·综述·

跨膜蛋白16A及其抑制剂的研究进展

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摘要 跨膜蛋白16A(TMEM16A)是一种具有电压依赖性的钙激活氯离子通道,广泛表达于癌细胞中。在多种癌症中,TMEM16A不仅可以调控癌细胞的增殖、侵袭和转移,还与癌症治疗的预后相关。近年来,TMEM16A以及TMEM16A抑制剂在癌症领域的相关研究不断深入。本文总结了近10年来的相关研究,旨在为今后TMEM16A抑制剂在癌症治疗中的临床应用提供新的治疗策略。

关键词 跨膜蛋白16A;钙激活氯离子通道;抑制剂;癌症;研究进展
中图分类号 R969 **文献标志码** A **文章编号** 0258-4646(2024)05-0468-05
网络出版地址 https://link.cnki.net/urlid/21.1227.R.20240511.1130.014
DOI:10.12007/j.issn.0258-4646.2024.05.014

Research progress on transmembrane protein 16A and its inhibitors

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Abstract Transmembrane protein 16A (TMEM16A) is a voltage-dependent calcium-activated chloride channel that is widely expressed in cancer cells. In a variety of cancer types, TMEM16A regulates the proliferation, invasion, and metastasis of cancer cells and is correlated with the prognosis of cancer under treatment. In recent years, TMEM16A and its inhibitors have been intensively studied in cancer treatment. This review summarizes relevant studies conducted over the past 10 years, aiming to provide a novel therapeutic strategy for the clinical application of TMEM16A inhibitors in future cancer therapy.

Keywords transmembrane protein 16A; calcium-activated chloride channel; inhibitor; cancer; research progress

跨膜蛋白16A(transmembrane protein 16A,TMEM16A)的结构为一个同源二聚体,每个单体都是一个具有独立功能的通透阴离子孔道,并含有2个Ca^{2+}结合位点。孔道结构由TM3~TM7跨膜螺旋包围形成。酸性氨基酸E654、E702、E705、E734和D738共同形成2个Ca^{2+}结合位点[1]。TMEM16A在上皮细胞中高表达,如气道上皮细胞、肠上皮细胞等,上皮细胞中的TMEM16A可以介导气道上皮细胞分泌黏液,调控肠腔氯离子分泌。TMEM16A功能异常可以诱发多种疾病,如囊性纤维病、哮喘、胃肠运动障碍、癌症等[2]。TMEM16A的基因位点位于11q13,这一染色体区域发生基因扩增在人类癌症中最为常见[3]。TMEM16A在多种癌症中发挥重要作用,包括结直肠癌、乳腺癌、肝细胞癌、前列腺癌、胃癌、肺癌[4]。由于肿瘤异质性和细胞特异性,TMEM16A在不同癌细胞中发挥的作用不尽相同。根据近年的研究热点,本文总结了TMEM16A在几种常见癌症中对生物学表型的影响和调控机制,汇总了TMEM16A抑制剂在癌细胞增殖、侵袭、转移中的作用以及具体调节机制,为TMEM16A作为癌症治疗靶点、TMEM16A抑制剂的研发提供了理论依据。

1 TMEM16A与癌症

1.1 结直肠癌

与正常结直肠组织相比,结直肠癌组织中*TMEM16A* mRNA表达显著增加[5]。研究[6]报道,TMEM16A的表达量与结直肠癌的TNM分期呈正相关;还有研究[7-8]报道,TMEM16A与肿瘤的位置、大小和分化程度无相关性,但是与肿瘤的浸润深度、淋巴

基金项目:国家自然科学基金(82203020)
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收稿日期:2023-05-18
网络出版时间:2024-05-14 14:32:25

结转移、Dukes分期和患者的不良预后显著相关。在结直肠癌细胞中高表达的TMEM16A，参与了结直肠癌细胞的侵袭和转移[9]。多数结直肠癌发病与Wnt/β–连环蛋白（β-catenin）信号通路的激活有关[10]，下调TMEM16A蛋白会减少Wnt/β-catenin信号通路相关蛋白的表达，抑制结直肠癌的进展[6]。结直肠癌细胞中高表达的TMEM16A虽然不影响丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）相关蛋白MEK或ERK1/2的总表达水平，但会影响其磷酸化水平，使细胞周期蛋白（cyclin）D1表达量增加，加速结直肠癌细胞的增殖[9]。

1.2　乳腺癌

在15%的乳腺癌患者中，11q13区域被扩增，表现为TMEM16A高表达。TMEM16A高表达不仅与乳腺癌细胞的侵袭、转移相关，还与不良预后有关[3]。TMEM16A的表达水平与乳腺癌患者的年龄、绝经状态、家族史、肿瘤大小、组织学分级、淋巴结转移均无显著相关性，但与某些PR阳性或HER2阴性乳腺癌患者化疗后预后良好相关[11]。研究[12-13]报道，启动EGFR/STAT3信号转导能够促进TMEM16A过表达，而TMEM16A过表达进一步激活乳腺癌细胞的EGFR/STAT3通路，以这种正反馈方式促进乳腺癌细胞的增殖和迁移。TMEM16A在乳腺癌细胞中高表达与细胞凋亡相关，当TMEM16A被抑制后，凋亡相关蛋白胱天蛋白酶（caspase）3和caspase 9表达量增加，癌细胞凋亡水平上升[3]。ROCK1磷酸化Moesin增加了TMEM16A通路的活性，进一步激活EGFR/STAT3信号通路，促进ROCK1的表达，这样的协同调控促进了乳腺癌的转移[14]。

