RhoA的泛素化降解机制及功能

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摘要 Rho小G蛋白(Ras homology frowth-related, RhoG)家族作为分子开关(molecular switch)在GTP结合的激活形式和GDP结合的非激活形式之间转换, 发挥着重要的生物学功能, 细胞内Rho小G蛋白的含量可由泛素–蛋白酶体系统(ubiquitin-proteasome system, UPS)降解途径来调控。RhoA(Ras homolog gene family member A, RhoA)是Rho小G蛋白家族成员, 其功能涉及细胞极性、细胞迁移、细胞周期调控、神经系统发育等, 通过UPS途径对该蛋白在细胞内的含量进行调控, 可保证细胞的相关正常生理功能。在RhoA泛素化降解过程中, 不同的泛素连接酶(ubiquintin ligases, E3)发挥了重要的作用。该文将简单介绍UPS的过程和RhoA蛋白质的结构、功能, 详细论述RhoA泛素化降解过程的分子机制和生物学功能。

关键词 RhoA; 泛素连接酶E3; 生物学功能

The Mechanisms and Functions of Ubiquitin-mediated RhoA Degradation

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Abstract The GTP-binding active form and GDP-binding inactive form can be transformed each other by RhoG (Rho small GTPases) family. And RhoG acts as the molecular switches to regulate multiple celullar processes, the cellular RhoG can be degradedby UPS (ubiquitin-proteasome system). RhoA is a classical member of Rho small GTPases, which plays important roles in controlling cell polarity, migration, cell cycle and nervous system development. The UPS mediated regulations of RhoA ubiquitination guarantee the normal cellular function. Distinct E3 types play an important role during the UPS mediated degradation of RhoA. This review will give an outline of the UPS and the structure and function of RhoA, summarize the current understanding about the molecular mechanisms and physiological functions of UPS-mediated RhoA degradation.

Keywords RhoA; ubiquitin ligase E3; biological function

在哺乳动物细胞中, 泛素蛋白酶复合体系统(ubiquitin-proteasome system, UPS)作为主要的蛋白质降解机制, 控制着信号转导调控蛋白等在内的多种蛋白质的活性与含量, 调控着抗原的呈递、炎症反应的感应、细胞周期的连续等生理过程[1-3]。

UPS介导的蛋白质降解途径需要泛素激活

收稿日期: 2016-01-23 接受日期: 2016-03-24
内蒙古大学本科创新基金项目(批准号: 201514216)、中国博士后科学基金第7批特别资助(批准号: 2014T10237)和内蒙古自治区高等学校科学研究项目(批准号: NJZY14005)资助的课题
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Received: January 23, 2016 Accepted: March 24, 2016
This work was supported by the Undergraduate Students' Innovation Foundation Project of Inner Mongolia University (Grant No.201514216), China Postdoctoral Science Foundation funded Project (Grant No.2014T10237) and Higher Scientific Research Project of Inner Mongolia Autonomous Region (Grant No.NJZY14005)
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网络出版时间: 2016-05-26 16:53:03 URL: http://www.cnki.net/kcms/detail/31.2035.Q.20160526.1653.010.html

酶(ubiquitin activating enzyme, E1)、泛素结合酶(ubiquintin conjugating enzyme, E2)、泛素连接酶(ubiquintin ligase, E3)的参与, 在ATP的协助下将数个泛素连接到底物上, 泛素化的底物由蛋白酶体介导降解[3-5]。依据E3催化底物泛素化机制的不同, E3可以划分为四种类型: HECT(homologous to E6AP C-terminus)型E3、RING-finger型E3、U-box型E3和PHD-finger型E3。其中, HECT型E3和RING-finger型E3高度保守的半胱氨酸残基序列决定其连接酶活性; 泛素化底物的特异性主要取决于E3的类型, 不同类型的泛素连接酶在其底物上有不同的泛素化位点, 从而特异地介导底物的泛素化[3,5-6]。

在UPS途径中, Rho家族成员RhoA能被HECT型E3 smad泛素化调节因子1(smad ubiquitylation regulatory factor 1, Smurf1)和Ring-finger型E3 Cullin-RING连接酶(Cullin-Ring ligases, CRLs)特异性识别, 进而被泛素化介导降解[7-12]。研究表明, 多种E3介导的RhoA降解, 精密调控着细胞内处于激活形式和非激活形式RhoA的含量, 保证RhoA在细胞周期、细胞极化和细胞迁移中正常发挥功能[13-14]。因此, 在本综述中, 首先简要介绍RhoA的结构和功能, 然后详细论述Smurf1、CRLs介导的RhoA降解的机制及生物学功能, 最后对所述内容进行总结的同时, 提出未来关于UPS介导的RhoA降解研究方向的思考。

