·综述·

内部核糖体进入位点与肠道病毒

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【摘要】人肠道病毒属于小RNA病毒科，为无包膜单股正链RNA病毒，两端为非编码区（UTR），中间仅有一个编码大分子多聚蛋白的开放阅读框。5'-UTR包含IRES结构，病毒感染宿主后，在关闭帽子依赖翻译的同时，可促进IRES介导的翻译从而有利于病毒的翻译，研究IRES与肠道病毒的关系对于抗病毒治疗至关重要。

【关键词】内部核糖体；进入位点；肠道病毒

Relationship of internal ribosomal entry site (IRES) and enterovirus *Ni Xuefei, Li Xingwang. Infectious Diseases Research Center, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China*
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【Abstract】 Human enteroviruses belonging to Picornaviridae family are nonenveloped virus, which contain a single positive-stranded genomic RNA. The viral genome has 5'-untranslated region (5'-UTR), single open reading frame of encoding polyprotein precursor and 3'-untranslated region (3'-UTR). 5'-UTR RNA contains an internal ribosomal entry site (IRES). When virus infect host, the IRES-mediated initiation of translation enhance the translation of viral RNA, while at the same time host cell translation is shut off. Research on the relationship between IRES and enterovirus is vitally important to antiviral treatment.

【Key words】 Internal ribosomal; Entry site; Enterovirus

人肠道病毒（human enteroviruses，HEVs）属于小RNA病毒科（Picornaviridae），是一类形态最小、具有相同的形态结构和生物学特点的无包膜单股正链RNA病毒，具有二十面体衣壳。主要包括脊髓灰质炎病毒（poliovirus）、柯萨奇病毒（Coxsackievirus）、埃可病毒（echovirus）和新型肠道病毒（new enteroviruses）。其中，新型肠道病毒包括68、69、70和71型等。肠道病毒主要引起多种肠道外感染性疾病，如脊髓灰质炎、心肌炎、急性出血性结膜炎、无菌性脑膜炎以及手足口病等，危及人类健康[1]。

其基因组为单股正链RNA分子，两端为非编码区（UTR），中间仅有一个编码大分子多聚蛋白的开放阅读框[2]。病毒RNA的5'-末端共价结合一个小分子蛋白质VPg和3'-末端多聚腺苷酸。然而，每个小RNA病毒属的区别位于UTRs和编码区[3-4]。

一、依赖帽子翻译起始和依赖IRES翻译起始

1. 依赖帽子翻译起始：真核细胞执行依赖帽子和依赖IRES蛋白质合成。在细胞中95%～97% mRNA经过依赖帽子途径进行翻译。在依赖帽子翻译中，翻译起始依赖于通过经典起始因子复合物对mRNA 5'-末端7甲基鸟苷（m7GpppN）的识别[5]。真核起始因子（eukaryotic initiation factor，eIF）4F包括eIF4A（DEAD盒RNA解旋酶）、eIF4E（帽子结合蛋白）和eIF4G（多结构域脚手架蛋白）能够结合帽子结构，招募40 S核糖体亚基、三元复合物（eIF2-GTP-Met-tRNAiMet）作为43 S起始复合物的部分，可与eIF3和eIF4G之间相互作用。一旦组装形成48 S起始复合物：该复合物沿着mRNA 5' -UTR扫描，解旋酶eIF4A可帮助分辨任何具有抑制作用的复杂和潜在的二级结构，可扫描获得最佳Kozak序列中的AUG[6]。eIF5介导的eIF2结合GTP水解可触发起始因子的释放。复合物的分解使核糖体60 S亚基结合40 S而形成完整的80 S核糖体。核糖体从而进入翻译延伸阶段[7-9]。

