

新型钙离子通道TRPV5和TRPV6与胃肠肿瘤的研究进展

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■背景资料

胃肠肿瘤的发生率目前呈现升高趋势, 钙及维生素D能显著降低结肠癌的发生率, 瞬时受体阳离子通道亚家族V成员5(transient receptor potential cation channel, subfamily V, member 5, TRPV5)和TRPV6是新发现的高选择性的Ca²⁺跨膜转运通道, 与人体内多种肿瘤(如骨肿瘤、乳腺癌、前列腺癌及结肠癌等)形成过程相关。本文作者主要从TRPV5和TRPV6与胃肠肿瘤关系等方面进行论述。

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Novel calcium ion channels TRPV5 and TRPV6 and gastrointestinal tumors

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Abstract

Transient receptor potential cation channel, subfamily V, member 5 (TRPV5) and TRPV6 are the subfamily members of the transient receptor potential (TRP), representing new highly selective Ca²⁺ membrane transport channels, which are mainly responsible for active transport of Ca²⁺ across the cell membrane and participate in regulation of many physiological activities in the body. This paper discusses the structures and electrophysiological properties of TRPV5 and TRPV6, their related factors and their relationship with gastrointestinal tumors, highlighting the role of TRPV5 and TRPV6 in the formation of gastrointestinal tumors.

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Key Words: Calcium ion channels; TRPV5; TRPV6; Gastrointestinal tumors

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摘要

瞬时受体阳离子通道亚家族V成员5(transient receptor potential cation channel, subfamily V, member 5, TRPV5)和TRPV6为瞬时性受体电位通道(transient receptor potential, TRP)的亚家族成员, 是新发现的高选择性的Ca²⁺跨膜转运通道, 其主要负责Ca²⁺由细胞外向细胞内的主动跨膜运输, 在机体内参与多项生理活动的调节, 本文作者从TRPV5和TRPV6的结构、电生理特性和调控相关因素及其与胃肠肿瘤关系等方面进行论述, 探索TRPV5和TRPV6在胃肠肿瘤形成过程中的作用及其机制。

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关键词: 钙离子通道; TRPV5; TRPV6; 胃肠道肿瘤

核心提示: 通过对新型钙离子通道瞬时受体阳离子通道亚家族V成员5(transient receptor potential cation channel, subfamily V, member 5, TRPV5)和TRPV6的蛋白结构、生理特性、组织表达及其与肿瘤关系方面的研究进展进行总结, 阐述了TRPV5和TRPV6在人类胃肠肿瘤形成过程中的作用及其机制。

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0 引言

随着我国工业化城市化进程加快, 人民生活水平逐步提高, 胃肠肿瘤的发生率也呈现升高趋势, 如何预防胃肠肿瘤的发生已经引起研究者的普遍重视^[1]. 流行病学研究表明, 钙及维生素D能显著降低结肠癌的发生率^[2-4]. Lamprecht等^[5]研究指出, 结肠隐窝表面与细胞内维持正常的钙离子梯

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度对于结肠细胞的终末分化和凋亡起着重要的调节作用,这种钙离子梯度与维生素D水平有关。在结肠肿瘤发生的过程中,钙离子梯度则被破坏。此外,钙离子也可以通过干预细胞血管形成和调控细胞周期来影响结直肠癌的发展进程^[6,7]。Sheinin等^[8]发现细胞外钙浓度升高对分化程度高的结肠癌细胞有抑制作用,但是对低分化的细胞则影响很小。但钙离子对结肠肿瘤影响的具体机制目前仍尚不清楚。

