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氯离子细胞内通道蛋白1的功能及其在疾病中的研究进展

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摘 要:氯离子细胞内通道蛋白1(chloride intracellular channel protein 1,CLIC1)是一类广泛分布于哺乳动物细胞胞质及多种细胞器质膜上的氧化还原敏感型通道蛋白,主要以可溶性和膜结合两种形式存在。作为细胞氧化应激响应中关键的感受器与效应器,CLIC1是多种疾病的潜在生物标志物或治疗靶点,具有良好的应用潜力。基于此,本文系统概述了CLIC1的结构特征、可溶性与膜结合形式的转换特性及其作为氧化应激感受器和离子通道蛋白的核心功能,聚焦于CLIC1对ERK/MAPK、Nrf2/HO-1及PI3K/Akt/mTOR等信号通路的调控,系统梳理了该蛋白在肿瘤、神经系统疾病、炎症及病毒感染中发挥关键作用的分子机制研究进展,希望为CLIC1相关疾病的机制解析、生物标志物筛选及靶向治疗策略开发奠定理论基础。

关键词:氯离子细胞内通道蛋白1;结构与功能;肿瘤;细胞凋亡;病毒感染
中图分类号:Q257; Q513; R363 **文献标识码**:A

Research progress on chloride intracellular channel protein 1 in diseases

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Abstract: Chloride intracellular channel protein 1 (CLIC1) is a redox-sensitive metamorphic protein widely distributed in the cytoplasm and membranes of various organelles in mammalian cells. It exists in two interconvertible forms—soluble and membrane-bound—and functions as a key sensor and effector in cellular oxidative stress responses. This review systematically summarizes the structural characteristics of CLIC1, the molecular mechanisms governing its soluble-to-membrane form conversion, and the regulatory factors influencing its membrane localization, including pH, cholesterol, zinc ions, and temperature. We comprehensively discuss the dual biochemical activities of CLIC1—glutathione S-transferase (GST)-like enzymatic activity and chloride ion channel activity—and their functional coupling. Accumulating evidence has established CLIC1 as a critical regulator of multiple signaling pathways, including ERK/MAPK, Nrf2/HO-1, and PI3K/Akt/mTOR, thereby contributing to the pathogenesis of various diseases. In oncology, CLIC1 promotes tumor cell proliferation, migration, invasion, and metabolic reprogramming while also modulating chemotherapy resistance. In neurological disorders, CLIC1 drives neuroinflammation by activating microglial NLRP3 inflammasome and serves as a potential biomarker for Alzheimer's disease and multiple sclerosis. In vascular diseases, CLIC1 mediates endothelial dysfunction, atherosclerosis, and thrombosis. Furthermore, CLIC1 functions as a key host factor in viral replication, participating in different stages of the viral life cycle for Chikungunya virus, influenza A virus, and porcine reproductive and respiratory syndrome virus. The pleiotropic roles of CLIC1 across diverse pathological conditions highlight its potential as a diagnostic biomarker and therapeutic target. Future research should focus on elucidating the tissue-specific regulatory networks of CLIC1 and

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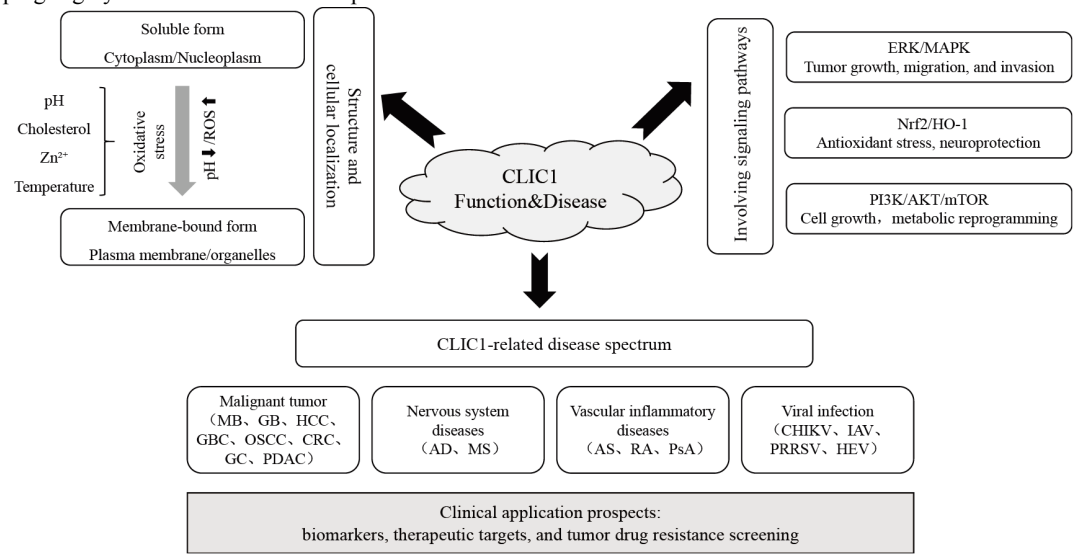
developing highly selective inhibitors for precision treatment of CLIC1-associated diseases.



