient receptor potential (TRP) ion channels, which are a type of non-specific cation channel proteins, are widely expressed in the sensory nerve fiber and non-nerve cells of the respiratory tract. They can respond to a variety of stimuli to participate in the occurrence and development of respiratory diseases. TRPA1, TRPV1, TRPV4 and TRPM8 have become hotspots of research related to respiratory diseases in recent years, which play an important role in the development of respiratory tissue damage and inflammation. This review focuses on the roles of TRPA1, TRPV1, TRPV4 and TRPM8 in the pathogenesis of respiratory diseases such as cough, asthma and chronic obstructive pulmonary disease, and suggests that TRP channels can be potential drug targets for respiratory diseases.

Key words: transient receptor potential; cough; asthma; chronic obstructive pulmonary diseases

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