1999年以前,对钙离子的跨膜转运的研究主要集中在Ca²⁺-ATP酶和钠-钙交换这2种形式上,也就是钙离子从细胞中转运到细胞外的过程,但对细胞外钙离子如何进入小肠、肾、和骨细胞的机制并不了解。自1999年Hoenderop等^[9,10]首次报道瞬时受体阳离子通道亚家族V成员5(transient receptor potential cation channel, subfamily V, member 5, TRPV5)和TRPV6,并证实其与钙离子细胞转运有关后,近十年间,相继发现了多种钙离子的跨膜转运通道,且主要集中在瞬时性受体电位通道(transient receptor potential, TRP)超家族这一类新型钙离子转运蛋白通道。因其位于细胞膜,最早发现于果蝇的视觉系统,突变体果蝇对持续的光刺激只产生瞬时而非持续的锋电位而得名。目前,大约30种TRP通道已被明确,他们分为TRPC、TRP超家族中V亚家族(transient receptor potential vanilloid receptor, TRPV)、TRPM、TRPML、TRPP、TRPA和TRPN七个不同的家族^[11]。TRPV5和TRPV6是TRPV中唯一已知的2种钙离子高选择性通道。因为首先发现其存在于上皮组织,曾分别被命名为上皮性钙通道1(epithelial calcium channel, ECaC1)和ECaC2。研究表明,TRPV5和TRPV6同源性高达75%,具有高度的钙离子选择性(PCa/PNa>100)。雌激素、甲状旁腺激素(parathyroid hormone, PTH)、维生素D、钙离子等通过影响TRPV5/TRPV6通道的表达,调节钙离子的代谢^[12,13]。

1 TRPV5和TRPV6蛋白的结构

TRPV5和TRPV6受体最初分别克隆于兔的肾脏和鼠的小肠,实验研究表明,其蛋白序列具有高度的同源性,某些功能区结构完全相同。研究人员用多种实验方法对TRPV5和TRPV6复合物进行分子量测定,证实这些通道可以形成同源或异四倍体通道复合物,当构成包括4个TRPV5和/或TRPV6亚基的连环通道时,TRPV5和TRPV6

亚基比例的差异导致了TRPV5和TRPV6通道的混合特性。Hellwig等^[14]在2005年时发现,鉴于TRPV其他通道优先形成同源四聚体,TRPV5和TRPV6似乎是唯一形成异四倍体的通道。因此,在TRPV5和TRPV6共同表达的组织中对TRPV5和TRPV6相对表达量的调节可能是精细调节钙转运动力学的机制。此外,两者的化学结构仍存在着区别。如TRPV6的TM6羧基端存在组氨酸残基(H587)突变体,而TRPV5则未发现该突变体。TRPV6的羧基末端没有蛋白激酶C磷酸化位点,而TRPV5羧基末端存在3个蛋白激酶C磷酸化位点。通道化学结构的差别引起电生理学特点的差异,表现为:(1)TRPV6的失活特点首先是一个快速失活过程,随后是一个缓慢的过程,而TRPV5在整个过程中都表现为一个缓慢失活的过程;(2)TRPV5中Ba²⁺/Ca²⁺电流比值明显比TRPV6高;(3)通道阻滞剂钆红对TRPV6阻滞作用比TRPV5弱100倍。由于TRPV5和TRPV6化学结构与电生理学的差别,决定了两者表达部位及生理功能的差异^[15]。

2 TRPV5和TRPV6的组织表达

TRPV5和TRPV6作为钙离子高选择性通道,在多数具有钙离子跨细胞转运功能的器官,包括肾脏、十二指肠、空结肠、骨组织、胎盘等组织和前列腺、胰腺、乳腺等外分泌器官均有不同程度的表达^[16]。但最主要表达在肾脏和小肠的上皮细胞中^[17-19]。TRPV5主要发生在肾脏,TRPV6主要表达在肠上皮细胞,在实验中发现人结肠癌细胞(Caco-2与SW480细胞株)也存在表达^[20-22]。此外,在大鼠表达胆囊收缩素1(cholecystokinin 1)受体的迷走神经节状神经元也发现TRPV5表达^[23]。

