综述

Caldesmon及其磷酸化调节肠道平滑肌收缩舒张功能研究进展

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摘要 肠道平滑肌的收缩和舒张与粗细肌丝的调节密切相关。Caldesmon作为一种肌动蛋白结合蛋白, 是参与肠道平滑肌粗细肌丝调节的重要收缩蛋白之一, 可通过与肌动蛋白、肌球蛋白和原肌球蛋白交联, 阻碍肌动蛋白与肌球蛋白的结合, 从而抑制肠道平滑肌的收缩。然而, Caldesmon的磷酸化修饰可以逆转这种抑制作用。Caldesmon可以被不同信号通路中的蛋白激酶刺激, 引起自身的磷酸化, 促进肌动蛋白与肌球蛋白的结合, 进一步导致肠道平滑肌的收缩, 在肠道动力障碍疾病中起到关键作用。分别以“Caldesmon”、“平滑肌”、“磷酸化”和以“Caldesmon”、“smooth muscle”、“phosphorylation”、“actin”、“myosin”、“contraction and relaxation”为主题词在中国知网(CNKI)、百度学术和PubMed数据库中查找Caldesmon与平滑肌或肠道平滑肌相关文献。该文就Caldesmon及其磷酸化参与调节肠道平滑肌收缩舒张的功能以及介导Caldesmon磷酸化的相关上游信号通路等方面进行综述, 旨在为以基于Caldesmon及其磷酸化调节肠道平滑肌收缩舒张为靶点的临床疾病治疗提供理论依据。

关键词 Caldesmon; 肠道平滑肌; 磷酸化; 肌动蛋白; 肌球蛋白; 收缩舒张

Caldesmon and Its Phosphorylation in Regulating Contraction and Relaxation of Intestinal Smooth Muscle

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Abstract The contraction and relaxation of intestinal smooth muscle are closely related to the regulation of thick and thin muscle filaments. As an actin-binding protein, Caldesmon is one of the important contractile proteins involved in the regulation of the thick and thin filaments of intestinal smooth muscle. It can cross-link with

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actin, myosin and tropomyosin to prevent the binding of actin and myosin, thus inhibiting the contraction of the intestinal smooth muscle. However, phosphorylation modifications of Caldesmon can reverse this inhibition. Caldesmon plays a key role in intestinal motility disorders, and can be stimulated by protein kinase activated through different signaling pathways to cause its own phosphorylation, thereby enhancing the binding of actin and myosin, and further causing the contraction of intestinal smooth muscle. In CKNI, Baidu Academic and PubMed databases, Caldesmon, smooth muscle, phosphorylation, actin, myosin and contraction and relaxation were used as keywords to find relevant literature. To provide a theoretic basis for clinical diseases targeting the regulation of intestinal smooth muscle contraction and relaxation based on Caldesmon and its phosphorylation, this article reviews the function and related upstream signaling pathways involved in the regulation of intestinal smooth muscle contraction and relaxation by Caldesmon and its phosphorylation.

Keywords Caldesmon; intestinal smooth muscle; phosphorylation; actin; myosin; contraction and relaxation

肠道平滑肌的收缩和舒张是肠道动力调节的重要环节, 肠道动力是引起肠动力障碍性疾病发生的关键因素, 因此肠道平滑肌正常的收缩和舒张对肠动力障碍性疾病的治疗具有重要的意义[1]。调节肠道平滑肌的经典机制是粗肌丝(thick filaments)相关调节机制, 又被称为Ca^{2+}/钙调蛋白(calmodulin, CaM)-肌球蛋白轻链(myosin light chain, MLC)磷酸化机制, 肌球蛋白轻链磷酸化后促进肌球蛋白(myosin)与肌动蛋白(actin)结合, 同时肌球蛋白上ATP酶被激活, 粗细肌丝相互滑动, 导致肠道平滑肌随之收缩[2]。但是目前研究发现肠道平滑肌收缩的强度不与肌球蛋白轻链磷酸化程度成正比, 因此除了粗肌丝调节方式外, 可能还存在其他调节机制[3]。近年来发现钙调蛋白结合蛋白Caldesmon在调节平滑肌收缩和舒张方面发挥着重要的作用[4]。