1 RhoA的结构和功能

1.1 RhoA的结构

RhoA由位于人三号染色体上的*ARHA*基因编码, 是一种大小约为21~25 kDa的Rho小G蛋白家族成员[15-16]。RhoA由G结构域(G domain)、高度可变区(hypervariable region)、多元区(polybasic region)和CAAX盒子(CAAX Box)构成[14-17](图1A)。

RhoA G结构域中的开关区域I(switch region I, SRI)和开关区域II(switch region II, SRII)会在RhoA激活和非激活状态的转换过程中, 发生显著的构象变化; 在向下游靶蛋白传递信号的过程中, SRI和SRII也发挥着重要作用[14-15,17]。RhoA的第6、7、135位赖氨酸残基是其发生泛素化的位点, RhoA的翻译后修饰对其生物学功能也有重要作用[14]。

1.2 RhoA的功能

Rho小G蛋白质家族是一类分子开关蛋白, 通过在细胞内两种存在形式(GTP结合的激活形式、GDP结合的非激活形式)的转换来发挥其生物学功能: 调控肌动蛋白的聚合、细胞的迁移、细胞的极性、细胞的形状、细胞周期的进程、细胞的增殖和肿瘤细胞的形态学变化[18-20]。

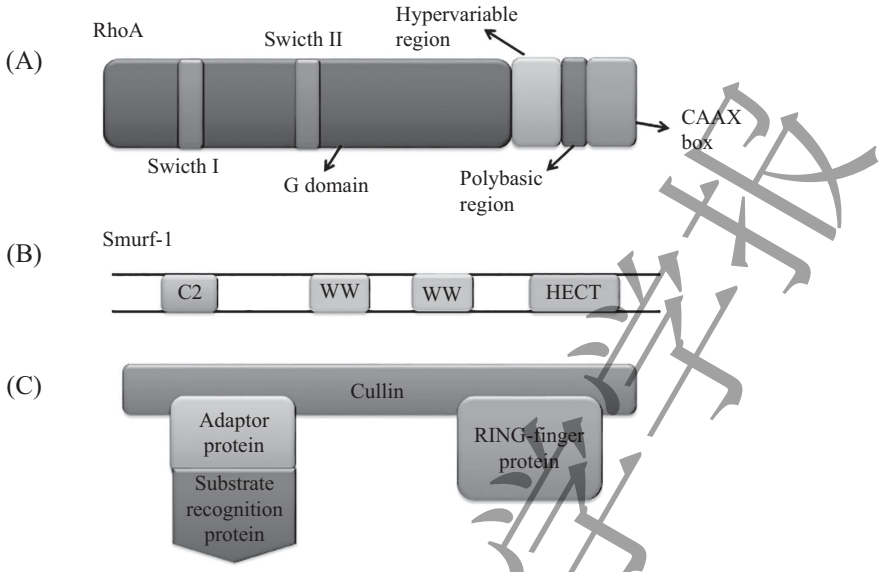
作为Rho小G蛋白家族的成员, RhoA通过调控应力纤维的形成和M-钙黏蛋白的溶酶体降解过程, 在细胞骨架的稳定、细胞的迁移和细胞的分裂中发挥重要的作用[14,21-23]。RhoA能够活化Rho相关蛋白激酶(the Rho-associated protein kinases, ROCK), 活化的ROCK通过活化LIM激酶(LIM kinase, LIMK), 使其磷酸化丝切蛋白(cofilin)来稳定F-肌动蛋白(F-actin), 促进细胞骨架的构建[14,23]。RhoA还能够通过调控下游肌球蛋白轻链的磷酸化(the phosphorylation of myosin light chain, MLCP)控制肿瘤细胞衍生微囊泡(tumor cell-derived microvesicles, TMV)的产生和释放, 从而促进肿瘤细胞的迁移[21]。此外, RhoA可以通过调控细胞突出物(cell protrusion, CP)的方向和数量, 影响细胞的迁移速度[22]。

2 RhoA的泛素化降解机制及生物学功能

RhoA的泛素化降解, 一方面通过精确地调控RhoA的含量, 另一方面影响RhoA下游的信号通路, 从而实现对细胞许多生物过程的调控[24]。在RhoA的泛素化降解过程中, E3在底物的选择、泛素化过程中发挥着重要的作用。近年来, 对HECT型E3、RING-finger型E3作用于RhoA的机制以及RhoA泛素化降解的生物学功能有较为详细的研究。