3 TRPV5和TRPV6的生理作用

3.1 TRPV5和TRPV6在胃肠道中的功能及影响 TRPV5和TRPV6是TRP离子通道家族成员中最显著的Ca²⁺选择性通道,对肠道Ca²⁺吸收发挥了重要作用^[17-19]。实验证明,TRPV5和TRPV6的功能是相互连接的,TRPV5基因敲除的小鼠,由于TRPV5介导的Ca²⁺在肾脏重吸收的损失,而立即上调肠道TRPV6的表达来补偿以致达到负钙平衡。相反,TRPV6基因敲除的小鼠发生继发性甲状旁腺功能亢进,却没有显示任何补偿机制。TRPV5和TRPV6的表达和功能还共同受饮食条件及多种钙调激素的调节^[18,24]。其中,饮食中

■研发前沿

近十年间,相继发现了多种钙离子的跨膜转运通道,且主要集中在瞬时性受体电位通道(transient receptor potential, TRP)超家族这一类新型钙离子转运蛋白通道。而TRPV5和TRPV6是该家族中V亚家族中唯一已知的两种钙离子高选择性通道,目前研究发现TRPV5和TRPV6与人体内多种肿瘤(如骨肿瘤、乳腺癌、前列腺癌及结肠癌等)形成过程相关。

■相关报道

研究表明TRPV5、TRPV6通过调控细胞内钙离子的浓度影响细胞生物学行为,在人乳腺癌、前列腺癌、结肠癌等多种肿瘤中呈高表达。

■创新盘点

本文反映出了近期在TRPV5和TRPV6与胃肠肿瘤形成关系方面的最新研究成果,对今后此领域的研究方向提出了自己的见解,认为TRPV5和TRPV6在胃肠道一些慢性炎症、癌前疾病和癌前病变中的表达可成为胃肠肿瘤防治的一个新的研究方向。

的钙缺乏对增加TRPV6在小鼠十二指肠黏膜的表达是一个重要的因素^[25];除此之外,短链脂肪酸、低聚果糖的发酵产品、姜黄素等也可发挥类似作用,增加大鼠结肠上皮细胞及Caco-2细胞中TRPV6的表达^[13],促进钙的吸收,对结肠癌起防御作用^[20]。

此外,与肠道黏膜TRPV5和TRPV6的表达相关的还有甲状旁腺激素和1,25-二羟维生素D₃[1,25-dihydroxyvitamin D₃, 1,25-(OH)₂D₃]^[18,21]。在鸡的肠上皮细胞,1,25-(OH)₂D₃和甲状旁腺激素通过刺激蛋白激酶A途径释放β葡萄糖醛酸来增加钙吸收,这反过来又激活了TRPV6通道^[26]。因此,1,25-(OH)₂D₃诱导的钙吸收是可以被TRPV6 siRNA阻断的。实验研究发现十二指肠黏膜中TRPV6的表达可随1,25-(OH)₂D₃暴露的增加而增加^[27]。但是,维生素D和肠道TRPV6基因之间虽具有密切的功能连接,二者功能却也可彼此独立发挥。在实验研究发现,在TRPV6基因敲除的小鼠中也发生肠钙的吸收现象,提示1,25-(OH)₂D₃诱导的小鼠十二指肠钙转运并不完全依赖TRPV6^[28];反之,在肠钙吸收增加和十二指肠TRPV6表达上调的孕期和哺乳期大鼠中,发现甚至缺乏维生素D受体^[29]。除此之外,另一些激素对肠钙吸收也具有影响,例如,泌乳素与1,25-(OH)₂D₃协同诱导大鼠十二指肠上皮TRPV6 mRNA的表达等^[30]。

3.2 TRPV5和TRPV6通道的调节 目前为止,仍没有发现确切的TRPV5和TRPV6直接激活剂。但有研究表明,在质膜内的TRPV5和TRPV6通道表现出持续的活性,因此,所有可影响质膜通道密度的化学生理因子都有可能调节TRPV5和TRPV6的表达。因此,TRPV5的表达受1,25-(OH)₂D₃^[31]、钙结合蛋白S100A10、膜联蛋白II^[32]及胞外碱化的影响^[33];钙调素与TRPV5和TRPV6结合后至少可促进TRPV6的激活^[34]。

