综述

HSV-1 *UL41*基因编码蛋白的RNase活性及其调控

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摘要 单纯疱疹病毒1型(herpes simplex virus type-1, HSV-1)*UL41*基因编码一种皮层蛋白, 该蛋白质具有核糖核酸酶(ribonuclease, RNase)活性, 能特异性地降解一些宿主和病毒信使RNA(messenger RNA, mRNA), 参与宿主免疫逃逸, 与其他蛋白质相互作用调控其RNase活性。该文概述了HSV-1*UL41*基因编码蛋白的RNase活性及其调控机制, 以期为该基因的深入研究提供参考。

关键词 HSV-1; *UL41*基因; 编码蛋白; RNase活性

RNase Activity and Regulation of the *UL41* Gene Encoding Protein of HSV-1

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Abstract The tegument protein encoded by *UL41* gene of herpes simplex virus type-1 (HSV-1) acts as an mRNA-specific RNase activity, which involved in host immune evasion and associated with other proteins to regulate its RNase activity. This paper reviewed the RNase activity and regulation mechanism of this protein, and provided a reference for further study of this gene.

Keywords HSV-1; *UL41* gene; encoding protein; RNase activity

疱疹病毒是一种双链DNA病毒, 由核心、衣壳、皮层和囊膜组成, 被划分为α、β和γ三类亚科[1]。其中, α亚科疱疹病毒感染的特点之一是宿主细胞蛋白质合成的关闭, 且有研究报道单纯疱疹病毒1型(herpes simplex virus type-1, HSV-1)宿主细胞内大分子合成的关闭是由*UL41*基因编码病毒宿主关闭蛋白(virus host shut-off protein, VHS)pUL41介导的, 此蛋白质具有核糖核酸酶(ribonuclease, RNase)活性, 能特异性降解一些宿主和病毒信使RNA(messenger RNA, mRNA), 降低宿主免疫力, 影响病毒毒力[2-3]。本文就HSV-1*UL41*基因、编码蛋白的结构特点及其RNase活性作一简要综述, 便于以后深入研究。

1 HSV-1 *UL41*基因及其编码蛋白的特点

HSV-1基因组是由相互共价结合的长独特区(unique long region, UL)和短独特区(unique short region, US)以及两侧的重复序列组成。*UL41*基因位于UL区, 高度保守, 为病毒晚期(late, L)基因, 是病毒复制的非必需基因[4-5]。据报道, pUL41的同源基因仅存在于现已测序的α亚科疱疹病毒基因组中, 不存

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在于β和γ亚科中[6]。不同α亚科疱疹病毒*UL41*基因的长度差异较大, 如伪狂犬病毒(pseudorabies virus, PRV)*UL41*基因编码365个氨基酸, HSV-1 *UL41*基因编码489个氨基酸, 且两者同源性仅为39.3%[5,7]。

pUL41在HSV-1感染晚期被装配进入成熟病毒颗粒的皮层中, 是一种皮层蛋白, 在病毒囊膜和宿主细胞膜融合后进入细胞质[8]。Mbong等[9]报道, HSV-1 pUL41氨基酸序列具有3个高度保守区域(第1~103位、165~265位和365~489位氨基酸残基), 前两个区域与哺乳动物、酵母、细菌和噬菌体的核酸酶相比同源性较高, 且分析发现, α亚科疱疹病毒pUL41同源物和人、酵母、细菌和噬菌体核酸酶家族序列都有9个高度保守的亲水性氨基酸, 分别为第34、82、86、192、194、211、213、215、261位氨基酸残基, 且这些保守性氨基酸位于核酸酶的酶活性中心[10]。

