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宿主和病毒的F-Box蛋白在病毒感染过程中作用的研究进展

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[摘 要] F-Box蛋白家族是一类含有F-Box结构域的蛋白，与细胞S期激酶相关蛋白1（SKP1）、Cullin1和环框蛋白1（RBX1）共同形成SKP1-CUL1-F-Box（SCF）E3泛素连接酶复合物，该复合物介导底物发生泛素化修饰并经蛋白酶体途径降解。宿主F-Box蛋白在整个病毒感染周期中发挥关键作用。F-Box蛋白能够调控人类免疫缺陷病毒（HIV）-1和EB病毒（EBV）等多种RNA病毒及DNA病毒的复制，且调控机制均不同。在病毒进入宿主细胞后，宿主F-Box蛋白可以调控病毒复制过程中关键蛋白质的稳定性和降解，也可增强病毒感染后宿主细胞的免疫应答，抑制病毒复制。部分F-Box蛋白能通过降解宿主限制因子、抑制病毒激活和干扰素信号通路等方式协助病毒完成复制周期。病毒也可通过编码含F-Box结构域的蛋白与宿主SKP1、Cullin1和RBX1蛋白结合，降解宿主因子促进自身复制。F-Box蛋白调控在病毒感染过程中发挥的作用差异较大，一种F-Box蛋白能够调控多种病毒的复制，一种病毒也能被多种F-Box蛋白所调控，现从宿主F-Box蛋白和病毒F-Box蛋白角度，对F-Box蛋白在病毒感染过程中的作用机制进行综述，探讨以F-Box蛋白作为靶点，开发新型抗病毒药物的意义及潜在价值。

[关键词] F-Box蛋白；病毒；泛素蛋白酶体途径；S期激酶相关蛋白1；环框蛋白1
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Research progress in role of host and viral F-Box proteins in process of viral infection

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ABSTRACT The F-Box protein family is one kind of proteins containing the F-Box domain, which are together with S-phase kinase associated protein 1 (SKP1), Cullin1, and ring box protein 1 (RBX1) to form the SKP1-CUL1-F-Box (SCF) E3 ubiquitin ligase complex; this complex mediates substrate ubiquitination modification and subsequent degradation via the proteasome pathway. The host F-Box protein plays an important role during the whole viral infection. The F-Box protein can regulate the replication of various RNA virus and DNA virus such as human immunodeficiency virus (HIV) and epstein-barrvirus(EB), and the regulation mechanisms are different. After the virus enters the host cells,

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the host F-Box protein can regulate the stability and degradation of the key proteins during virus replication, enhance the immune response of host cells after virus infection, and inhibit the virus replication. Some F-Box proteins can assist the virus in completing the replication cycle by degrading the host restriction factors and inhibiting the virus activation and the interferon signaling pathway. The viruses also degradade the host factors and promote their own replication by encoding proteins containing the F-Box domain to bind to host SKP1, Cullin1, and RBX1 proteins. There are significant differences in the role of F-Box protein regulation during virus infection; one F-Box protein can regulate the replication of multiple viruses, and one virus can also be regulated by multiple F-Box proteins. This study systematically reviews the role of F-Box proteins in the process of viral infection from the perspectives of host F-Box proteins and viral F-Box proteins, and further explores the significance and potential value of F-Box proteins as targets for developing novel antiviral drugs.

KEYWORDS F-Box protein; Virus; Ubiquitin-proteasome pathway; S-phase kinase-associated protein 1; Ring box protein 1

F-Box蛋白是一类广泛分布于生物体内的含有F-Box结构域的蛋白，能与人S期激酶相关蛋白1（S-phase kinase associated protein 1，SKP1）、Cullin1和环框蛋白1（ring box protein 1，RBX1）共同形成SKP1-CUL1-F-Box（SCF）E3泛素连接酶复合物，通过F-Box结构域招募磷酸化底物，使底物泛素化并被26S蛋白酶体降解。宿主F-Box蛋白作为E3泛素连接酶的重要组成部分在体内发挥重要作用，主要参与转录、细胞信号转导、细胞周期和细胞凋亡等生理过程的调控，也参与机体抗病毒作用的调节。如F-Box基序和WD重复的蛋白（F-Box with WD 40 amino acid repeats，FBXW）1能够识别磷酸化的核因子κB抑制蛋白（inhibitor of kappa B，IκB），使其被泛素化，促使核因子κB（nuclear factor kappa B，NF-κB）转录；FBXW1也可识别并泛素化β连环蛋白（β-catenin），进而调控Wnt/β-catenin通路和NF-κB受体活化因子（receptor activator of nuclear factor-kappaB，RANK）/NF-κB通路；S期激酶相关蛋白2（S-phase kinase-associated protein 2，SKP2）、FBXW7和FBXW1等F-Box蛋白通过促进细胞周期蛋白及细胞周期蛋白依赖性激酶（cyclin-dependent kinases，CDKs）的降解，调控细胞周期；SKP2能与控制参与细胞生长、细胞凋亡和肿瘤发生的原癌基因（c-MYC）相互作用，参与其泛素化和降解。此外，病毒编码的F-Box蛋白含有与宿主F-Box一致的同源序列基序，也具有将底物结合到宿主SCFE3泛素连接酶复合物上的功能，如禽痘病毒编码的FPV014蛋白与SKP1蛋白相互作用，促进病毒感染。