Key words: chloride intracellular channel protein 1; structure and function; tumor; apoptosis; viral infection

氯离子(Cl^-)作为参与细胞生理的重要阴离子,其浓度变化会导致细胞功能的差异性调控,进而影响细胞的周期进程、增殖、凋亡、迁移与侵袭等[1]。氯离子细胞内通道蛋白家族(chloride intracellular channels,CLICs)是一类主要转运氯离子的家族蛋白,包括6个高度保守的成员(CLIC1、CLIC2、CLIC3、CLIC4、CLIC5、CLIC6)[2]。CLIC1在哺乳动物组织和细胞中广泛分布,是目前研究最为广泛的CLICs成员,它作为调控细胞离子稳态、氧化应激和炎症反应的关键分子,在肿瘤进展、中枢神经系统疾病发生及病毒感染过程中展现出广泛的研究潜力[2-4]。本文概述了CLIC1的结构与定位、可溶性与膜结合形式的转换特性及其相应的生物学功能,聚焦并分析CLIC1在肿瘤、神经系统疾病、血管疾病及病毒感染中的关键作用与分子机制,重点突出其在信号通路调控、疾病病理进程中的多效性及作为潜在靶点的应用价值,旨在为深入探究CLIC1调控疾病发生发展的分子机制及临床应用开发奠定理论基础。

1　CLIC1的结构与细胞定位

CLICs存在膜结合蛋白和可溶性胞质蛋白两种形式,通常以可溶性形式存在于细胞质和核质中,但在特定刺激下会转化为膜结合形式,选择性转运氯离子。CLICs具有氧化还原酶活性,家族成员之间具有高度的结构和序列同源性[1]。CLIC1由241个氨基酸组成,在膜结合形式中,C末端在膜内侧,而N末端具有硫氧还蛋白样结构域(图1),是细胞膜结合位点,其中第49~51位的3个氨基酸是跨膜结构域中最重要的序列[5];CLIC1可溶性形式的C末端具有高度保守的谷胱甘肽S-转移酶(glutathione S-transferase,GST)折叠结构域,能与谷胱甘肽发生可逆性结合[6]。GST结构域包含一个保守的“半胱氨酸-任意两个氨基酸-半胱氨酸”基序(即CXXC基序)和一个C末端结构域,后者通常由α螺旋构成,可能参与膜相互作用的调节[7,8](图1)。

CLIC1的构象转换是氧化还原依赖性的精密过程。其GST样结构域中的保守CXXC基序(Cys24-Cys27)是关键的氧化还原传感器。在还原状态下,CLIC1以可溶性单体形式存在于胞质中。当发生氧化应激时,CXXC基序被氧化,促使分子内二硫键形成或与氧化型谷胱甘肽发生S-谷胱甘肽化,诱导N端结构域(包括α2和α4螺旋)发生显著构象重排,暴露出隐藏的疏水区。与此同时,原本柔性的C末端结构域转变为稳定的两亲性α螺旋。这些变化共同驱动CLIC1靶向并插入生物膜[7-10]。

CLIC1可定位于质膜、线粒体膜、溶酶体膜以及核膜,其膜定位受多种因素调控,如pH、胆固醇、Zn^{2+}及温度等。酸性pH是驱动其从可溶性形式向膜结合通道转换的关键信号。在体外实验中,CLIC1仅在酸性条件下(pH 5.0~6.5)才能有效插入脂质双层并形成功能性氯离子通道,这一过程被描述为依赖pH的双态组装过程[11];酸性pH可能通过

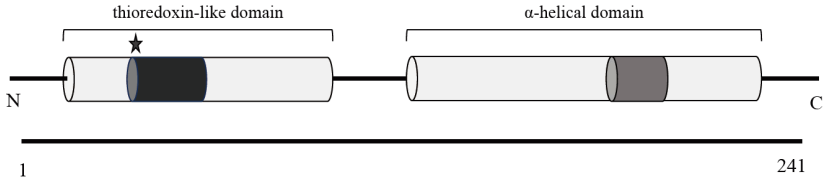


图1 CLIC1的结构域

CLIC1的N端含硫氧还蛋白样结构域(thioredoxin-like domain)和C端α-螺旋结构域(α-helical domain)。硫氧还蛋白样结构域具有一个假设的跨膜区域(黑色),α-螺旋结构域具有一个核定位信号(灰色)。星号标记了反应性Cys残基(Cys24)。水平线表示氨基酸数量。