2 HSV-1 *UL41*编码蛋白的RNase活性

大量研究表明, HSV-1 pUL41本身就是一个核酸酶, 且体外表达的HSV-1 pUL41和RNase A具有相似的底物特异性, 偏向于在单链RNA的3′端胞嘧啶核苷酸和尿嘧啶核苷酸处切割[11]。HSV-1 pUL41在多聚核糖体对核糖体RNA(ribosomal RNA, rRNA)和转运RNA(transfer RNA, tRNA)中不起作用, 但能选择性地降解mRNA, 比如降解宿主稳定mRNA[3-磷酸甘油醛脱氢酶(glyceraldehyde-3-phosphate dehydrogenase, *GAPDH*)和β-肌动蛋白(*β-actin*)]、降解由免疫反应介导产生的在3′端非编码区(untranslatedregions, UTR)含AREs[adenylate-uridylate (AU)-rich instability elements]的mRNA[*IEX-1*(immediate-early response gene X-1)]、降解病毒立早(immediate early, IE)基因*ICP0*(infectedcellpolypeptide 0)的mRNAs[8,12-13]。尽管如此, 大部分宿主mRNA仍然会抵抗pUL41的降解, HSV-1感染宿主后一部分宿主mRNA的丰度还会增加, 可能是对pUL41-RNase的活性不敏感, 如锌指蛋白36(tristetraprolin 36, *TTP36*)和*GADD45β*(growth arrest and DNA damage-inducible protein 45 β)的mRNA就不会被pUL41降解[12,14-15]。此外, 病毒晚期和真正晚期基因的mRNA也不会被降解, 具体原因需进一步探究。虽然*UL41*基因在α亚科疱疹病毒中高度保守, 但是马疱疹病毒-1型(equine herpesvirus-1, EHV-1)同源基因*ORF19*(open reading frame 19)没有RNase活性且不会抑制细胞蛋白质合成[16]。

HSV-1 pUL41-RNase降解不同类型mRNA的机制差异较大。HSV-1感染细胞后, 病毒IE基因和宿主稳定基因的mRNA在细胞质中快速被降解, pUL41-RNase联合帽结合复合物eIF4F(eukaryotic initiation factor 4F)、细胞翻译起始因子eIF4H(eukaryotic initiation factor 4H)去掉mRNA的5′帽子结构, 在多聚核糖体中从3′→5′开始切割, 随后在5′核糖核酸外切酶Xrn1(exoribonuclease 1)的作用下从5′→3′被降解。对于含AREs的应激mRNA的降解方式有所不同, AREs的宿主诱导蛋白是TTP, TTP结合在ARE处, pUL41-RNase再结合TTP, 在mRNA的AREs附近脱腺苷酸并切割, 3′切割产物(含ARE部分)由于没有帽子结构的保护快速从5′→3′被降解, 5′切割部分在细胞质中存留数小时, 可能是由于缺少将RNA从3′→5′降解的酶[15,17-18]。图1是HSV-1 pUL41在细胞中降解一些mRNAs的模式图。

PRV-pUL41也能降解RNA, 且实验进一步证明, 第152、169、171~173、343、345、352、356位保守性氨基酸残基有助于PRV-pUL41降解RNA[7,19]。但由于PRV和HSV-1的pUL41同源性只有39.3%, 所以PRV-pUL41和HSV-1-pUL41的生物化学特性有所不同, 和HSV-1-pUL41相比, PRV-pUL41不仅可以降解mRNA, 还可以降解rRNA, 且PRV-pUL41降解RNA的模式比较复杂, 会产生很多中间体[7,20]。

Krikorian等[21]研究表明, HSV-1pUL41介导的RNase活性不能被RNase抑制剂抑制, 也不依赖能量组分如三磷酸腺苷(adenosinetriphosphate, ATP)、三磷酸鸟苷(guanosine triphosphate, GTP), 却依赖于一些阳离子, 如Mg^{2+}、K^{+}。Liu等[7]研究表明, Mg^{2+}单独存在时会促进PRV-pUL41对RNA的降解, 当K^{+}浓度达到200 mmol/L时, pUL41介导的RNA降解效率极高, 但当浓度高于500 mmol/L就不会影响其活性。虽然ATP对于pUL41的活性不是必需的, 但在Mg^{2+}和ATP同时存在时也可以增强pUL41降解RNA的能力。

HSV-1感染早期, pUL41通过降解宿主已有的和新转录的mRNA, 并破坏之前存在的多聚核糖体导致宿主蛋白质合成快速关闭, 但目前pUL41宿主关闭功能的精确机制尚不清楚[19]。特异性地降解mRNA可以促进许多宿主和病毒mRNA的更新。宿主mRNA的更新加快使细胞从宿主基因转向表达病

毒基因, 抑制宿主细胞蛋白质翻译, 便于提高病毒mRNA进入细胞翻译机制[22-23]。它介导病毒mRNA的更新加快不仅决定了许多病毒mRNA水平, 还调节病毒不同时期基因之间的有序表达, pUL41功能缺失时, 一种或几种IE或早期(early, E)基因的过度表达会延迟一些L基因的表达[24]。