F-Box蛋白作为E3泛素连接酶复合物亚基，调节蛋白的泛素化过程、参与细胞的多种生理过程，如植物逆境胁迫、生长发育、先天免疫、肿瘤和生殖等，但关于F-Box蛋白如何调控病毒复制尚缺少系统性的综述报道。本研究探讨F-Box蛋白在病毒感染过程中的作用，对于了解病毒复制和宿主免疫的分子机制具有重要意义。

1 F-Box蛋白的发现及其结构组成

1.1 F-Box蛋白的发现 1996年，BAI等[1]在细胞周期蛋白F（CyclinF）中发现了能够与SKP1等发生相互作用的共同基序，并将其命名为F-Box结构域，该基序包含1个约由50个氨基酸组成的保守序列，第8和20位多为亮氨酸（L）或甲硫氨酸（M），第9位多为脯氨酸（P），第16位多为异亮氨酸（I）或缬氨酸（V），第32位多为丝氨酸（S）或半胱氨酸（C）[2]。随后，人类基因组编码的78种F-Box蛋白被陆续鉴定出来[3]。

1.2 F-Box蛋白的结构组成 F-Box蛋白作为E3泛素连接酶的接头蛋白发挥作用，人类基因组编码的F-Box蛋白是由N端F-Box结构域和C端功能域组成。研究[4]显示：病毒也能编码F-Box蛋白。痘病毒（vaccinia virus，VV）编码的锚蛋白含有与人类基因组编码的F-Box蛋白序列的同源基序，由C端F-Box结构域和N端功能域组成。

人F-Box蛋白家族根据其C端的底物结合功能域不同，可分为FBXW、含有F-Box基序和富含亮氨酸重复（leucine rich repeats，LRRs）的蛋白（F-Box with leucine rich amino acid repeats，FBXL）以及含有F-Box基序、含有或不含有其他基序（F-Box only with uncharacterized domains，FBXO）3个亚家族。

FBXW亚家族有17个家族成员，均含有色氨酸（W）和天冬氨基（D）构成的WD-40重复结构域，其常见的底物结合基序为PROPELLER[5]，但其识别的底物特征并不唯一，如FBXW1识别丝氨酸/苏氨酸磷酸化（pS/pT）序列以及有1个可变的L［I/L/P］［pS/pT］P序列也能够被FBXW亚家族蛋白识别[6]。FBXL亚家族包括22个家族成员，均含有富含亮氨酸重复序列（leucine-rich repeat，LRR）的结构域，FBXL家族蛋白将底物结合至LRR弧的凹表面[7]。FBXO亚家族有39个家庭成员，通常含有calponin同源性结构域（calponin homology，CH）和蛋白质激酶样结构域（tyrosine kinase domain-like，TDL）等其他与底物结合的结构域，也存在FBXO2和FBXO3等仅含有F-Box结构域的蛋白，其底物结合的相关基序还有待进一步鉴定[8]。

1.3 F-Box蛋白的生物学功能 泛素蛋白酶体系统由E1、E2、E3和26S蛋白酶体组成，E1是泛素活化酶，E2是泛素结合酶，能够结合被E1激活的泛素，E3是泛素连接酶，识别被降解的蛋白并催化泛素与E2分离，并将泛素连接至底物上，26S蛋白酶体负责降解多泛素化蛋白。E1和E2在进化过程中较为保守，目前在哺乳动物中仅发现2种E1和40种E2，而已发现有600多种E3[9]，其中SCF复合物是E3中的一种重要复合物，由SKP1、Cullin1、RBX1和1个含F-Box结构域的蛋白组成。

F-Box结构域介导F-Box蛋白与SKP1的相互作用，SKP1将F-Box蛋白连接至由RBX1、细胞分裂周期53（cell division cycle 53，CDC53）/Cullin1和E2偶联酶细胞分裂周期34（cell division cycle 34，CDC34）组成的泛素连接酶复合体[10]。F-Box蛋白的C端功能域以一种依赖于磷酸化的方式与靶标底物相互作用，决定了F-Box蛋白与底物结合的特异性[11]。现已发现5种含有保守G端结构域的F-Box蛋白（FBXO2、FBXO6、FBXO17、FBXO27和FBXO44），其可通过识别糖基化或甘露糖寡糖化的降解决定子（E3连接酶识别的底物蛋白中的局部序列元件）招募底物，从而组装成SCF复合物，行使泛素化功能[12]，如FBXO2可以识别N端连接高甘露糖修饰的糖蛋白gB使其发生泛素化并降解[13]。