Figure 1 Domains of CLIC1

The N-terminal thioredoxin-like domain and C-terminal α-helical domain of CLIC1 are shown, respectively. The thioredoxin-like domain has a putative transmembrane region (black), and the α-helical domain contains a nuclear localization signal (gray). A asterisk marks the reactive Cys residue (Cys24). The horizontal line represents the number of amino acids.

稳定CLIC1 N端结构域的特定构象,从而促进其与膜的相互作用和后续的寡聚化[12]。胆固醇是调控CLIC1膜定位与功能的核心脂质伴侣。研究表明,胆固醇能显著增强CLIC1向脂双层的插入效率,并在膜中稳定其功能性寡聚通道,从而产生稳健的氯离子电流[13];此外,Zn^{2+}是CLIC1功能的重要变构调节剂。Zn^{2+}能以高亲和力直接与CLIC1结合,并高效抑制其谷氧还蛋白样酶活性。由于CLIC1的酶活性与通道功能通过共同的氧化还原敏感结构域偶联,Zn^{2+}的结合很可能作为一个关键的分子开关,同时调控其氧化还原传感与离子通道活性[14]。温度也是调控CLIC1功能的关键物理因素。体外酶学研究揭示,CLIC1的GST样酶活性表现出显著的热敏性:其在生理温度(37℃)下活性最高,而在高于45℃时会发生不可逆的变性失活。这一特性不仅确保了CLIC1在正常生理条件下的高效运作,也暗示它可能作为细胞对发热或局部热微环境(如炎症、肿瘤)的感应与响应分子[15]。

2 CLIC1的生物学功能

CLIC1具有双重生化活性:氧化还原GST活性与离子通道活性。首先,CLIC1的GST样活性使其能够催化谷胱甘肽与亲电子底物的结合,在维持细胞氧化还原稳态与毒性物质代谢中发挥关键作用;其次,作为离子通道,CLIC1主要通透Cl^-,对其他阴离子有一定通透性,其阴离子选择性由膜结合形式形成的同源寡聚体(如六聚体)中央孔道(孔径和孔道内带正电残基)决定[16]。CLIC1可与其他离子通道协同,通过调控跨膜Cl^-流,维持细胞容积、细胞内环境稳定,并间接调节如内体或溶酶体等细胞器及胞质的酸碱平衡[1]。值得注意的是,CLIC1的通道活性与酶活性可能相互影响:氧化还原状态通过修饰CXXC基序调控通道的开放,而离子流的变化可能反过来影响局部氧化还原微环境[7]。CLIC1作为氧化应激的感受器和效应器,在应激条件下易位至质膜并形成通道,其激活可能是细胞响应氧化损伤信号通路的一部分,可能进一步影响凋亡或炎症等过程[17,18]。除了上述功能,CLIC1还通过直接结合周期蛋白依赖性激酶2,调控该酶的活性及下游信号通路,进而影响细胞有丝分裂G_1/S期转换和细胞周期进程[19]。

3 CLIC1通过调控关键信号通路影响疾病进程

CLIC1是一种多功能蛋白质,除了上述正常生理学功能外,还在多种细胞信号通路中扮演重要角色,调控肿瘤等疾病的发生和发展(图2)。

3.1 ERK/MAPK信号通路

丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)信号通路是肿瘤细胞分化、增殖、迁移和血管生成等过程中的关键组成部分,该信号通路失调可导致多种癌症的发生[20]。细胞外调节蛋白激酶(extracellular regulated protein kinases,ERK)的激活通常会促进细胞增殖,其活性失调是多种癌症的标志[21]。MAPK/ERK信号通路的异常激活是驱动肿瘤恶性进程的核心机制之一[20,21]。研究表明,CLIC1作为该通路的关键上游调节因子,通过正调控ERK磷酸化,在多类实体肿瘤中发挥广泛的促癌作用[22-27]。在结肠癌(colorectal cancer cells,CRC)与前列腺癌(prostatic cancer,PCa)中,CLIC1通过激活ERK/MAPK通路,分别促进肿瘤细胞的增