3 几种HSV-1编码蛋白对pUL41-RNase活性的调控

HSV-1感染早期, pUL41通过与病毒其他蛋白质相互作用来调控其功能, pUL41先结合皮层蛋白pUL47, 然后结合IE蛋白ICP27(infected cell polypeptide 27), 在多聚核糖体内和酶相互作用。感染后期, pUL41活性被另外两种皮层蛋白VP16和VP22抑制[25]。

3.1 HSV-1 pUL47对pUL41-RNase活性的调控

HSV-1UL47基因编码皮层蛋白pUL47, 又被称为VP13/14[26]。Shu等[27]研究表明, HSV-1 pUL47结合在mRNA的3′端多聚A结合蛋白[poly(A)-binding protein, PAPB]上来调节pUL41-RNase的功能。野生型HSV-1感染细胞后, pUL41-RNase靶向作用于感染前稳定的mRNA和含AREs的mRNA, 大量保留感染后的病毒mRNA, 这种选择性的保留由pUL41和pUL47相互作用所致[25]。pUL47和pUL41-RNase相互作用可以减缓pUL41-RNase对宿主稳定mRNA和病毒mRNA的降解, 但是对感染后诱导产生的含AREs的mRNA的稳定无影响, 也不能参与pUL41-RNase和TTP的相互作用[27]。

HSV-1 pUL41-RNase可在细胞质和细胞核中发挥作用, 在核、质中均有分布, 但是HSV-1 pUL41仅含有核输出信号(nuclear export signal, NES)而没有核定位信号(nuclear localization signal, NLS), 它不能自主定位到细胞核中, 和HSV-1 pUL47共转染时可以在细胞核中定位。进一步研究表明, HSV-1 pUL47能在细胞核与细胞质中来回穿梭, 其穿梭机制可能归因于该蛋白的NES和NLS, 表明pUL47可能参与将pUL41-RNase转移到细胞核的过程[25,28]。

3.2 HSV-1 ICP27对pUL41-RNase活性的调控

HSV-1感染细胞后, 病毒IE蛋白ICP27可以和pUL41一起作用降低宿主蛋白质的合成[29]。Taddeo等[30]研究表明, HSV-1 ICP27在mRNA的5′帽子结构处结合pUL41-RNase, 并且阻止pUL41-RNase切割游离的mRNA, ICP27还在感染后期负责某些mRNA的往返移动。这可能是感染后期的mRNA没有被一