2. 依赖IRES翻译起始：70年代早期脊髓灰质炎病毒（PV）复制研究显示病毒mRNA在结构上不同于细胞mRNA，因为其不包含5'-末端帽子结构，而VPg蛋白质共价结合在5'-末端[10]。除此之外，脊髓灰质炎病毒5'-UTR为长的具有丰富二级结构[11]并且包含多个上游AUG密码子。最后，PV进入宿主细胞从而引起宿主细胞翻译关闭[12]，但病毒翻译未受影响，表明病毒依赖新的翻译起始机制。通过双顺反子mRNA分析表明高度结构化的脊髓灰质炎病毒

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5′ -UTR能够直接招募43 S核糖体亚基而促进翻译起始，这是第一个病毒IRES的特征[13]。IRES为RNA序列/结构促进40 S核糖体亚基结合到mRNA的内部序列。这一机制发现几乎适用于EMCV[14]和其他类型RNA病毒如丙型肝炎病毒（HCV）[15]和某些DNA病毒[16-17]。

真核生物的IRES可确定第一个编码免疫球蛋白重链结合蛋白（immunoglobulin heavy-chain-binding protein，BiP）的mRNA。脊髓灰质炎病毒感染期间，几个经典的起始因子被抑制时，BiP翻译仍在继续[18]。含有IRES的mRNAs蛋白质可调控细胞的生长和死亡[19]。病毒IRES的独有特征为一级序列中保守序列或模块的缺失[20-21]。病毒IRES元件通常具有共同的结构特点，例如长的结构化5'-UTRs、位于真实起始密码子前的几个上游AUG三联体及RNA 5′-末端缺乏帽子结构。这些特性与有效的依赖帽子翻译不相容，且反映了依赖IRES翻译起始机制。自1989年发现IRES以来，已有关于病毒、酵母、植物和更高真核生物的超过80种细胞和56种病毒IRES序列的描述[21-24]。

二、肠道病毒IRES元件

肠道病毒IRES 属于Ⅰ型IRES，跨度约450 nts，由相对于茎环结构Ⅱ～Ⅵ的5个结构域构成。沿着这些茎环结构，保守核苷酸出现在结构域Ⅱ、Ⅳ和Ⅴ的中心区（图1）。结构域Ⅳ存在一个GNRA模块（N代表任何核苷酸和R代表嘌呤）[25-26]和富含C区，而在Ⅱ型IRES元件则相对保守。Ⅴ结构域在脊髓灰质炎病毒生命周期中起重要作用[27]。这个茎环结构是脊髓灰质炎病毒神经毒力的主要决定因素[28]。除几个宿主因素参与内部起始外，支持相关IRES功能还包括Ⅴ结构域在48 S复合物组装过程中提供eIF4G和eIF4A结合位点[29]。

三、RNA和蛋白质的相互作用涉及肠道病毒IRES活性

除前文描述的真核起始因子（eIFs）外，被称为IRES反式作用因子（IRES trans-acting factors，ITAFs）的辅助因子可促进IRES活性的调节（刺激或抑制）。早期研究表明，在网织红细胞裂解液中脊髓灰质炎病毒IRES活性依赖于在Hela细胞表达的因子[30]，这证实截短的IRES序列有能力和eIF4G、eIF3、eIF4B和PTB相互作用但不足以促进整个IRES活性[31]，提示此过程还有其他因素参与。

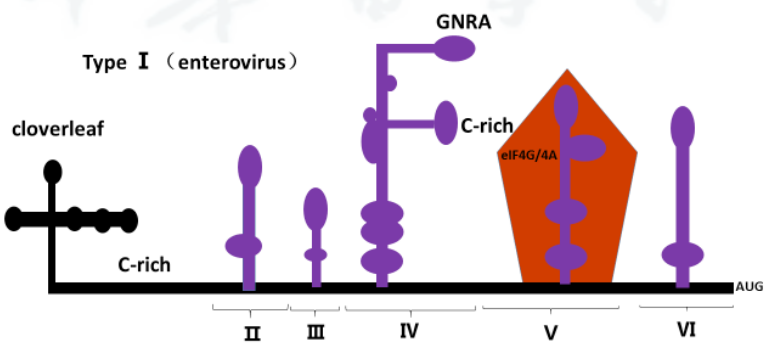
ITAFs蛋白质被认为参与调节转录、剪接、RNA运输、RNA稳定性或翻译控制。ITAFs蛋白包括PTB、PCBP2、SR剪接因子（SRp20）、远离上游元件结合蛋白2（FBP2）、狼疮抗原（La）、Unr（N-ras上游）、核仁蛋白、Gemin5、DAP5及其他蛋白[32-38]，见表1。