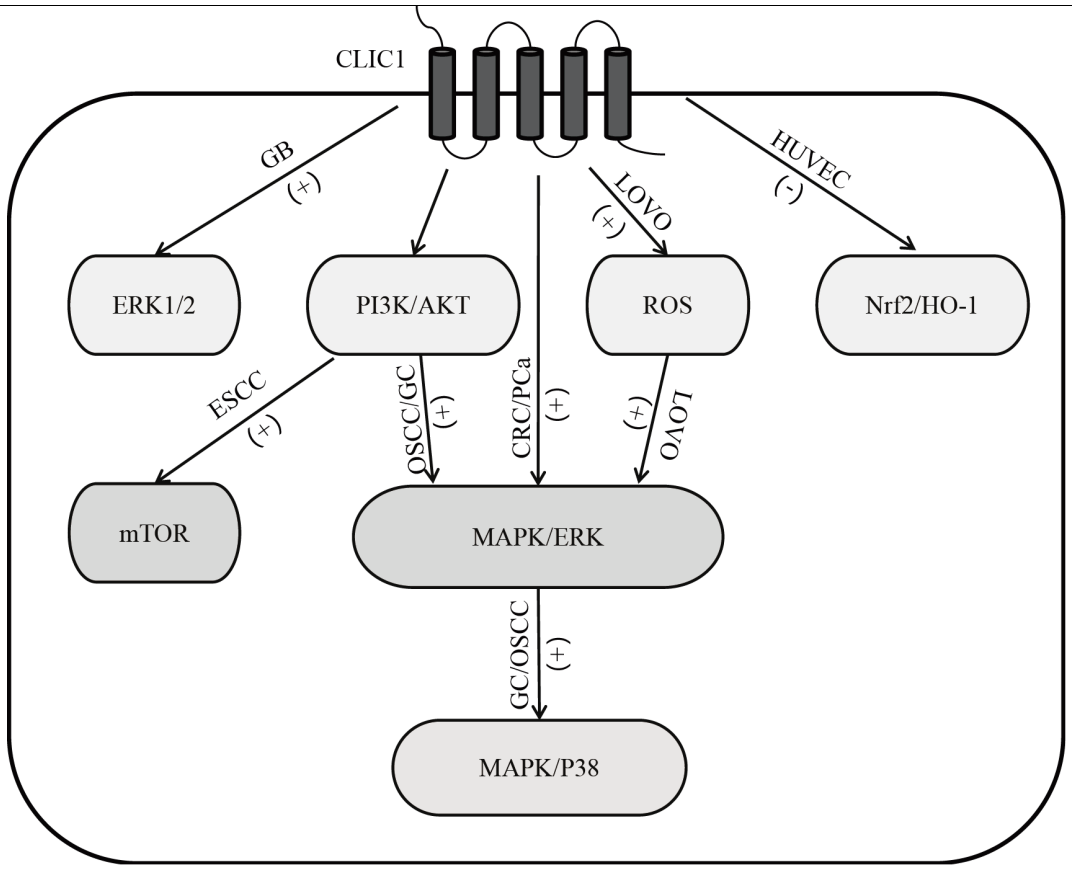


图2 CLIC1参与的多种信号通路

CLIC1通过ERK/MAPK、Nrf2/HO-1、PI3K/Akt/mTOR等信号通路在肿瘤、神经系统疾病、血管炎症等过程中的调控机制。(+)表示激活关系,(-)表示抑制关系。

Figure 2 Various signaling pathways involving CLIC1

CLIC1 regulates tumor, nervous system disease, and vascular inflammation processes through signaling pathways such as ERK/MAPK, Nrf2/HO-1, and PI3K/Akt/mTOR. (+) indicates activation, and (-) indicates inhibition.

殖与迁移侵袭[22,23];在胃癌(gastric carcinoma,GC)中,CLIC1通过上调整合素(ITGα3、ITGαv、ITGβ1)表达,激活PI3K/AKT、MAPK/ERK及p38 MAPK等多条下游通路,驱动肿瘤生长、抑制凋亡并增强侵袭能力[24,25];在口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)中,CLIC1通过整合素/ERK通路发挥类似的促进作用[26];在胶质母细胞瘤(glioblastomas,GB)中,CLIC1通过激活ERK1/2信号,促进肿瘤细胞的增殖、侵袭、上皮-间质转化(epithelial-mesenchymal transition,EMT)及体内肿瘤进展,并与患者不良预后相关[27]。这些发现共同确立了CLIC1在肿瘤中作为MAPK/ERK通路共通性激活节点的重要角色,凸显了其作为跨癌种治疗靶点的潜力。