1981年, SOBUE等[5]首次在鸡胗中发现Caldesmon的存在, 作为重要的肌动蛋白结合蛋白, Caldesmon通过抑制肌动蛋白与肌球蛋白的结合, 降低肌动蛋白激活的肌球蛋白Mg^{2+}-ATP酶活性, 从而影响平滑肌的收缩[6-7]。此外, Caldesmon的作用还与磷酸化修饰相关[8]。Caldesmon(Ser657和Ser687)被p21活化蛋白激酶(p21-activated kinases, PAKs)刺激发生磷酸化, 与肌动蛋白–原肌球蛋白(tropomyosin)的亲和力降低, 气道平滑肌收缩力增强, 导致非特异性支气管高反应性以及哮喘的发生[9]。Caldesmon(Ser789)被有丝分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)激活, 发生磷酸化, 削弱Caldesmon对肌动蛋白激活的肌球蛋白Mg^{2+}-ATP酶活性的抑制作用, 从而促进了血管或肠道平滑肌的收缩[10-11]。因此, Caldesmon及其磷酸化可以调控平滑肌的收缩或舒张功能。

肠道平滑肌的收缩或舒张障碍是肠道障碍性疾病的重要病理机制之一[12]。Caldesmon作为平滑肌收缩舒张功能的重要调控靶点, 在肠道平滑肌中可能也发挥着重要作用。研究表明, 通过敲除*Caldesmon*的表达可以增强野生型斑马鱼幼虫和缺乏肠神经的突变型斑马鱼幼虫的肠道蠕动[13]。此外, 在电针刺激足三里穴对大鼠肠道动力影响的实验中, 针刺组大鼠肠道平滑肌细胞中Caldesmon的表达水平下调, 而肠道平滑肌的收缩力和肠道运动功能均增强[14]。由此可见, Caldesmon可能通过调节肠道平滑肌的收缩和舒张来影响肠道的运动功能, 这对肠道动力障碍性疾病的机制研究具有更进一步的借鉴意义。

综上, Caldesmon在调控肠道平滑肌的收缩舒张过程中可能发挥着重要功能, 但是目前对于Caldesmon在肠道平滑肌收缩和舒张中表达和功能的报道较为零散, 其作用机制尚不明确。为了进一步阐明Caldesmon及其磷酸化在肠道平滑肌中的作用机制, 本文将从Caldesmon的基本特性、Caldesmon在调节肠道平滑肌功能中的作用以及不同信号通路介导Caldesmon磷酸化参与肠道平滑肌收缩三个方面进行综述。

1 Caldesmon的基本特性

1.1 Caldesmon的结构和分型

Caldesmon是一种平滑肌肌球蛋白和钙调蛋白结合的蛋白, 由位于7q33的*CALD1*基因编码, 含有

表1 H-caldesmon与L-caldesmon之间的差异

Table 1 The difference between H-caldesmon and L-caldesmon

差异 Difference	H-caldesmon	L-caldesmon	参考文献 References
Amino acidcomposition	793	538	[19]
Tissue distribution	Expressed predominantly indifferentiated smooth muscle cells, and only a few in platelets, colorectal pericryptal fibroblasts, and myoepithelial cells of galactophorous sinuses of human breast tissue	Exists mainly in non-muscle tissue and probably in the non-muscle cells present in the interstitium of the smooth muscle tissue	[20-22]
Expression in smooth muscle cells	Specific expression	Low-level expression	[23]
Functions	Regulates smooth muscle contraction	Involved in cell division, diffusion, migration, proliferation, apoptosis, and intragranular movement Regulates actin assembly	[4,20,24]
Clinical diagnosis	Differential diagnosis of true smooth muscle tumor from myofibroblastoma, and ovarian/peritoneal serous papillary carcinoma from epithelioid mesothelioma Combined with CD10 to distinguish leiomyoma from endometrial stromal sarcoma	As a potential serum marker for glioma	[7,25]
Effects after phophorylation	Promotes smooth muscle contraction	Promotes stress fiber decomposition, actin cytoskeletal remodeling, cell proliferation and migration	[6,26]