2.1 Smurf-1介导的RhoA泛素化降解机制及生物学功能

Smurf-1是HECT型E3 NEDD4(neural precursor cell expressed developmentally down regulated protein 4, NEDD4)家族的成员[8]。Smurf-1由C2结构域(C2 domain)、WW结构域(WW domain)、HECT结构域构成(图1B)。C2结构域调控Smurf-1的细胞定位和底物的特异性, WW结构域能够识别、结合具有特异性氨基酸残基修饰的转接蛋白和底物蛋白, HECT



A: RhoA由G结构域、高度可变区、多元区和CAAX盒子构成。在G结构域中有两个开关区, 可以与GTP或GDP结合来调控RhoA的活性; 高度可变区、多元区和CAAX盒子与RhoA的翻译后修饰相关, CAAX盒子的异戊烯化影响着RhoA的活性。B: Smurf-1由一个C2结构域、两个WW结构域(WW1、WW2)和一个HECT结构域构成。C2结构域对Smurf-1的细胞定位和功能具有重要影响; WW结构域能使Smurf-1结合转接蛋白或底物; HECT能将泛素从E2连接到底物上。C: CRLs由Cullin支架蛋白、结合在Cullin C-末端为E2提供“着陆点”的RING-finger蛋白、结合在Cullin N-末端的转接蛋白以及结合在转接蛋白上的底物募集蛋白构成。

A: RhoA is composed of G domain, hypervariable region, polybasic region and CAAX box. There are two switch region in the G domain, which mediate the interaction with GDP or GTP to regulate the activity of RhoA. The hypervariable region, polybasic region and CAAX box all play key roles in the post-translational modifications of RhoA, especially the prenylation in the CAAX box has an important influence on theRhoA activity. B: Smurf-1 is composed of C2 domain, two WW domain (WW1, WW2) and HECT domain. The C2 domain has significant influence on both subcellular localization andfunction of Smurf1. The WW domains can help Smurf-1 to interact with adaptor proteins or substrates. The HECT domin can transfer the ubiquitin from E2 to the substrate. C: CRLs is composed of the scaffold protein Cullin and the RING-finger protein which binds the C terminal of the Cullin protein and provides the landing point for E2. In addition, the ligase contains the adaptor protein binding to the N terminal of the Cullin and the substrate recognition protein binding to the adaptor protein.

图1　RhoA、Smurf-1的结构和CRLs的构成

Fig.1　The structures of RhoA, Smurf-1 and the general composition of CRLs

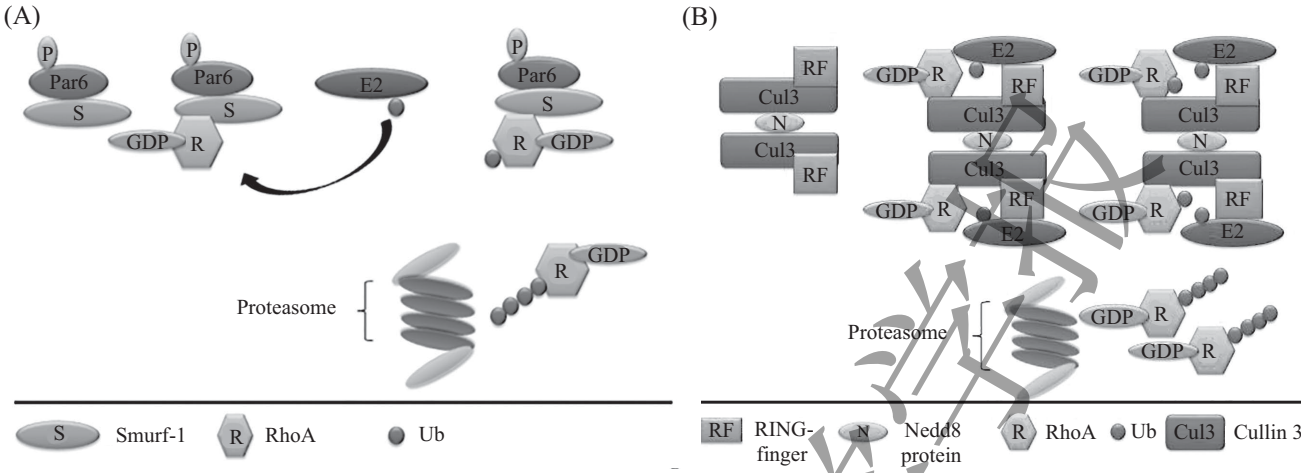
结构域能够与泛素相结合, 并将其连接到底物上。Smurf-1通过调控GTPase蛋白质来调控细胞的生长、极化和迁移, 这与Smurf-1能够识别非激活形式的RhoA有很大的联系[8,12,25-26]。