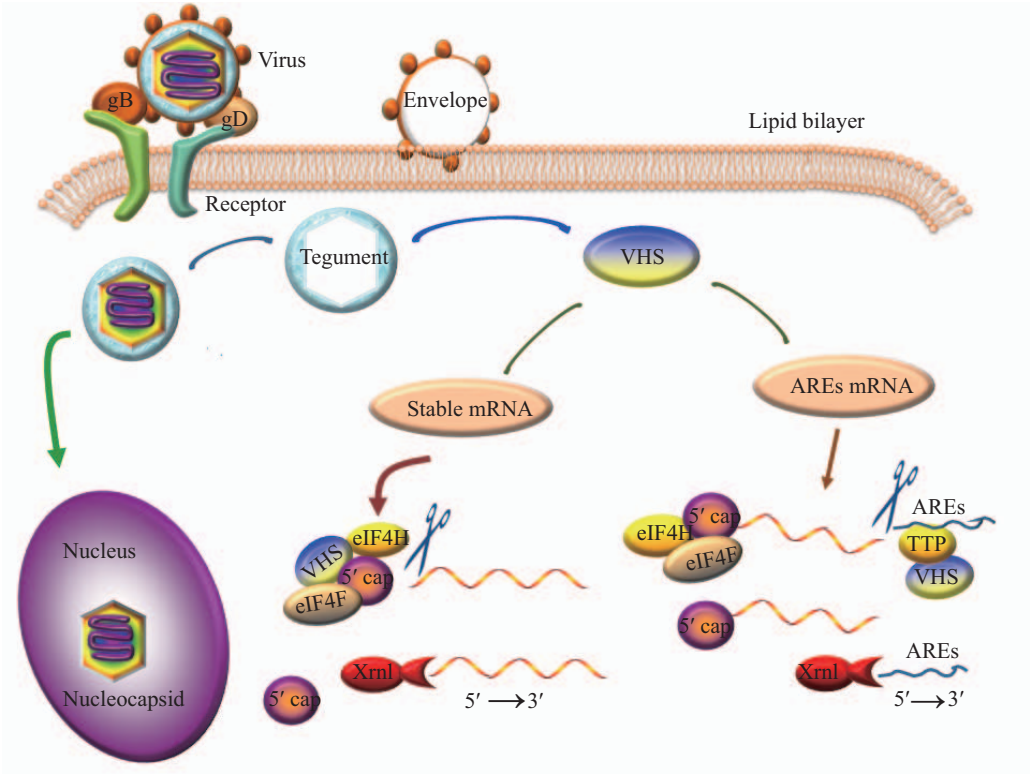

图1 HSV-1 pUL41在细胞中降解一些mRNAs的模式图(根据参考文献[12]修改)

Fig.1 Themodel of HSV-1 pUL41 in the cell to degrade mRNAs (modified from reference [12])

些仍有活性的pUL41-RNase降解的原因。HSV-1基因转录开始后, ICP27和pUL41调节细胞内mRNA前体的加工和病毒mRNA的表达, 缩短了病毒mRNA的半衰期, 并加快了病毒mRNA的更新, 推动不同时期病毒基因的有序表达, 进一步降低宿主细胞mRNA的丰度, 从而减少宿主蛋白质的合成[29,31]。

3.3 HSV-1 VP16、VP22对pUL41-RNase活性的调控

HSV-1感染后期皮层蛋白VP16(viral protein 16)可以抑制pUL41-RNase活性, 促进pUL41的积累。HSV-1的pUL41与VP16可形成异质融合蛋白质复合体, Schmelter等[31]通过酵母双杂交等实验表明, HSV-pUL41第310~330位氨基酸残基对pUL41与VP16互作是必需的。然而, Strand等[32]发现, 这20个氨基酸残基对pUL41和VP16的相互作用并不是必需的, 且删除这20个氨基酸残基后对pUL41-RNase的活性也无明显影响。VP22(HSV-1的另一种皮层蛋白)也能抑制pUL41-RNase的活性, 但pUL41不能直接和VP22相互作用, 必须通过VP16作为中间体, VP16和pUL41直接相互作用, VP22再和VP16结合, 形成一个稳定的VP22-VP16-pUL41复合物[9]。Taddeo等[33]的研究表明, HSV-1 VP16和VP22利于*UL41* mRNA的翻译, 因此VP16和VP22对pUL41的积累有重要作用。

4 宿主细胞蛋白对pUL41-RNase活性的调控

pUL41偏向于在一些mRNA的翻译起始处切割, 这可能是由于pUL41和翻译起始因子相互作用导致的。此外, 对于含有脑心肌炎病毒(encephalomyocarditis virus, EMCV)内部核糖体位点(internal ribosome entry site, IRES)的mRNA, 体外翻译的pUL41在IRES下游处切割[14,34]。有研究报道称, HSV-1 pUL41通过和细胞翻译起始复合物eIF4F(eukaryotic initiation factor 4F)相互作用来选择性地活化要翻译的mRNAs, 且HSV-1 pUL41前211个氨基酸对pUL41和eIF4F的相互作用是必需的[35]。eIF4F[由eIF4E(eukaryotic initiation factor 4E)、eIF4AI(eukaryotic initiation factor 4AI)、eIF4AII(eukaryotic initiation factor 4AII)和eIF4G(eukaryotic initiation factor 4G)组成]结合在mRNA的5′帽子结构上, HSV-1 pUL41-RNase和解旋酶共因子eIF4H(eukaryotic initiation factor 4H)、eIF4B(eukaryotic initiation factor 4B)以及eIF4AII相互作用, 有利于mRNA的翻译[36]。

eIF4H对于HSV-1pUL41介导许多mRNA的降解是必需的。通过GST pull-down实验和酵母双杂交实验证明, pUL41可以和eIF4H相互作用, 且eIF4H的第97、102、114位氨基酸残基对其相互作用是必需的[34,37]。有实验表明, HSV-1 *pUL41*突变后如果不能与eIF4H结合, 就不能降解mRNA, 说明pUL41和eIF4H的相互作用具有重要的生物学意义, 但是eIF4H在pUL41介导去帽过程中的具体作用还不清楚, 猜测pUL41结合eIF4H后可能对其靶向特异性有重要影响[34,38]。

