

ANO1 表达的多层级调控机制及其在肿瘤中的作用

王嘉琪 刘思铭 廖琳达 罗欣燃 王铭钰 桂兰蕙 董墨含 白立川*
中国医科大学

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[摘要] Anoctamin1(ANO1)是钙激活氯离子通道,参与上皮分泌、平滑肌收缩及细胞稳态,并与肿瘤发生发展相关。ANO1在肿瘤中的表达受多层次机制调控:基因扩增、转录调控、表观遗传调控、翻译后修饰。本文就ANO1多层次调控机制及其作为肿瘤诊断标志物与治疗靶点的潜在价值作一综述。

[关键词] ANO1(TMEMP16A); 表达调控; 肿瘤; 诊断; 治疗

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The multi-level regulatory mechanism of ANO1 expression and its role in tumors

Jiaqi Wang Siming Liu Linda Liao Xinran Luo Mingyu Wang Lanhui Gui Mohan Dong Lichuan Bai*
China Medical University

[Abstract] Anoctamin1 (ANO1) is a calcium-activated chloride ion channel, involved in epithelial secretion, smooth muscle contraction and cellular homeostasis. It is related to tumorigenesis and progression. The expression of ANO1 in tumors is regulated by multi-level mechanisms: gene amplification, transcriptional regulation, epigenetic regulation, posttranslational modification. In this review, we focused on the multi-level regulatory mechanism of ANO1 and its potential value as a tumor diagnostic marker and therapeutic target.

[Key words] ANO1 (TMEMP16A); expression regulation; tumor; diagnosis; treatment

1 引言

近年来研究表明,钙激活氯通道ANO1在乳腺癌、肺腺癌等多种恶性肿瘤组织中高表达,并参与调控肿瘤细胞增殖、迁移、侵袭及肿瘤微环境重塑等多种生物学过程。ANO1表达受多层次分子机制调控,包括基因扩增、细胞信号通路转导、转录调控、表观遗传调控以及翻译后修饰等。深入阐明ANO1的表达调控机制,有助于发现新的肿瘤生物标志物及潜在治疗靶点,为精准治疗提供理论依据。因此,本文重点综述ANO1在肿瘤发生发展中的表达调控机制及其潜在临床意义。

2 基因扩增

基因扩增是肿瘤发生发展的重要遗传变异形式之一,可导致驱动基因mRNA及蛋白水平显著上调,并通过激活多种促癌信号通路赋予肿瘤细胞增殖、侵袭和转移等恶性生物学特性。

研究表明,ANO1基因扩增具有明显的肿瘤亚型特异性。BRITSCHGI A等在乳腺癌亚型分析中发现,ANO1基因扩增在三阴性乳腺癌中发生率约为22%^[2];HU C等证实肺腺癌中ANO1扩增发生率约为18%,是ANO1高表达的重要驱动因素^[3]。ANO1定位于染色体11q13.3-q13.4区域,ODRIGO JP等发现该区域是头颈部鳞状细胞癌的高频扩增位点^[1]。

在前列腺癌中,ANO1扩增同样与肿瘤进展密切相关。KUMAR S等证实ANO1在转移性前列腺癌细胞系中高表达,并通过激活

MAPK信号通路促进肿瘤细胞增殖、侵袭及骨转移^[4];SHIN Y等进一步发现ANO1高表达可促进前列腺癌向胫骨骨转移并形成溶骨性病变^[5]。

在临床应用方面,ANO1基因扩增具有重要转化价值。一方面,可作为头颈鳞癌、肺腺癌及前列腺癌的诊断与预后评估标志物;另一方面,ANO1为肿瘤靶向治疗提供潜在方向。DUVVURI U等发现极光激酶抑制剂可降低ANO1表达并抑制其促癌效应^[6];ZHANG X等证实千金藤素等ANO1特异性抑制剂能够阻断氯通道功能,在扩增阳性肿瘤中表现出显著抗肿瘤活性^[7]。此外,联合靶向ANO1及11q13区域EGFR、CCND1等基因的策略可能通过协同抑制多条促癌信号通路以克服单一靶点治疗的耐药问题^[1]。

3 转录调控

转录调控是ANO1异常表达的重要调控层面。多种细胞因子、生长因子及转录因子通过构建复杂的调控网络影响ANO1转录水平,并表现出明显的组织特异性和病理状态依赖性。不同信号通路之间还存在交叉调控与协同放大效应,从而形成多层次的转录调控网络,对ANO1表达的精细调节在肿瘤细胞增殖、迁移及肿瘤微环境重塑过程中发挥重要作用。

3.1 细胞因子与生长因子信号轴

IL-4/IL-13-STAT6轴与IL-6/EGF-STAT3轴是调控ANO1转录的重要信号通路。IL-13可通过激活STAT6结合ANO1启动子区域,

从而上调AN01转录,并诱导启动子区组蛋白H3K4三甲基化以增强表达^[8]。IL-6/EGF信号则通过激活STAT3促进AN01转录,同时AN01过表达又可增强EGFR磷酸化水平,形成EGFR-STAT3正反馈调控环路,进一步促进乳腺癌细胞增殖与肿瘤生长^[9]。

此外,其他信号通路亦参与调控。DENG L等发现AN01可通过激活ERK1/2及p38信号通路促进肝癌细胞增殖与迁移^[10]; CROTTÈS D等证实EGFR介导的钙信号级联反应参与AN01的激活过程,为胰腺癌靶向治疗提供新的研究方向^[11]。