2.1.1　Smurf-1介导的RhoA泛素化降解机制　Smurf-1介导的非激活形式RhoA的泛素化降解机制如图2A所示: 在磷酸化的Par6(partitioning defective 6 protein, Par6)协助下, Smurf-1依赖于其C2结构域识别、结合RhoA, HECT结构域将携带的泛素, 以共价键形式连接到RhoA的第6或7位赖氨酸残基上, 泛素化标记的RhoA由蛋白酶体介导降解[14,26-27]。

2.1.2　Smurf-1介导的RhoA泛素化降解的生物学功能　Smurf-1介导的RhoA泛素化降解, 一般是通过影响应力纤维的聚集来发挥其生物学功能的[2,11,24,28-29]。

在CP合成活跃的部位, 活化的细胞分裂周期蛋白42(cell division control protein 42 homolog, Cdc42)、Rac1(Ras-related C3 botulinum toxin substrate 1), 调控PAR6-PKCζ复合体(partitioning defective 6 protein kinase Cζ complex, PPC)靶向定位到细胞伪足区域, PKCζ募集Smurf1降解CP中的RhoA, 进而调控RhoA-ROCK-MLCP信号通路, 抑制CP内应力纤维的形成, 保证CP和板状伪足的形成、细胞的极化和迁移[2,24,28]。

在足细胞(podocyte)中, 突触极蛋白(synaptopodin)能够与Smurf-1竞争性结合非激活形式的RhoA, 拮抗Smurf-1介导的RhoA泛素化降解, 促进细胞应力纤维的形成、细胞的迁移[29]。突触极蛋白还可以抑制c-Cbl(c-casitas B-lineage lymphom, c-Cbl)介导的对Nck1(non-catalytic region of tryrosine kinase adaptor protein 1)的泛素化降解。Nck1能够通过竞



A: Smurf-1在Par6的协助下将RhoA-GDP泛素化标记, 并通过蛋白酶体途径将其降解, 保证CP的正常形成、细胞的运动; B: Cullin 3在Nedd8的辅助下二聚化, 通过其C-端结合的RING -finger结合E2, RING-finge介导E2上的泛素连接到RhoA-GDP上, 进而被蛋白酶体降解。

A: Smurf-1 marks the RhoA-GDP with the ubiquitin by the help of Par6 protein, and the RhoA-GDP can be degraded through the UPS, ensuring the CP forming as well as cell movement; B: Cullin 3 can be dimerized by the help of Nedd8, the RING-finger in the C terminal of Cullin 3 bind E2 and conjugates the ubiquitin to RhoA-GDP, followed by the proteasomemiadeated degradation.

图2 Smurf-1和CRL3介导的RhoA降解机制

Fig.2 The mechanism of Smurf-1and CRL3 mediated RhoA degradation

争性抑制Smurf-1介导的对RhoA的泛素化降解, 进而稳定RhoA, 促进应力纤维的形成, 保证足细胞正常丝状伪足的形成和迁移[11,29]。

2.2 Cullin介导的RhoA泛素化降解机制及生物学功能

在蛋白质翻译后修饰的泛素化过程中, Cullin蛋白质家族作为分子支架发挥重要作用, Cullin蛋白质家族的八个成员Cul1、Cul2、Cul3、Cul4、Cul5、Cul6、Cul7、Cul9拥有一些保守的结构: CH结构域(Cullin homology domain)、CR1(Cullin repeat 1)、类泛素化修饰位点(neddylation site)[30](图1C)。Cullin通过其CH结构域结合RING蛋白质、通过CR1结合转接蛋白和底物募集蛋白, 共同装成CRLs发挥功能: 泛素样蛋白质Nedd8类泛素化Cullin, 从而活化CRLs, RING蛋白质介导E2上的泛素转移到底物上, 泛素标记的底物经蛋白酶体降解[30-31]。相关的研究表明, CRLs可以介导RhoA的泛素化降解, 因此我们以下将介绍包含Cullin 1和Cullin 3的CRLs介导的RhoA的泛素化降解机制及生物学功能[32-40]。