1. ITAFs刺激IRES活性：研究已确定不均一核糖核蛋白（hnRNP）家族与肠道病毒IRES元件有关联的因子包括PTB（也称为hnRNP Ⅰ）、hnRNP A1、hnRNP K、PCBP1（hnRNP E1）和PCBP2（hnRNP E2）[39-40]。这些蛋白质识别poly-r（C）区域和共同具有KH RNA结合的结构域从而刺激肠道病毒IRES活性[41-42]。

大多数ITAFs和不同因子在大的核糖核蛋白复合物中相互作用。考虑到RNA结合蛋白质（RNA binding proteins，RBPs）能够识别多个靶点[43]，二级结构蛋白质-蛋白质桥或RNA-蛋白质桥能够促进IRES活性。剪接因子SRp20通过与PCBP2相互作用而上调PV IRES介导的翻译[44]。

ITAFs的共同特征为主要的核蛋白质，在感染细胞中移位至胞浆。首先被报道的是核仁素[45]与HAV、EMCV和PV IRES相互作用[46]。最近研究表明，几个ITAFs定位于感染细胞的胞浆中刺激EV71或PV IRES活性，如远离上游元件结合蛋白1（FBPI）、hnRNP A1、hnRNP K、hnRNP M、hnRNP C和SRp20[40, 44, 47-50]。

2. ITAFs下调IRES活性：尽管早期研究表明ITAFs可刺



注：肠道病毒5' -UTR具有IRES Ⅰ型。紫线为肠道病毒IRES结构域Ⅱ～Ⅵ，保守模块（GNRA、富含C）。红色模块代表eIF4G/4A与IRES结构域Ⅴ相互作用

图1 肠道病毒5'-UTRs结构模块示意图

激IRES活性，但亦有IRES活性下调的报道。如核蛋白FBP2做为一个具有KH结构域的蛋白在感染细胞中穿梭至胞浆而下调EV71 IRES活性[37]。双链RNA结合蛋白DRBP76:NF45也是一种异质二聚体蛋白，其与HRV IRES相互作用而抑制其在神经来源细胞中的活性[51]。同样，细胞mRNA衰减蛋白AU结合因子（AUF1）可负调节EV71和HRV感染[52]。另一个ITAF的阻抑蛋白为Gemin-5，胞浆蛋白直接与FMDV IRES结合而下调翻译表达[53]。因此，ITAFs通常为多功能蛋白，其能够作用在基因表达控制的多个方面。

表 1 与肠道病毒 IRES 相互作用的 RNA 结合蛋白质

蛋白质	IRES	作用
PTB	PV CBV3	刺激
PCBP1	PV	刺激
PCBP2	PV、CBV3、EV71、BEV	刺激
HnRNP A1	EV71	刺激
SRp20	PV	刺激
Unr	PV	刺激
La	PV、CBV3	刺激
FBP1	EV71	刺激
AUF1	EV71、PV、CBV	抑制
FBP2/KSRP	EV71	抑制
GARS	PV	刺激
HnRNP M	PV	刺激
HnRNP C	PV	刺激
DAP5	CBV3	刺激
HuR	EV71	刺激
Ago2	EV71	刺激
TIA-1 TIAR	EV71	刺激
Sam68	EV71	刺激
PABP	EV71	刺激
EGR1	EV71	刺激
GARS	PV	刺激