此外,另一个重要的调节途径是由组织的丝氨酸蛋白酶激肽释放酶引起的。激肽释放酶激活缓激肽受体-2,从而反过来通过磷脂酶C家族β异构体(phospholipase C-β, PLC-β)途径激活了蛋白激酶C(protein kinase C, PKC)依赖的甘油二酯途径,使TRPV5发生磷酸化作用增加了通道的膜插入并延迟其恢复^[35]。因此,PKC激活剂二酰基甘油类似物OAG(1-oleoyl-acetyl-sn-glycerol)也可增加细胞表面TRPV5的表达量;PTH可通过增加TRPV5通道在细胞内的电流密度,来共表达TRPV5和1型PTH受体。这种由PTH

引起的TRPV5的增加也可由PKC抑制剂、磷酸化A-Raf抗体anti-phospho-A Raf(Ser299)/磷酸化相似肿瘤抑制基因HUGL抗体(human homolog to the D-Ig1 gene protein)(ser654)及caveolin-1拮抗剂阻止。PKC的调控机制可能有助于PTH对肾脏Ca²⁺重吸收和TRPV5通道的短期激活作用^[36]。

TRPV5还受赖氨酸缺陷蛋白激酶4(protein kinase with no lysine 4, WNK4)的高度调控。WNK4基因的表达可增加细胞表面TRPV5的表达,由此来调节该通道并介导钙的重吸收。前蛋白尿激素Klotho(一种β葡萄糖醛酸苷酶)的影响主要限于上皮钙离子通道TRPV5和TRPV6,可水解胞外TRPV5/6通道上的糖残基,截留细胞膜内的TRPV5/6通道,促进TRPV5和TRPV6的积累^[37]。

当IC₅₀值介于0.1-1 μmol/L之间时,内膜钙通道抑制剂钌红(ruthenium red, RR)和抗真菌益康唑是TRPV5通道电流最有效的抑制剂。当IC₅₀值介于1到大约10 μmol/L之间时,二价阳离子对TRPV5的阻断情况是Pb²⁺ = Cu²⁺ > Zn²⁺ > Co²⁺ > Fe²⁺。值得注意的是,RR可阻断TRPV6,但对于TRPV6的亲和力却要比TRPV5低100倍^[38]。胞外Ca²⁺诱导的TRPV6通道失活发生在超极化时期, Ca²⁺引起的半数最大失活发生在钙浓度为约100 μmol/L时,而TRPV6通道失活这一过程,可被Ca²⁺依赖性PLC途径的激活和磷脂酰肌醇PIP2的消耗触发。因此,PLC抑制剂U73122和依地福新在十二指肠可诱导TRPV6持续激活,PLC调节剂则可作为新型的TRPV6通道钙离子吸收调节剂^[39]。

细胞外Mg²⁺对TRPV5和TRPV6通道的拮抗具有电压依赖性,且关键依赖于TRPV5/6孔隙选择过滤器中的单个天冬氨酸残基。同时,胞内Mg²⁺也具有电压依赖性拮抗作用,且此作用在通道去极化时被削弱,并有助于TRPV6通道时间依赖性的激活和失活^[40,41]。

TRPV6通道与蛋白酪氨酸磷酸酶1B(protein tyrosine phosphatase-1B, PTP-1B)相互作用,可能通过某种活性氧成份被Ca²⁺抑制。PTP-1B被拮抗导致酪氨酸去磷酸化作用被抑制,从而保证了TRPV6对钙离子内流的维持,产生正反馈作用^[42,43]。