1.3　胃癌

TMEM16A在多种胃癌细胞（包括AGS、MKN-45、BGC-823、SGC-7901和MKN-28）中高表达[15]，参与胃癌细胞的迁移和侵袭，并与胃癌的不良预后有关[16]。胃癌细胞中SP1介导MLL1被招募到ANO1启动子上，并激活ANO1转录，MLL1通过调控H3K4me3来控制ANO1的水平，导致胃癌细胞中ANO1的表达量高于正常人胃上皮细胞[17]。在胃癌细胞中高表达的ANO1虽然不会影响胃癌细胞的增殖，但是会影响胃癌细胞的侵袭和迁移，高表达的ANO1通过调控转化生长因子β（transforming growth factor-β，TGF-β）的分泌，下调E–钙黏蛋白（cadherin），促进胃癌的浸润、侵袭和转移[15]。通过microRNA-381直接靶向TMEM16A，抑制TGF-β通路和上皮–间质转化过程，可以抑制胃癌进程[16]。

1.4　其他癌症

在肝细胞癌中，TMEM16A通过调控p38和ERK1/2的激活，影响cyclin D1的表达，调控细胞周期进程，影响癌细胞的增殖和侵袭，但对细胞凋亡未产生影响[18]。在胰腺癌细胞中，虽然TMEM16A高表达，但与胰腺癌细胞的侵袭性无显著相关性，且未发现胰腺癌细胞中TMEM16A高表达与胰腺癌患者的不良预后相关[19]。与良性前列腺增生和癌旁良性腺体相比，TMEM16A在前列腺癌组织中高表达，且高表达的TMEM16A与前列腺癌的分级呈正相关[20]。前列腺癌细胞中高表达的TMEM16A促进癌细胞增殖，且TMEM16A表达与肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）呈负相关，而TNF-α的下游信号为FADD的磷酸化和caspase蛋白家族的激活，因此前列腺癌细胞中高表达的TMEM16A还可以抑制癌细胞凋亡[21]。

2　TMEM16A抑制剂

近年来，TMEM16A抑制剂的作用受到很多学者关注。应用全细胞膜片钳技术可以发现多种药物呈浓度依赖性抑制TMEM16A的电流，包括荷叶碱[22]、高三尖杉酯碱[23]、苯并啡啶类生物碱[24]、苦参碱[25]等。部分TMEM16A抑制剂可以下调TMEM16A的表达，从而实现对TMEM16A的抑制，如油酸、大蒜素等[26-27]。抑制通道活性和下调通道蛋白表达的作用并不冲突，如大蒜素既可以阻断TMEM16A的离子转运，也可以下调TMEM16A的表达[27]。某些抑制剂如钙通道阻断剂尼莫地平，可以通过减少跨膜的Ca^{2+}内流来发挥间接抑制TMEM16A的作用，进而松弛胃肠道平滑肌[28]。LIU等[29]发现，反式–ε–葡萄素抑制TMEM16A电流，但不影响细胞内Ca^{2+}浓度。一些TMEM16A抑制剂对TMEM16A通道的阻滞作用选择性不高，如孔阻断剂1PBC既阻滞TMEM16A也阻滞TMEM16B，但对TMEM16F无明显作用[30]。

2.1　抑制癌细胞增殖

研究报道，荷叶碱[22]、扎鲁斯特[31]、大蒜素[27]、咖啡酸[32]、络石苷[33]、原花青素[34]、高三尖杉酯碱[23]、水飞蓟素[35]、茶黄素[36]、千金藤素[37]、牛蒡苷元[38]、

阿维菌素[39]、苯并啡啶类生物碱[24]、苦参碱[25]可以抑制肺腺癌LA795细胞增殖。艾地苯醌可以抑制前列腺癌PC-3细胞和胰腺癌CFPAC-1细胞增殖[40]。另外，和厚朴酚可以抑制结直肠癌SW620细胞增殖[41]。TMEM16A抑制剂影响癌细胞增殖的具体机制：茶黄素采用“楔形插入模式”阻断TMEM16A离子传导孔道，诱导通道闭合，显著抑制肺腺癌细胞的增殖和迁移[36]；抑制TMEM16A降低了MAPK信号通路相关蛋白ERK1/2和MEK1/2的磷酸化，进而降低了cyclin D1的表达，从而阻断了细胞周期，使癌细胞停留在G_0/G_1期[27]；大豆苷元不仅可以降低LA795细胞中TMEM16A蛋白的表达，还会导致细胞周期G_1/S期阻滞[42]，细胞周期的阻滞抑制了癌细胞增殖。