至少17个外显子, 并且可以经外显子7和8选择性剪接产生两种亚型, 分别是重型Caldesmon(H-Caldesmon; 高分子量, 120~150 kDa)和轻型Caldesmon(L-Caldesmon; 低分子量, 70~80 kDa)[7,15]。正是由于基因剪接和转录的差异, 导致Caldesmon的两种亚型在组织分布、结构以及功能等方面存在差异(表1)。在肠道平滑肌中, H-Caldesmon主要表达于分化的肠道平滑肌细胞中, 位于收缩区域的细丝上; L-Caldesmon主要表达于去分化的肠道平滑肌细胞中, 主要在应力纤维上发挥作用[8]。

Caldesmon包括三个结构域, 即氨基端(N-terminus)结构域、中间螺旋结构域以及羧基端(C-terminus)结构域[16]。其中L-Caldesmon比H-Caldesmon缺少一段中间螺旋结构[17]。Caldesmon的N末端结构域1(约210个残基)主要与肌球蛋白和原肌球蛋白结合, 也可与钙调蛋白弱结合; 中心结构域2(约250个残基)是一条长而连续的α螺旋, 包含原肌球蛋白的结合位点; 中心结构域3(约180个残基)是相对较短的螺旋状, 包含肌球蛋白、原肌球蛋白以及可能的肌动蛋白结合位点; C末端结构域4包含了Caldesmon几乎所有的功能特性, 抑制肌动蛋白激活的肌球蛋白Mg^{2+}-ATP酶活性, 与肌动蛋白和肌球蛋白相互交联, 抑制肌动蛋白在肌球蛋白上的滑动[8], 其还可以与原肌球蛋白、Ca^{2+}/钙调蛋白和磷脂质等相互结合[4,18]。

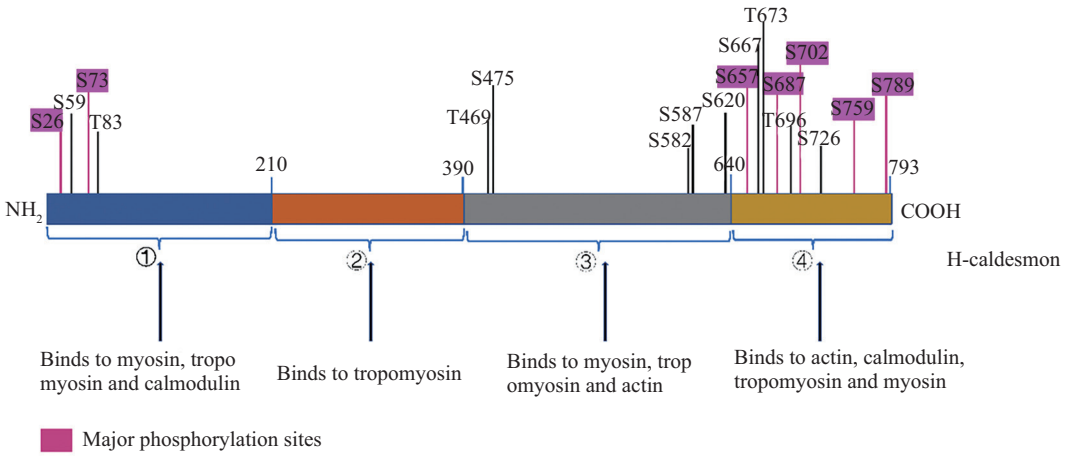
1.2 Caldesmon的磷酸化修饰

Caldesmon是多种蛋白激酶的底物, 具有近百个磷酸化位点, 可受多种激酶调控[27]。Caldesmon无论是处于游离的状态还是与肌动蛋白、肌动蛋白/原肌球蛋白或肌球蛋白结合的状态, 在Ca^{2+}和Mg^{2+}-ATP共同存在的情况下, 含有内源性激酶活性的Caldesmon都可以迅速发生磷酸化[6]。在肠道平滑肌中, Caldesmon主要磷酸化的位点位于N-端的肌球蛋白结合位点、钙调蛋白结合位点、原肌球蛋白结合位点, 或C-端的肌动蛋白结合位点、钙调蛋白位点、原肌球蛋白结合位点的氨基酸残基上(图1)。