3. 修饰的ITAFs在感染细胞和IRES活性：部分ITAFs的特点是可被小RNA病毒编码的蛋白酶识别（表2）。与原来完整的多肽相比，蛋白酶水解切割产生的片段具有不同的调节翻译作用。PTB、Gemin 5及FBP2均具有此特点。PV 3C/3D蛋白酶识别PTB 3种亚型产生截短多肽而抑制IRES活性[54]。CVB3 2A切割DAP5产生DAP5-N片段和DAP5-C片段，DAP5-N片段表达产物促进病毒复制和子病毒的释放，而DAP5-C片段表达产物对帽子依赖翻译起明显负调控作用，同时这两个片段表达产物对依赖IRES翻译蛋白起不同作用，最终促进宿主细胞死亡[55]；另一个ITAF的阻抑蛋白是FBP2在EV71感染细胞中水解。然而，丢失C-末端区域的片段可作为IRES刺激剂[56]。

四、信号转导通路与肠道病毒IRES的相互作用

对正链RNA病毒来说，蛋白质合成机制是病毒致病机制的重要因素。Raf-MEK-ERK1/2信号转导通路以依赖MNK1/2方式激活病毒IRES介导的翻译[57]。促有丝分裂的信号网络中Raf-ERK1/2信号转导通路主要与其翻译机制有关，抑制AKT（Rac）信号转导通路减弱富含丝氨酸/精氨酸蛋白质激酶（SRPK）活性从而增强Ⅰ型IRES翻译，同时在Ⅰ型IRES翻译中主要信号反应元件可能是起ITAF作用的RNA结合蛋白质，如AKT-SRPK信号转导通路中涉及的PCBP2/SR蛋白质[58]。Leong等[59]研究表明Misshapen/NIKs相关激酶（MINK）在EV71病毒RNA介导的IRES翻译中起着重要的作用。

表 2 肠道病毒蛋白酶水解细胞 RNA 结合蛋白

蛋白质	基因表达作用	病毒蛋白酶
eIF4GI、 eIF4GII	翻译起始	PV 2A、CBV3 2A、EV71 2A
PABP	翻译起始	PV 2A 3C、CVB3 2A、EV71 2A
eIF5B	翻译起始	PV 3C
PTB	IRES依赖的翻译	PV 3CD
PCBP2	从翻译到RNA复制转化	PV 3CD
CstF-64	细胞多聚腺苷酸化	EV71 3C
FBP2/KSRP	转绿激活，mRNA降解	EV71 3C
La	RNA聚合酶III转录	PV 3C
AUF1	mRNA稳定性	PV 3CD、CBV 3CD
Gemin 3	RNA解旋酶，U snRNP组装	PV 2A
Nup62、Nup98、Nup153	核孔	PV Rhino 2A
MAVS、TRIF	抗病毒反应	CBV3 3C
HnRNP M	前mRNA剪接	PV 3C、CBV3 3C
DAP5	翻译起始	CVB3 2A

五、结论

所有病毒IRESes均作为实体以5'-非依赖帽子方式招募核糖体。通过mRNA和核糖体小亚基间的直接接触或通过一组起始因子和（或）特定IRES反式作用因子（ITAFs）建立RNA-protein-ribosome相互作用。核糖体与IRES元件结合是许多病毒基因表达的关键步骤，因而IRES元件可作为一种很有前途的新的抗病毒策略。同时，考虑研究ITAFs相关蛋白的抗病毒作用。Leong等[59]研究表明在病毒蛋白翻译阶段，新的宿主激酶（MINK）可进一步探索作为潜在的抗病毒靶点而抑制EV71复制。因此，更好地理解IRES元件的结构基础、其吸引和结合核糖体的机制以及信号转导通路与IRES间的作用机制，有助于为多种致病病毒新治疗策略的开发提供科学依据。

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