3.2 转录因子网络调控

多种转录因子参与AN01表达调控。TOLOSA E J等发现Hedgehog通路下游转录因子Gli1与Gli2可结合AN01启动子并抑制其转录^[12];而ZENG X等在胃癌研究中发现转录因子SP1可结合AN01启动子并招募MLL1介导H3K4三甲基化,从而激活AN01转录并促进肿瘤细胞迁移与侵袭^[13]。这些研究表明转录因子对AN01的调控具有明显的细胞类型特异性,不同肿瘤类型中转录因子网络的差异可能决定AN01表达水平及其在肿瘤进展中的功能作用。

4 表观遗传调控

表观遗传调控是AN01组织特异性表达的重要机制,包括DNA甲基化、组蛋白修饰、非编码RNA及三维基因组结构等多层调控方式,在不改变DNA序列的情况下动态调节AN01表达水平。这些可逆性调控机制能够使细胞快速响应肿瘤微环境变化,并在肿瘤发生发展过程中持续影响基因表达模式。

4.1 表观调控特征

AN01表达受可逆化学修饰及RNA介导机制调控,使其能够动态响应肿瘤微环境变化,并参与肿瘤细胞表型转化过程。表观遗传调控通常与转录调控及信号通路调控协同作用,共同决定AN01在不同组织和病理状态中的表达水平。

4.2 直接表观遗传调控

DNA甲基化通过调控启动子CpG岛甲基化状态调节AN01表达。SHIN Y等在前列腺癌细胞系中发现AN01启动子区存在高甲基化状态,DNA甲基转移酶抑制剂5-aza-2'-脱氧胞苷可降低甲基化水平并上调AN01表达^[5]。AN01去甲基化可增强肿瘤细胞迁移和侵袭能力,该效应在AN01敲低后被消除,体内实验亦证实其促进骨转移作用^[5]。这些结果提示DNA甲基化状态的改变可能在肿瘤转移过程中发挥关键调控作用。

组蛋白修饰同样参与调控。ZENG X等发现MLL1介导的H3K4三甲基化可增强AN01启动子转录活性^[13];MATSUBA S等则发现HDAC3通过降低染色质乙酰化水平抑制AN01表达^[14]。

非编码RNA也参与调控。PARK Y R等发现miR-9可直接结合AN01 mRNA 3' UTR抑制其翻译^[5];MOKUTANI Y等证实miR-132也具有类似作用^[17];LI R等发现miR-671-5p可抑制食管鳞癌中AN01表达^[16]。

4.3 三维基因组调控

三维染色质结构也参与AN01表达调控。KIM K L等发现CTCF通过形成拓扑边界维持AN01表达稳定^[18];而在肿瘤中CTCF边界破坏可导致增强子与AN01启动子异常互作并促进过表达。BOURDIER S等在HPV阴性头颈鳞癌中发现11q13扩增可导致AN01与FGF基因

共扩增,并与放疗耐药相关^[19]。这些发现提示三维基因组结构变化可能在肿瘤相关基因异常表达中发挥重要作用。

5 翻译后修饰

翻译后修饰通过磷酸化、泛素化等方式调控AN01的活性、定位及稳定性,是AN01功能实现的重要调控层级。这些修饰能够快速改变蛋白质结构和功能,使AN01在细胞信号转导过程中发挥动态调节作用。

5.1 磷酸化修饰

AYON R J等发现CaMK II可磷酸化AN01的S528位点并抑制氯电流活性,而PP1/PP2A去磷酸化可恢复通道功能^[20]。STIM1介导的ER/PM交界区复合物亦参与调控,其中E-Syt1与E-Syt2分别通过不同复合物调节AN01的钙敏感性^[21]。此外,ZHENG Y等发现靶向AN01的单克隆抗体可通过抑制PI3K-AKT/JNK磷酸化通路抑制食管鳞癌进展^[22];REED E B等发现TGF-β通过AN01激活WNK1/mTORC2信号轴^[23]。这些研究表明磷酸化修饰不仅影响AN01通道活性,还可通过下游信号通路调控肿瘤相关细胞功能。

5.2 泛素化修饰

CAO X等发现E3泛素连接酶TRIM21与TRIM23通过不同类型的泛素化修饰调控AN01稳定性^[24]。TRIM21介导K48型泛素化促进蛋白降解,而TRIM23介导K63型泛素化稳定AN01蛋白。二者之间的动态平衡决定AN01蛋白水平,并进一步影响其在肿瘤细胞中的功能。

5.3 潜在SUMO化修饰

尽管目前尚无直接证据证明AN01存在SUMO化修饰,但考虑到SUMO化常调控离子通道蛋白的定位与稳定性,AN01可能同样受到该机制调控^[25,26]。未来相关研究有望进一步完善AN01翻译后修饰调控网络,并为开发新的靶向治疗策略提供理论依据。

6 结论与展望

AN01作为钙激活氯通道,在多种恶性肿瘤中高表达,其扩增频率与肿瘤恶性程度密切相关。本文总结了AN01在基因扩增、信号通路转导、转录调控、表观遗传调控及翻译后修饰等方面的表达调控机制。未来从AN01调控肿瘤恶性表型的分子机制出发,将有助于开发针对AN01高表达肿瘤的靶向治疗策略,并为精准医学提供新的研究方向。

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作者简介:

王嘉琪(2005--),女,汉族,安徽省宿州市人,本科。

白立川(1981--),男,汉族,辽宁省葫芦岛市人,硕士,单位:中国医科大学药学院离子通道研究室,职称:讲师,研究方向:钙激活氯通道ANO1的门控动力学及促结肠癌转移的机制研究。