2.2　抑制癌细胞迁移

荷叶碱呈浓度依赖性抑制肺腺癌LA795细胞迁移[22]。牛蒡苷元通过抑制TMEM16A，抑制肺腺癌细胞迁移[38]。其他可以抑制癌细胞迁移的抑制剂有茶黄素[36]、艾地苯醌[40]、阿维菌素[39]、苯并啡啶类生物碱[24]、苦参碱[25]。BAI等[27]报道，大蒜素下调与细胞黏附和上皮–间质转化相关的β-catenin、N-cadherin、波形蛋白，上调E-cadherin，这些蛋白表达的改变增强了细胞的黏附，从而削弱了肺腺癌LA795细胞的运动性。

2.3　诱导癌细胞凋亡

荷叶碱[22]、大蒜素[27]、咖啡酸[32]、络石苷[33]、高三尖杉酯碱[23]、水飞蓟素[35]、CaCCinh-A01[21]、艾地苯醌[40]、阿维菌素[39]、千金藤素[37]、苯并啡啶类生物碱[24]等通过抑制TMEM16A，抑制癌细胞凋亡。研究[23,27,35]报道，抑制TMEM16A导致癌细胞凋亡相关蛋白caspase 3和caspase 9的表达量升高，诱导癌细胞凋亡。药物在不同剂量和浓度下发挥的作用不同，如千金藤素在低浓度时抑制癌细胞增殖，高浓度时诱导癌细胞凋亡[37]。

除人工合成化合物、中药和食物提取物等外源性物质外，还有一些内源性物质也可以抑制TMEM16A通道蛋白。包括油酸在内的脂肪酸，可以呈电压依赖性抑制TMEM16A钙激活氯电流。雌激素可以轻微抑制TMEM16A钙激活氯电流。胆固醇通过上调DNMT1，减少了TMEM16A蛋白的表达，最终促进血管内皮细胞生成。

2.4　阻滞作用与Ca^{2+}调控

多数TMEM16A抑制剂对其产生的阻滞作用可能与细胞内Ca^{2+}调控有关。常用的TMEM16A抑制剂如苯溴马隆、MONNA、CaCCinhA01，可以通过与雷诺丁受体直接作用，导致肌浆网储存的Ca^{2+}释放入胞质；几种TMEM16A阻断剂（尼氟酸、苯溴马隆和氯硝柳胺）同时也是线粒体毒素，因此可能会干扰线粒体Ca^{2+}的处理，从而导致线粒体中Ca^{2+}释放入胞质；一些经典的氯离子通道阻滞剂，包括二磺二苯乙烯衍生物和尼氟酸，甚至可以直接改变插入脂质双层的雷诺丁受体的门控特性，引起胞质Ca^{2+}浓度的改变。但是TMEM16A抑制剂导致胞质Ca^{2+}浓度的改变与其对TMEM16A通道的抑制作用是否直接相关，仍需进一步研究。

3　结论与展望

越来越多的证据表明，钙激活氯离子通道TMEM16A高表达会促进癌症的发展，TMEM16A作为多种癌症的潜在生物标志物和治疗靶点，在癌细胞中的表达与转录调控、表观遗传调控和翻译后水平调控有关。TMEM16A通过调节细胞内外氯离子浓度，并与多种胞内蛋白相互作用，共同调控癌症的发生和发展。它与多种增殖、迁移和凋亡蛋白相互作用，进而调控MAPK、TGF-β、EGFR/STAT3、Wnt/β-catenin等信号通路，实现对癌细胞增殖、迁移和侵袭的调控。

随着TMEM16A抑制剂相关研究的不断深入，TMEM16A抑制剂的抗肿瘤潜力不断被发掘。近年来，随着越来越多的TMEM16A抑制剂的作用位点被预测，其中的共同位点是否与TMEM16A抑制剂抑制肿瘤增殖、侵袭、转移的机制相关，仍需进一步挖掘。同时，部分TMEM16A抑制剂对胞质Ca^{2+}浓度的影响是否与TMEM16A抑制剂抑制肿瘤的增殖、侵袭、转移存在联系仍不明确，还需深入探究。

开发特异性靶向TMEM16A而不影响其他氯离子通道或蛋白质的抑制剂，对减少不良反应至关重要。与许多癌症治疗一样，癌细胞可能对TMEM16A抑制剂产生耐药性，因此需要持续研究联合疗法和新的抑制剂。虽然临床前研究显示了TMEM16A抑制剂在癌症治疗中的可行性，但TMEM16A抑制剂的有效性和安全性需要严格的临床试验来证实，其在癌症治疗中的临床应用仍需进一步研究。本文在总结

TMEM16A及其抑制剂在肿瘤中的研究进展的同时，还为未来TMEM16A抑制剂应用于恶性肿瘤的治疗提供了新的研究方向。

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