2.2.1 CRL3介导的RhoA泛素化降解机制及生物学功能 以Cullin3为支架蛋白构成的CRL3, 包含了Cullin 3、RBX1(RING-box protein 1, RBX1)、具有转接蛋白、底物募集蛋白功能的含有BTB结构域的蛋白质(BTB domain containing protein, BDCP)组分, BDCP与PID(protein-protein interaction domain, PID)相互作用作为底物和Cullin 3联系的桥梁, CRL3在Nedd8的辅助下能够形成二聚体发挥泛素转移酶的功能[32-36](图2B)。研究表明, CRL3中高度保守的、包含BTB结构域的BACURD转接蛋白家族, 能够结合RhoA, RhoA非激活形式更有利于Cullin 3对它的泛素化降解[34]。

细胞中Cullin 3或BACURD的缺失, 均会导致RhoA泛素化降解受到抑制、细胞内应力纤维不正常产生[35]。CRL3介导的RhoA泛素化降解调控着细胞的聚缩和延伸, 而RhoA过度积累会导致异常的细胞活动[36]。研究表明, 血管平滑肌核受体过氧化物酶体增殖物激活受体γ(the nuclear hormone receptor peroxisome proliferator-activated receptor γ, PPARγ)的突变, 影响着CRL3组分Rho BTB1的表达, 从而抑制CRL3对RhoA的降解, 细胞内升高的RhoA会增强主动脉环在兴奋剂介导下的收缩, 导致高血压的发生。

2.2.2 SCF介导的RhoA泛素化降解机制及生物学功能 Cullin 1、Skp1(S-phase kinase associated protein 1)、F-box蛋白质构成了SCF复合体(Skp1-Cullin-F-box

complex), Cullin 1作为SCF复合体的支架蛋白, 其氨基末端结合的转接蛋白Skp1能够结合底物募集蛋白F-box, 而其羧基端结合的RBX1拥有E2结合位点[31]。

F-box蛋白家族的成员FBXL19可以识别Rac1, 并对Rac1166位的赖氨酸进行泛素化标记[39]。有关研究表明, 肺上皮细胞中FBXL1通过泛素化RhoA的135位的赖氨酸, 介导其泛素化降解[40]。SCF^{FBXL19}介导的底物泛素化降解依赖于底物蛋白的磷酸化, MAPK1(mitogen-activated protein kinase 1)对RhoA的磷酸化可以促进SCF^{FBXL19}介导的RhoA泛素化降解[39-40]。

SCF^{FBXL19}介导的RhoA泛素化降解, 影响着RhoA介导的p27的磷酸化以及细胞的分裂, 与肺的损伤、修复以及肺部肿瘤的发生相关, 并且FBXL19的过表达会降低肌球蛋白轻链的磷酸化程度, 阻碍应力纤维的形成[9,39-40]。

3　小结与展望

Rho小G蛋白家族成员RhoA, 通过控制细胞应力纤维的形成和细胞骨架的收缩性, 在调控细胞周期、细胞分裂、细胞极性和细胞运动等过程中发挥着重要的作用[18-23]。生物体通过UPS降解机制精确调控RhoA的含量, 从而稳定细胞的各项生理功能[21-23]。在UPS降解RhoA的过程中, E3发挥着至关重要的作用。HECT型E3 Smurf-1在CP区域介导RhoA的泛素化降解, 而突触极蛋白通过直接或间接方式, 拮抗Smurf-1在足细胞中介导的RhoA泛素化降解[2,11,24,28-29]。Ring-finger型E3以Cullin为支架蛋白, 在Cullin特异性的转接蛋白、底物募集蛋白和RING-box蛋白质的参与下, 介导RhoA的泛素化降解, 调控RhoA下游信号通路。这一机制可以和高血压、肺损伤、肿瘤发生在内的疾病联系到一起[34-40]。

值得注意的是, 关于RhoA泛素化降解的研究还有很多问题需要探索, 比如Smurf-1和突触极蛋白是否通过某种机制相互协调, 保持RhoA含量处于一种动态平衡, 保证某些处于特定生理状态的细胞正常地极化和迁移。鉴于Smurf-1在细胞的迁移过程中的重要作用, Smurf-1可以作为肿瘤治疗的一个分子靶标, 是否可以通过对Smurf-1在细胞内的表达量以及活性的调控实现抑制肿瘤细胞迁移的效果。是否还存在其他类型CRLs介导的RhoA泛素化降解以及其相应的生物学机制也有待于探究。

总之, RhoA的泛素化降解由于E3的多样性呈现出复杂状态, 但是基于泛素化降解的基本机制, 结合恰当的研究方法, 对RhoA的泛素化降解的机制及生物学功能的理解将会逐步深入。

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