其中最主要参与Caldesmon磷酸化调节环节的激酶有以下几种: MAPK[11,28]、热休克蛋白27(heat shock protein 27, HSP27)[29]、Ca^{2+}/钙调蛋白依赖性蛋白激酶II(Ca^{2+}/calmodulin-dependent protein kinase II, CaMKII)[30]和蛋白激酶C(protein kinase C, PKC)[31-32]等。

2 Caldesmon在调节肠道平滑肌功能中的作用

在肠道平滑肌中, Caldesmon可以通过影响肌球



在肠道平滑肌中, H-caldesmon有多个磷酸化位点, 分布在四个不同的结构域, 其中主要的磷酸化位点位于C-端和N-端, 分别是S657、S687、S702、S759、S789、S26和S73位点。

In intestinal smooth muscle, H-caldesmon has multiple phosphorylation sites, which are distributed in four different domains. The major phosphorylation sites are located at the C and N terminals, which are S657, S687, S702, S759, S789, S26 and S73 respectively.

图1 肠道平滑肌中的Caldesmon磷酸化位点

Fig.1 The phosphorylation sites of Caldesmon in intestinal smooth muscle

蛋白与肌动蛋白的结合, 调节平滑肌细胞收缩或舒张[33]。Caldesmon以一定的间隔出现在原肌球蛋白的双螺旋结构上, 与原肌球蛋白和肌动蛋白紧密相连, 同时原肌球蛋白的存在掩盖了肌动蛋白上肌球蛋白的结合位点, 使Caldesmon与肌动蛋白的结合更加紧密, 肌球蛋白与肌动蛋白的结合受到阻碍, 从而抑制肠道平滑肌的收缩[8]。当Caldesmon受到某种刺激发生磷酸化时, 构象可能发生改变, 随着原肌球蛋白一起滑动, 与肌动蛋白和肌球蛋白部分解离, 暴露肌动球蛋白结合位点, 削弱对肌球蛋白Mg^{2+}-ATP酶活性的抑制, 恢复肌动蛋白与肌球蛋白结合(图2), 从而引起肠道平滑肌的收缩[8]。

在肠道平滑肌中, 除了Caldesmon的磷酸化修饰外, 其中Ca^{2+}的浓度以及肌球蛋白的磷酸化水平也是影响Caldesmon调节肠道平滑肌收缩舒张功能的重要因素。