3.2 Nrf2/HO-1信号通路

核因子E2相关因子2(nuclear factor erythroid 2-related factor 2,Nrf2)是细胞应对氧化应激的关键转录因子,通过激活下游靶基因如血红素加氧酶-1(heme oxygenase-1,HO-1)的表达,发挥重要的抗氧化保护作用[28]。

CLIC1作为氧化应激感受器,可通过负向调控Nrf2/HO-1通路参与多种疾病的病理过程。在神经系统损伤模型中,CLIC1表达上调会抑制Nrf2/HO-1通路,加剧氧化应激、细胞凋亡及NOD样受体家族含pyrin结构域蛋白3(NOD-like receptor pyrin domain-containing protein 3,NLRP3)炎症小体介导的细胞焦亡,而沉默CLIC1则能通过激活Nrf2/HO-1通路发挥神经保护作用[18]。在循环系统中,CLIC1同样通过抑制Nrf2/HO-1通路(可能涉及AMPK信号)促进内皮细胞的氧化损伤、衰老及功能障碍,抑制CLIC1则可激活该通路,改善线粒体功能,显示出心血管疾病防治潜力[29]。这些发现共同揭示了

CLIC1-Nrf2/HO-1轴在氧化应激相关疾病中的核心调控作用,为针对该通路的治疗策略开发提供了重要依据。

3.3 PI3K/Akt/mTOR信号通路

PI3K/Akt/mTOR信号通路是调控细胞生长、增殖与代谢的核心通路,其异常活化常见于多种人类恶性肿瘤[30]。雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)作为该通路的关键激酶,在整合生长因子、营养与应激信号以驱动肿瘤进展中发挥核心作用。研究表明,CLIC1能够正向调控该通路,进而促进肿瘤发生发展。在食管鳞状细胞癌(esophageal squamous cell cancer,ESCC)中,CLIC1表达显著上调,其敲除可抑制mTOR磷酸化及其下游效应分子Rictor(mTORC2的新型结合伴侣)的表达与真核翻译起始因子4E结合蛋白1(eukaryotic translation initiation factor 4E-binding protein 1,4EBP1)的磷酸化,从而抑制肿瘤细胞增殖;而过表达mTOR则可逆转CLIC1敲除所致的增殖抑制,证实了CLIC1通过激活mTOR信号通路促进ESCC进展[31]。这些结果说明,除参与基础生理过程外,CLIC1还通过调控mTOR等多种关键信号通路,广泛影响肿瘤细胞的生长、迁移与侵袭等恶性行为(表1)。

4 CLIC1在多种疾病中的作用机制及临床应用前景

4.1 CLIC1在神经退行性疾病、血管炎症与全身性炎症中的作用

在神经退行性疾病中,CLIC1不仅是潜在的生物标志物,更是驱动神经炎症的关键效应分子。阿尔茨海默病(Alzheimer's disease,AD)患者外周血单核细胞膜上存在CLIC1特异性积聚,提示其可作为中枢神经变性的外周监测指标[32]。在AD的病理进程中,CLIC1通过调控小胶质细胞功能,促进细胞内ROS生成,激活NLRP3炎症小体通路,导致白细胞介素-1β(IL-1β)等促炎因子释放,加速神经元损伤[33-35]。机制上,源自淀粉样蛋白前体蛋白(amyloid precursor protein,APP)基因的环状RNA circAPP可通过调控CLIC1表达与通道活性,进一步促进小胶质细胞病理性活化[33]。此外,在多发性硬化症(multiple sclerosis,MS)中,CLIC1抗体在以视神经和脊髓受累为主的MS患者中被检出,表明CLIC1可能作为抗原参与特定MS亚型的自身免疫发病机制,为其诊断分型提供了新的血清学依据[36]。

在血管炎症性疾病中,CLIC1作为内皮细胞氧化应激的感受器与放大器,参与动脉粥样硬化(atherosclerosis,AS)的发生发展。在AS模型中,CLIC1表达上调通过促进肿瘤坏死因子-α(TNF-α)、IL-1β等炎症因子释放及氧化应激反应,加剧内皮功能障碍与血管损伤[37,38]。传统中药活性成分丹参酮IIA磺酸钠(sodium tanshinone IIA silate,STS)的心血管保护作用部分通过抑制CLIC1表达及膜转位实现,从而减少ROS生成并改善内皮功能[39]。在风湿免疫性疾病如类风湿关节炎(rheumatoid arthritis,RA)和银屑病性关节炎(psoriatic arthritis,PsA)中,CLIC1的表达与炎症小体激活相关,可作为评估炎症活动与治疗反应的潜在生物标志物[40]。最新研究还表明,CLIC1通过支持血小板活化相关机制参与血栓形成过程,进一步扩展了其在血管病理中的功能维度[2]。