eIF4B和eIF4H具有69%序列同源性, 都相似地激活eIF4AI、eIF4AII的RNA解旋酶活性[34,39]。eIF4B和eIF4H可能是通过以下三个方面来提高HSV-1pUL41-RNase活性: (1)eIF4H和eIF4B直接结合pUL41, 直接诱导pUL41/结合后复合物的构象改变, 由此产生一个活性更高的核糖核酸酶; (2)eIF4H/eIF4B可能会提高pUL41/结合后复合物与RNA底物的结合率, 因为eIF4H和eIF4B都包含一个保守的RNA识别位点, 所以pUL41/结合后复合物可以直接与特异性的RNA序列结合; (3)eIF4H/eIF4B可能会改变整个pUL41-RNase活性发挥的模式[39]。尽管如此, HSV-1 pUL41和eIF4B之间相互作用明显弱于pUL41和eIF4H, 且eIF4B对于pUL41降解mRNA不是必需的。目前为止, 还没有足够的证据表明为什么eIF4H对于pUL41降解许多mRNA是必需的, 而eIF4B不是[14,34]。

GST pull-down等实验证实, HSV-1 pUL41和eIF4A(eIF4AI、eIF4AII)也能相互作用, eIF4AI和eIF4AII对于pUL41降解看家基因mRNA是必需的, pUL41可以直接结合eIF4AII, 不需要eIF4H作为中间桥梁, 但具体作用机制尚不清楚。eIF4H、eIF4AII和pUL41三个蛋白质可以两两相互作用, 且两者之间的相互作用是独立的[14,34,38]。

5 HSV-1 pUL41与宿主免疫逃逸

HSV-1的pUL41-RNase在病毒逃逸先天和获得性免疫反应方面也有重要作用。HSV-1 pUL41为干扰素-α/β(interferon-α/β, IFN-α/β)抗性因子, 通过降解一些抗病毒蛋白mRNA来妨碍IFN诱导的抗病毒机制的建立[3]。如tetherin[又称为BST2(bone marrow

stromal antigen 2)]是IFN诱导产生的膜糖蛋白, 具有抗病毒活性, HSV-1-pUL41诱导*tetherin* mRNA的降解从而抑制tetherin的表达[40]。Viperin(virus inhibitory protein, endoplasmic reticulum-associated, interferon-inducible)是一种IFN-γ诱导产生的抗病毒蛋白, HSV-1 pUL41也可通过减少*viperin*的mRNA积累来减弱它的抗病毒活性[2]。Su等[41]还证实了HSV-1的pUL41通过降解人锌指抗病毒蛋白(human zinc finger antiviral protein, *hZAP*)mRNA来减弱hZAP的抗病毒活性。肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)是先天免疫反应中的一种重要因子, 可以对抗多种感染, 且研究表明, PRVΔ *UL41*缺失株感染小鼠后, 脾脏中TNF-α的表达量会显著提高[42]。

此外, HSV-1、牛疱疹病毒1型(bovine herpes virus-1, BoHV-1)pUL41妨碍主要组织相容性复合体-I型(major histocompatibility complex-I, MHC-I)分子的抗原递呈, 并且pUL41帮助感染HSV-2和BoHV-1的细胞抵制细胞毒性T细胞的裂解, HSV-1感染U937细胞时抑制几种促炎细胞因子和趋化因子[IL-1β(interleukin-1β)、IL-8(interleukin-8)、MIP-1α(macrophage inflammatory protein-1α)]的分泌[6,43-45]。HSV-1 pUL41通过病毒识别的一个Toll样受体(toll-like receptor, TLR)的独立通路抑制树突状细胞(dendritic cell, DC)的活化。Cotter等[46]报道, 在感染HSV-1的人和小鼠中, pUL41能抑制常规DC(conventional DC, cDC)释放细胞因子, 对类浆细胞DC(plasmacytoid DC, pDC)细胞因子分泌无影响。

6 展望

目前, 有关*UL41*基因编码蛋白RNase活性的报道大多源于HSV-1, 在其他α亚科疱疹病毒中研究较少。例如, 在鸭瘟病毒中几乎没有任何关于其功能的报道。pUL41-RNase能降低宿主免疫力, 是病毒毒力的重要决定因素, *pUL41*缺失后的病毒仍具有感染能力, 但致病性显著降低, 毒力显著减弱, 不能建立或激活潜伏感染, 这使得*pUL41*缺失病毒有望成为一种新型疫苗。此外, *UL41*基因是病毒复制的非必需基因, 这为外源基因插入构建重组病毒提供了一个潜在位点, 值得进一步深入研究。

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