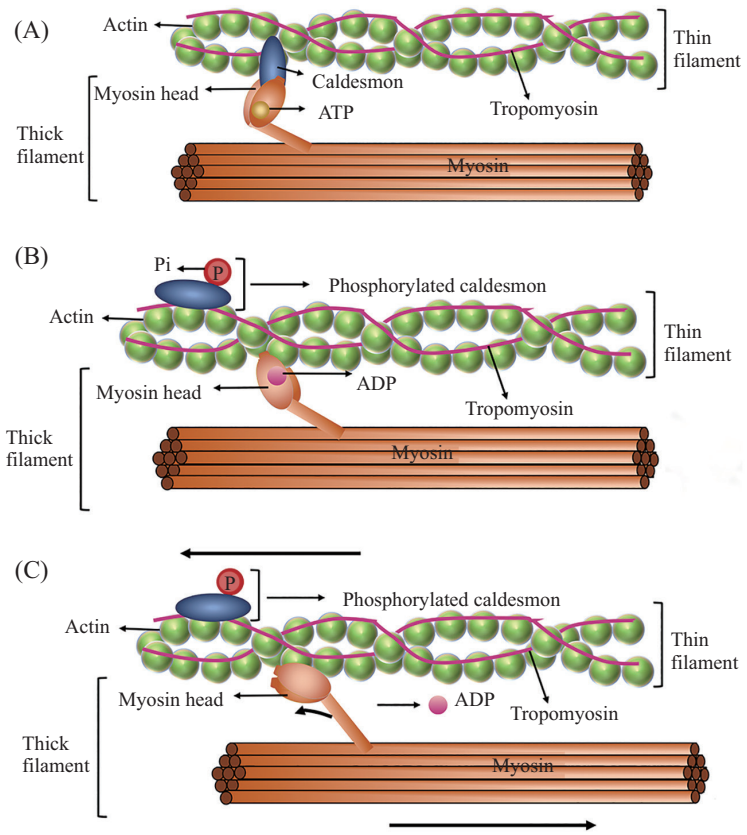
2.1 Ca^{2+}参与Caldesmon调节肠道平滑肌功能

Ca^{2+}的浓度会影响Caldesmon调节肠道平滑肌收缩舒张的功能[34], 在肠道平滑肌中, Caldesmon以Ca^{2+}依赖的方式与钙调蛋白结合, 以Ca^{2+}非依赖的方式与肌动蛋白结合[35]。在体外构建的收缩系统模型(含有Caldesmon、肌球蛋白、原肌球蛋白、肌动蛋白和钙调蛋白)中, 当Ca^{2+}的浓度低于1 μmol/L时, 与单独的肌动蛋白相比, Caldesmon与肌动蛋白的亲和力增加($K=10^7\ M^{-1}$)[36]。所以, 在Ca^{2+}浓度较低(<1 μmol/L)的情况下, Caldesmon可能与原肌球蛋白/肌动蛋白结合, 并抑制肌动球蛋白Mg^{2+}-ATP酶活性, 使得肌动蛋白与肌球蛋白结合更加紧密, 粗细肌丝相互交联, 阻碍肌丝滑行, 维持肠道平滑肌的舒张状态[37-38]。当Ca^{2+}的浓度逐渐升高, 达到1 μmol/L时, Caldesmon与肌动蛋白结合的复合物与Caldesmon-Ca^{2+}/钙调蛋白的复合物的形成处于平衡状态; 当Ca^{2+}的浓度高于1 μmol/L时, Caldesmon与钙调蛋白的亲和力逐渐增加($K=10^6\ M^{-1}$)[36]。所以, 当Ca^{2+}浓度升高并且>1 μmol/L时, Caldesmon可能倾向与Ca^{2+}/钙调蛋白的复合物进一步结合, 削弱Caldesmon与原肌球蛋白/肌动蛋白的相互作用, 这一过程诱导Caldesmon从原肌球蛋白/肌动蛋白上部分解离, 暴露肌动蛋白与肌球蛋白的结合位点, 同时减弱Caldesmon对肌动球蛋白Mg^{2+}-ATP酶活性的抑制作用, 从而促进肌动蛋白与肌球蛋白结合, 利于肠道平滑肌发生收缩产生张力[7,39]。

因此, Caldesmon可以随着Ca^{2+}浓度的变化, 分别与原肌球蛋白/肌动蛋白或钙调蛋白结合, 影响肌动蛋白与肌球蛋白的相互作用, 从而调节肠道平滑肌收缩或舒张功能。

2.2 肌球蛋白磷酸化与Caldesmon共同调节肠道平滑肌功能

Caldesmon对肠道平滑肌收缩舒张功能的调节还与肌球蛋白轻链的磷酸化水平有着密切的联系[40]。众所周知, 当肠道平滑肌受到收缩刺激时,



A: 静息状态下, Caldesmon阻碍肌动蛋白与肌球蛋白的相互作用; B: Caldesmon发生磷酸化, 肌球蛋白头部(myosin head)构象也随之发生改变, 同时ATP激活水解释放能量, 促进肌动蛋白与肌球蛋白的结合; C: 横桥扭动, 粗肌丝肌球蛋白丝向M线方向运动, 细肌丝(thin filaments)肌动蛋白丝向相反方向运动, 发生肌丝滑行, 引起肠道平滑肌收缩。

A: during the relaxed state, caldesmon obstructs the interaction between actin and myosin. B: when caldesmon is phosphorylated, the conformation of myosin head is also changed, and ATP is activated to release energy by hydrolysis, which promotes actin-myosin binding. C: when the cross-bridge twists, the myosin filaments move in the direction of M line, and the actin filaments move in the opposite direction. Then the thick and fine muscle filaments glide, causing intestinal smooth muscle to contract.