在系统性炎症综合征中,CLIC1的作用已超越局部组织范畴,成为连接免疫失调与多器官损伤的分子节点。研究发现,CLIC1与干扰素诱导跨膜蛋白2(interferon induced transmembrane protein 2,

表1 CLIC1相关信号通路在不同疾病/肿瘤类型中的作用及其潜在治疗意义

Table 1 Role of CLIC1-related signaling pathways in different diseases/tumor types and their potential therapeutic significance

信号通路	疾病/肿瘤类型	细胞	调节机制	生物学功能
ERK/MAPK	结肠癌	LOVO细胞	激活MAPK,调节ROS生成	调控肿瘤细胞迁移和侵袭[22]
ERK/MAPK	前列腺癌	PCa细胞	激活MAPK通路	促进细胞增殖与迁移[23]
ERK/MAPK	胃癌	GC细胞	调控AKT、ERK、p38磷酸化	影响生长、代谢与凋亡[24,25]
ERK/MAPK	口腔鳞状细胞癌	OSCC细胞	调控ERK磷酸化	促进侵袭与凋亡[26]
ERK/MAPK	胶质母细胞瘤	GB细胞	正调控ERK1/2信号通路	促进EMT与肿瘤进展[27]
Nrf2/HO-1	神经退行性疾病/血管疾病	HUVEC/脑缺血再灌注	激活Nrf2/HO-1信号通路	抗氧化、抗炎、神经保护[18,29]
PI3K/Akt/mTOR	食管鳞状细胞癌	ESCC细胞	调控mTOR磷酸化	促进细胞增殖与代谢[31]

IFITM2)可作为连接败血症相关认知障碍与AD的共享免疫标志物,揭示不同疾病间存在共同的免疫失调通路[41]。更深入的机制研究将CLIC1定位为败血症病理过程中连接免疫细胞过度活化、炎症因子风暴与调节性细胞死亡的关键枢纽分子,使其成为败血症机制研究与治疗开发的重要候选靶点[42]。

综上所述,CLIC1在神经退行性病变、血管炎症性疾病及全身性炎症反应中均处于调控网络的核心位置,不仅作为疾病进程的参与者与生物标志物,更成为连接不同病理过程的共同分子桥梁。针对CLIC1的干预策略有望为包括阿尔茨海默病、多发性硬化症、动脉粥样硬化、类风湿关节炎及败血症在内的多种炎症相关疾病提供新的治疗方向。

4.2 CLIC1参与多种病毒的复制过程

CLIC1不仅是细胞内的信号调节分子,也作为关键宿主因子,广泛参与多种病毒的复制生命周期,但其具体作用阶段与机制因病毒而异。

在基孔肯雅病毒(Chikungunya virus,CHIKV)感染中,CLIC1是病毒基因组高效复制所必需的宿主因子。功能缺失实验证实,氯离子通道抑制剂或特异性敲低CLIC1均可剂量依赖性地降低病毒滴度。机制上,CLIC1可能与CHIKV的非结构蛋白3(non-structural protein 3,NSP3)发生相互作用,参与病毒复制复合体的形成或稳定,因而成为抗CHIKV感染的潜在药物靶点[43]。

在甲型流感病毒(influenza A virus,IAV)感染中,CLIC1主要参与病毒复制晚期过程。IAV感染可上调CLIC1表达,但在CLIC1缺失或抑制的细胞中,尽管病毒蛋白合成正常、细胞内病毒RNA大量积累,子代病毒颗粒的释放却显著受阻,表明CLIC1在病毒粒子的组装、出芽或释放环节中发挥关键作用[44]。

在猪繁殖与呼吸综合征病毒(porcine reproductive and respiratory syndrome virus,PRRSV)感染中,CLIC1可能发挥宿主防御功能。研究发现,PRRSV通过上调宿主miR-27a-5p来抑制CLIC1表达,促进病毒复制;反之,抑制该miRNA可上调CLIC1并抑制病毒增殖,提示CLIC1具有抗病毒活性,而PRRSV则通过主动抑制CLIC1以逃逸宿主防御。然而,CLIC1在此过程中的具体作用机制尚需进一步验证[45]。