4 TRPV5和TRPV6与肿瘤的关系

与正常组织或细胞相比,TRPV6 mRNA或蛋白的表达在前列腺癌、结肠癌、乳腺癌、甲状腺癌和卵巢癌组织中有大幅度的增加^[44,45]。研究显示,

前列腺癌组织切片中TRPV6 mRNA的表达与肿瘤侵袭程度成正比, 其可作为前列腺癌临床诊治的一个预测指标^[46-48]. TRPV6特定的siRNA处理可通过以下几个方面来控制人前列腺LNCaP细胞的增殖: (1)直接降低细胞增殖率; (2)减少在细胞S期积聚的细胞数量; (3)降低增殖细胞核抗原(proliferating cell nuclear antigen)的表达^[49]. 此外, TRPV6在乳腺癌组织中也有强烈表达, 且可通过雌激素、孕激素及他莫昔芬等来调节, 对乳腺癌细胞增殖产生较大影响, 可能会成为钙通道抑制剂治疗乳腺癌的新的靶基因. 在大鼠嗜碱性粒细胞白血病细胞中TRPV5/TRPV6也被证明有表达, 其存在于白血病细胞裂解液和粗膜制剂内. 另一方面, Vasil'eva等^[50]采用RT-PCR分析出, 在人类Jurkat白血病细胞株和K562红白血病细胞系中均有TRPV5 mRNA的表达. 其中K562细胞可共表达TRPV5和TRPV6钙通道, 两通道相互作用, 调节白血病细胞分化和增殖.

目前研究显示, 结肠TRPV6表达水平的增加与早期结肠癌相关^[19]. TRPV6在I期结肠肿瘤中66%过表达, 在II期结肠肿瘤中17%过表达, 但在III、IV期结肠肿瘤中却几乎检测不到. 在高水平表达TRPV6mRNA的结肠癌细胞株Caco-2实验中, 经用TRPV6特异性siRNA来处理, TRPV6 mRNA水平显著降低了约50%, 同时减少了40%细胞增殖和增加了两倍以上的细胞凋亡. 在结肠隐窝增生模型实验中显示出, TRPV6 mRNA表达发生显著性增强, 且广泛分布于结肠隐窝的增殖区, 而当动物被喂以高钙饮食时, 增生模型中TRPV6的过表达可被逆转^[51,52]. 由此, 我们可预测TRPV6促进结肠上皮细胞增殖, 可能是早期结肠癌发生发展的一个重要致病因素, 这需要更多的实验来证明.

5 结论

TRPV5和TRPV6作为钙离子高选择性通道, 其表达与多种肿瘤的发生发展密切相关, 尤其是在胃肠肿瘤组织的早期发展阶段. 但TRPV5和TRPV6是通过何种机制来影响细胞生长及肿瘤的发生, 仍需要进一步研究. 特别是对TRPV5和TRPV6在胃肠道一些慢性炎症、癌前疾病和癌前病变中的表达的研究, 将为胃肠肿瘤的防治研究提供新的方向.

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■应用要点

本文总结论述了近几年新型钙离子通道TRPV5和TRPV6与胃肠肿瘤的研究进展, 认为对TRPV5和TRPV6在胃肠道一些慢性炎症、癌前疾病和癌前病变中的表达的研究, 将为胃肠肿瘤的防治研究提供新的方向.

■名词解释

- TRPV5和TRPV6是TRP超家族中V亚家族中唯一已知的两种钙离子高选择性通道。因为首先发现其存在于上皮组织,曾分别被命名为上皮性钙通道1(etpithelial calcium channel, ECaC1)和ECaC2。研究表明,TRPV5和TRPV6同源性高达75%,具有高度的钙离子选择性,其存在于具有钙离子跨细胞转运功能的器官。
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■同行评价

本文对近十年来TRPV5和TRPV6与胃肠肿瘤形成关系方面的研究进展进行了总结论述, 文章的科学性和可读性较好地反映该领域基础研究的先进水平. 对同行在TRPV5和TRPV6钙离子通道方面的研究有一定的参考价值.

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