图2 Caldesmon与肌动球蛋白之间的相互作用

Fig.2 The interaction between Caldesmon and actomyosin

肌球蛋白被肌球蛋白轻链激酶刺激发生磷酸化, 促进肌球蛋白与肌动蛋白相互作用, 肠道平滑肌产生初始快速收缩[41]。但是随着肌球蛋白轻链的磷酸化水平达到峰值后再降低(磷酸化程度低于100%), 肠道平滑肌仍然保持紧张收缩[6]。这可能主要是因为在肌球蛋白轻链去磷酸化的过程中, 肌球蛋白轻链激酶以Ca^{2+}/钙调蛋白依赖的方式磷酸化Caldesmon肌动蛋白区域的Thr626和Thr693位点, 使Caldesmon与肌动蛋白的结合减弱, 与磷酸化的肌球蛋白亲和力增加, 从而促进肌动蛋白与肌球蛋白的结合, 维持肠道平滑肌的持续有效收缩[42]。所以, Caldesmon可能在肌球蛋白尚未完全磷酸化的情况下, 受到磷酸化修饰, 介导肌动蛋白与肌球蛋白的结合, 使肠道平滑肌在低ATP消耗的情况下, 仍然可以保持紧张收缩[43]。

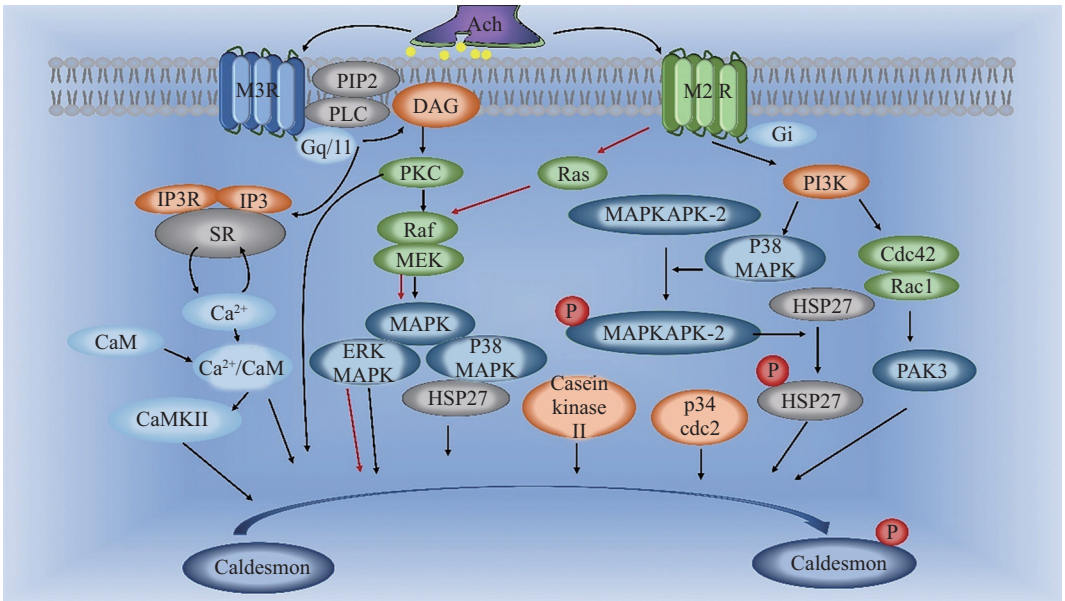
因此, 在肠道平滑肌中, 肌球蛋白轻链的磷酸化程度也会影响Caldesmon调节肠道平滑肌的收缩或舒张功能的作用。

3 不同信号通路介导Caldesmon磷酸化参与肠道平滑肌收缩

Caldesmon是各种信号通路调节肠道平滑收缩或舒张的重要靶点, 通过磷酸化修饰可以促进肠道平滑肌的收缩, 涉及Caldesmon磷酸化的三个主要通路: MAPK信号通路、HSP27信号通路、CaMKII信号通路(图3)。

3.1 MAPK信号通路

MAPK作为介导Caldesmon磷酸化的重要激酶之一, 可通过多条信号通路调节肠道平滑肌的收缩。Caldesmon通过M2受体介导的Ras/Raf/MEK/ERK



Caldesmon需要通过一定的信号通路诱导发生磷酸化, 这些信号通路中都有一个或几个关键的蛋白激酶, 相关蛋白激酶通过不同的途径被激活, 刺激Caldesmon上的磷酸化位点发生磷酸化, 从而促进肠道平滑肌细胞的收缩。目前已知的信号通路包括Ca^{2+}/CaM信号通路、CaMKII信号通路、PKC信号通路、MAPK信号通路、HSP27信号通路、酪蛋白激酶II信号通路、p34cdc2信号通路和PAK信号通路。

Caldesmon phosphorylation needs to be induced through certain signaling pathways to regulate the contraction and relaxation of intestinal smooth muscle. Each of these signaling pathways has one or several key protein kinases that are activated through different pathways to stimulate phosphorylation sites on Caldesmon. Currently known signaling pathways include Ca^{2+}/CaM, CaMKII, PKC, MAPK, HSP27, casein kinase II, p34cdc2, and PAK.