关于CLIC1在病毒感染过程中的研究相对较少,但基于上述可见,CLIC1在不同病毒的生命周期中扮演着不同角色:对于CHIKV,它可能是复制复合体的组成部分;对于IAV,它是生命周期晚期时病毒粒子产生的辅因子;而对于PRRSV,它可能是拮抗病毒的宿主防御因子。这种作用机制的多样性表明CLIC1可参与不同病毒生命周期的不同阶段,凸显了其在病毒-宿主相互作用网络中功能的多样性,但对于CLIC1以哪种形式(可溶性或膜结合)参与病毒感染还有待进一步探讨。

4.3 CLIC1在肿瘤发生、进展及治疗抵抗中的多重作用与机制

CLIC1在口腔癌、鼻咽癌、肺癌、胃癌、胆囊癌、卵巢癌、神经胶质瘤等恶性肿瘤中高度表达,并与较差的临床预后密切相关,提示CLIC1是一个肿瘤诊断和预后判断的重要因子[46]。

4.3.1 CLIC1调控肿瘤的发生、发展

CLIC1对肿瘤细胞周期的调控是其促癌功能的核心机制之一,尤其在肿瘤干细胞亚群中扮演维持增殖和自我更新的关键角色。

在髓母细胞瘤(medulloblastoma,MB)中,CLIC1在细胞周期的G_1和S期定位于细胞膜,并通过其离子通道活性发挥作用。沉默CLIC1表达会降低G_1期和M期的总离子电流,提示其通道功能在多个细胞周期阶段均不可或缺[47]。更重要的是,在GB的肿瘤干细胞(cancer stem cell,CSC)中,CLIC1及其介导的氯离子流对于维持CSC的稳态、增殖与自我更新能力至关重要。抑制CLIC1可导致GB CSC周期停滞于G_1期,并在体内实验中显著抑制肿瘤生长[48,49]。这些发现表明,CLIC1是驱动高侵袭性肿瘤干细胞群体持续增殖的关键分子。

此外,CLIC1的氧化还原状态及其与抗氧化系统的相互作用也直接影响细胞周期进程。研究表明,过氧化物还原酶6(peroxiredoxin-6,Prdx6)通过与CLIC1的GST结构域相互作用,调控其Cys191残基的氧化还原状态。在肝细胞癌(hepatocellular carcinoma,HCC)中,特异性敲低Prdx6会扰乱CLIC1的氧化还原修饰,进而引发代谢重塑、膜结构改变和囊泡运输异常,最终导致细胞周期在G_1/S期转变时停滞[50]。这表明CLIC1的氧化还原敏感特性,经由Prdx6介导的Cys191修饰,耦合细胞代谢与结构完整性,进而发挥G_1/S期检查点的枢纽调控作用。

综上所述,CLIC1通过其离子通道功能及氧化

还原依赖的蛋白质相互作用,在多个层面精密调控肿瘤细胞周期进程,尤其对于肿瘤干细胞的维持具有重要作用。靶向CLIC1及其相关通路,有望成为干预肿瘤细胞周期、抑制肿瘤生长的新型策略。

4.3.2 CLIC1调控肿瘤的侵袭转移等恶性进程

CLIC1通过多种分子机制驱动不同实体肿瘤的恶性进展,其功能主要涉及细胞的增殖、凋亡抵抗、迁移侵袭、代谢重编程及肿瘤微环境重塑等多个方面。

在HCC和GBC中,CLIC1的表达受上游miRNA的精准调控,并直接影响患者预后。在HCC中,抑癌性miR-124通过直接靶向下调CLIC1的表达来抑制肿瘤细胞的迁移和侵袭[51]。在GBC中,CLIC1在癌组织中的表达水平显著高于正常组织,其高表达与患者术后生存率降低相关。功能上,沉默CLIC1能有效促进GBC细胞凋亡,并抑制其增殖、迁移与侵袭能力[52,53]。

在消化系统肿瘤(如OSCC、CRC和GC)中,CLIC1主要通过调控关键信号通路和细胞物理特性来促进恶性表型。在OSCC中,CLIC1通过激活MAPK/ERK和p38信号通路,驱动肿瘤细胞的侵袭并抑制凋亡[30]。在CRC中,CLIC1可能通过调节细胞离子稳态和细胞容积,改变细胞形态与运动能力,从而促进其浸润和转移[54]。在GC中,CLIC1被鉴定为EMT负调控因子的下游靶基因,该调控因子通过转录抑制CLIC1表达而行使抑癌功能[55]。