图3 Caldesmon磷酸化调节肠道平滑肌收缩的不同信号通路(根据参考文献[26]修改)

Fig.3 The different signal pathways of Caldesmon phosphorylation regulate intestinal smooth muscle contraction (modified from the reference[26])

MAPK信号通路[44]、p38 MAPK/丝裂原活化蛋白激酶激活蛋白2(MAPKAPK-2)/HSP27信号通路[29]以及M3受体介导的PKC/MEK/ERK MAPK信号通路[45-46]发生磷酸化, 逆转Caldesmon对肌动蛋白激活的肌球蛋白ATP酶活性的抑制作用, 促进肌动蛋白与肌球蛋白结合, 降低Caldesmon对跨桥循环速率的抑制作用, 调控肌动蛋白组装以及诱导肠道平滑肌收缩。其中主要的磷酸化位点位于Caldesmon的C末端, 包括Ser789和Ser759, 其中以Ser789为主要的磷酸化位点, 有研究表明当肠道平滑肌受到收缩激动剂(毒蕈碱)刺激时, Ser789位点处的磷酸化水平会增加1.5~2.0倍[44]。

3.2 HSP27信号通路

Caldesmon的磷酸化与HSP27/PKC-α信号通路也密切相关[29,47]。在肠道平滑肌受到收缩激动剂(乙酰胆碱)的刺激时, HSP27发生磷酸化, 刺激PKC-α(Ser657)激活或易位。激活的PKC-α与Caldesmon结合, 导致Caldesmon(Ser789)磷酸化, 磷酸化的Caldesmon与激活的PKC-α分离, 结合磷酸化的HSP27, Caldesmon构象发生改变, 与原肌球蛋白/肌动蛋白部分分离, 肌球蛋白在肌动蛋白上滑动, 暴露肌球蛋白的结合位点, 促进肌动蛋白与肌球蛋白结合, 从而促进肠道平滑肌的收缩[10,48]。

当肠道平滑肌受到神经递质血管活性肠肽(vasoactive intestinal peptide, VIP)刺激时, 原肌球蛋白、Caldesmon和HSP27的磷酸化受到抑制, Caldesmon与原肌球蛋白/肌动蛋白结合, 阻碍肌动蛋白与肌球蛋白的相互作用, 终止收缩, 肠道平滑肌处于舒张状态[10]。除此之外, 由蛋白激酶A(PKA)激活的热休克蛋白20(heat shock protein 20, HSP20)也可以通过磷酸化修饰, 阻止原肌球蛋白与Caldesmon解离, 抑制肌球蛋白结合位点的暴露, 导致肠道平滑肌舒张[49]。

综上, 当肠道平滑肌受到不同的刺激时, HSP27可以通过影响下游Caldesmon的磷酸化或去磷酸化, 调节肠道平滑肌的收缩或舒张功能。

3.3 CaMKII信号通路

Caldesmon和CaMKII都是钙调蛋白下游的靶蛋白, 所以Caldesmon对肠道平滑肌收缩的抑制作用, 既受Ca^{2+}/钙调蛋白的调节, 也受CaMKII催化的磷酸化的调节[50]。CaMKII磷酸化Caldesmon的位点包括

丝氨酸残基(83.3%)和苏氨酸残基(16.7%)[51], 根据磷酸化的时间进程, 首先磷酸化的位点是Ser73, 其次是Ser26、Ser726、Ser587, 优先磷酸化的位点位于Caldesmon的N-端的肌球蛋白结合区域, 而磷酸化较慢的位点则位于C-端的肌动蛋白或钙调蛋白结合区域[52]。因此, CaMKII信号通路的激活可能通过刺激Caldesmon N-端磷酸化位点(Ser73), 逆转Caldesmon对肌动球蛋白Mg^{2+}-ATP酶活性的抑制作用, 解除Caldesmon与肌球蛋白的结合, 促进肌动蛋白与肌球蛋白相互作用, 从而调节肠道平滑肌的收缩[3,53]。

3.4 其他信号通路

除以上提到的三个主要的信号通路外, 还有一些蛋白激酶介导的信号通路也介导磷酸化的Caldesmon参与肠道平滑肌收缩功能的调节。酪蛋白激酶II可以催化Caldesmon中丝氨酸(Ser26、Ser73)或苏氨酸(Thr83)残基磷酸化, 减弱Caldesmon与肌球蛋白或原肌球蛋白之间的结合能力[18], 促进肌动蛋白和肌球蛋白相互结合, 从而引起肠道平滑肌的收缩[18,54]。在所有的磷酸化位点中, Ser73会导致Caldesmon N末端区域对原肌球蛋白的亲和力降低2~4倍, 是酪蛋白激酶II主要的磷酸化位点[54]。p34cdc2激酶与ERK MAPK一同作为脯氨酸定向激酶, 可以参与有丝分裂期间M期的肌动蛋白丝解离, 从而影响肠道平滑肌细胞骨架结构或者参与肠道平滑肌收缩的调节[55]。主要磷酸化Caldesmon的C末端区域肌动蛋白和钙调蛋白的结合位点, 包括Ser582、Ser667、Thr673、Thr696和Ser702, 其中Thr673约占总磷酸化水平的40%[56]。所以, p34cdc2激酶通过抑制Caldesmon与肌动蛋白和Ca^{2+}/钙调蛋白的结合, 促进肠道平滑肌的收缩[57-58]。PAK作为Ras相关C3肉毒素底物1(Rac1)和细胞分裂周期蛋白42(Cdc42)的关键下游效应因子之一, 其异构体GST-mPAK3通过磷酸化Caldesmon(Ser657和Ser687), 影响Caldesmon与钙调蛋白、肌动蛋白的结合, 降低Caldesmon对肌动球蛋白Mg^{2+}-ATP酶活性的抑制作用, 从而诱导肠道平滑肌的Ca^{2+}非依赖性收缩[59–61]。

4 总结与展望

综上所述, Caldesmon在肠道平滑肌收缩和舒张功能的调节中发挥重要的作用。在功能上, Caldesmon通过调节肌动蛋白与肌球蛋白的相互作用, 抑制肌动蛋白激活的肌球蛋白Mg^{2+}-ATP酶活性, 从而抑制肠道平滑肌收缩; 在结构上, Caldesmon通过交联肌动蛋白丝和肌球蛋白丝, 将肌丝稳定在正确的方向和空间结构上, 使肠道平滑肌在受到刺激时维持有效的收缩[7]。Caldesmon的调控机制相对复杂, 通过不同信号通路介导自身磷酸化, 影响其与肌球蛋白、肌动蛋白、原肌球蛋白和钙调蛋白的结合, 从而参与调节肠道平滑肌的收缩或舒张功能。

目前关于Caldesmon的相关研究热点仍在于它作为一种特殊的肿瘤标志物以及在血管及气道平滑肌中的作用[7,15]。目前研究发现肠道平滑肌细胞中Caldesmon的表达可能会通过影响肠道平滑肌收缩或舒张, 从而影响肠道动力, 因此研究Caldesmon在肠道平滑肌中相关的信号通路对肠道动力障碍性疾病的机制研究及治疗具有重要意义。但目前学界对于通过Caldesmon及其磷酸化修饰调节肠道平滑肌收缩舒张功能的机制研究尚不完全明确, 迫切需要大量的实验研究来证明Caldesmon在调节肠道平滑肌中的作用。同时对于其中涉及的蛋白与蛋白的相互作用的关系以及信号通路间的交互作用仍有待进一步研究。总之, 深刻了解Caldesmon及其磷酸化在调节肠道平滑肌功能中的作用机制, 将有利于我们进一步解析肠道动力障碍性疾病的发病机制, 从而为临床上治疗肠道动力障碍性疾病提供新的思路。

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