在胰腺导管腺癌(pancreatic ductal adenocarcinoma,PDAC)中,CLIC1扮演连接肿瘤物理微环境与代谢重编程的关键枢纽角色。当PDAC的细胞外基质硬度增加时,CLIC1表达上调,进而增强肿瘤细胞的糖酵解(瓦博格效应),为快速增殖提供能量和生物合成前体,从而驱动肿瘤生长[56]。

此外,在肾透明细胞癌(clear cell renal cell carcinoma,ccRCC)中,初步证据提示CLIC1的不同亚型可能与癌细胞转移和血管生成相关,而抗CLIC1抗体在临床前模型中显示出诱导肿瘤坏死和破坏肿瘤血管的治疗潜力,为其作为治疗靶点提供了直接证据[57,58]。

综上所述,CLIC1通过调控细胞信号转导、代谢途径、细胞力学以及微环境互动等多重机制,广泛参与从肿瘤增殖到侵袭转移的恶性进程,使其成为多种癌症中极具潜力的预后生物标志物和治疗干预靶点。

4.3.3 CLIC1在肿瘤治疗与耐药性中的调节作用

肿瘤耐药性是导致治疗失败的关键因素,其机制复杂,涉及药物外排、DNA修复、细胞凋亡逃逸及肿瘤微环境适应等多个方面[59]。近年研究发现,CLIC1在多种肿瘤的化疗反应性与耐药性形成中扮演重要调节角色,成为一个新兴的关注靶点。

CLIC1影响肿瘤细胞对化疗药物的敏感性。在不同肿瘤类型中,CLIC1的表达水平与药物疗效呈现相关性。在GBC中,CLIC1的高表达与细胞对二甲双胍的敏感性增强有关,CLIC1下调反而会削弱其抗增殖作用[60]。然而在GB中,CLIC1被证实是二甲双胍的直接作用靶点,二甲双胍直接靶向CLIC1,通过阻断其氯离子电流以选择性抑制肿瘤干细胞增殖,实现抗肿瘤作用[20,61,62]。这一发现提示,CLIC1可能作为某些代谢干预药物的效应分子,参与调节肿瘤细胞的代谢适应与存活。

CLIC1促进肿瘤细胞对经典化疗药物的耐药性。多项研究表明,CLIC1的过表达与肿瘤对多种化疗药物耐药性的形成密切相关。在GC中,CLIC1在长春新碱耐药细胞系中表达显著升高,过表达CLIC1可增强GC细胞对长春新碱的耐药性[63]。在卵巢癌(ovarian cancer,OC)中,CLIC1的表达水平与患者预后不良及对顺铂的耐药性显著相关;功能实验证实,敲低CLIC1不仅能减缓肿瘤生长,还能增强OC细胞对顺铂的敏感性[64,65]。这些结果提示,CLIC1可能通过调控细胞离子稳态、氧化应激响应或凋亡信号通路,帮助肿瘤细胞抵抗化疗药物诱导的死亡。

综上所述,CLIC1在肿瘤治疗反应中具有双重调节作用:一方面可作为某些药物(如二甲双胍)的敏感性标志或作用靶点;另一方面,其过表达又可能介导肿瘤细胞对多种化疗药物(如长春新碱、顺铂)的耐药性。因此,靶向CLIC1或以其作为生物标志物指导用药,可能为逆转肿瘤耐药、改善治疗应答提供新的策略。

5 展望

本文全方位综述了CLIC1作为重要的氯离子通道蛋白,在调节细胞体积、胞内pH及氧化还原平衡等方面发挥关键功能,参与多种肿瘤细胞的增殖、迁移和神经炎症等疾病过程,提示其作为潜在治疗靶

点的研究价值。与已发表的同类综述不同的是,本文不仅介绍了CLIC1在肿瘤、神经系统疾病、血管疾病及病毒感染等多领域的病理生理作用,还深入解析了其调控的 ERK/MAPK、Nrf2/HO-1等关键信号通路及分子机制,以及其在肿瘤耐药性形成中的调节作用,同时明确了其作为潜在生物标志物和治疗靶点的核心价值,弥补了既有综述多聚焦单一疾病领域,缺乏多领域整合分析及构象功能与疾病关联深度探讨的不足。结合当前研究现状,本文提出未来研究的潜在方向:一是需深入挖掘CLIC1可溶性与膜结合形式转换的精细调控机制,及其与疾病进展和病毒生命周期的动态关联;二是应聚焦高选择性CLIC1抑制剂的研发,解决现有抑制剂特异性不足的问题,同时关注其在抗病毒感染及多疾病联合治疗中的应用潜力,为CLIC1相关疾病的精准治疗提供全新思路。

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