泛素分子的7个赖氨酸残基（K6、K11、K27、K29、K33、K48和K63）、N端蛋氨酸残基（M1）和C端甘氨酸残基（G76）均可与另一个泛素分子C末端结合，形成多种拓扑形式的泛素链，介导蛋白与蛋白之间相互作用，调控蛋白质稳定性。K6连接的泛素链与线粒体自噬有关[14]，K11和K48连接的泛素链通常与蛋白酶体途径降解有关[15-16]，K27和K29连接的泛素链可以调控溶酶体途径降解[17]，K33和K29连接的多聚泛素链抑制磷酸腺苷（adenosine monophosphate，AMP）活化的蛋白激酶[18]，K63连接的泛素链参与NF-κB信号调节、DNA修复和自噬等功能[19]，M1和K63连接的泛素链协同参与NF-κB通路的信号转导[20]。F-Box能够调控K27[21]、K29[22]、K48[23]和K63[24]连接的底物多泛素化，参与转录、细胞信号转导、细胞周期和细胞凋亡的调控，如FBXW1增加K48连接的白细胞介素1受体相关激酶1（interleukin-1 receptor-associated kinase 1，IRAK1）多聚泛素化并经蛋白酶体系统降解，使TAK1-TRAF6复合物从细胞膜释放至细胞质，促使NF-κB激活[25]，FBXW7增加K27连接的抑癌基因编码的Brahma相关基因1（Brahma-related gene 1，BRG1）的多泛素化并介导其降解[26]。

F-Box蛋白介导的泛素化在细胞中行使多种生物学功能，现根据编码F-Box蛋白的生物不同，将其分为宿主F-Box蛋白和病毒F-Box蛋白，阐明其在病毒感染过程中的作用。

2 宿主F-Box蛋白在病毒复制周期中的调控作用

2.1 F-Box蛋白在病毒感染过程中的抑制作用 F-Box蛋白作为E3连接酶复合物中的重要成员，在病毒与宿主相互作用中所发挥的作用成为研究热点。FBXW1能抑制人类免疫缺陷病毒（human immunodeficiency virus，HIV）[27]和流感病毒（influenza A virus，IAV）[28]的复制，FBXW1可与磷酸化的HIV蛋白的病毒蛋白u（viral protein u，Vpu）相互作用，降解磷酸化Vpu，并促进磷酸化Ika-α降解，从而抑制NF-κB活性[27]；也能够抑制IAV的非结构蛋白1（non-structural protein 1，NS1）表达水平，抑制流感病毒的复制[28]。HIV除受FBXW1的调控外，还能被FBXO11和FBXO1抑制[23, 29]，敲低细胞中的FBXO11能够增加转录反式激活因子（transactivator of transcription，Tat）的反式激活，促进潜伏HIV-1的激活[29]；FBXO1能够参与组装SCF复合物，通过K48连接的泛素链降解病毒感染因子（viral infectivity factor，Vif）蛋白，促进抗病毒活性的宿主蛋白胞嘧啶脱氨

基酶（apolipoprotin B mRNA-editing catalytic polypeptide 3 protein G，A3G）的表达，从而抑制子代病毒粒子的感染性[23]。

与细胞周期调控相关的FBW7也是参与病毒复制的另一种重要宿主蛋白，可抑制IAV[30]、水疱性口炎病毒（vesicular stomatitis virus，VSV）[31]和流行性腹泻病毒（porcine epidemic diarrhea virus，PEDV）[32]的复制。FBXW7通过与非受体型蛋白酪氨酸磷酸酶SHP2相互作用，泛素化降解含Src同源2结构域蛋白酪氨酸磷酸酶2（Src homology region 2-containing protein tyrosine phosphatase 2，SHP2），破坏能够降解视黄酸诱导基因Ⅰ（retinoic acid inducible gene-Ⅰ，RIG-Ⅰ）的SHP2/c-Cbl复合物，稳定RIG-Ⅰ，增加宿主细胞的抗病毒反应，抑制IAV和VSV复制[30-31]；FBXW7也可以通过增强内源性RIG-Ⅰ和TANK结合激酶1（TANK-bliding kinase 1，TBK1）的表达并激活宿主干扰素信号通路，增加宿主细胞抗病毒反应，从而抑制PEDV感染[32]。FBXO21与FBXW7均可以抑制VSV，FBXO21通过增加K29连接的ASK1多聚泛素化修饰，上调c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）和p38信号通路，促进促炎细胞因子和Ⅰ型干扰素的产生，增加宿主体内抗病毒反应从而抑制VSV病毒的复制[22]；FBXO2通过募集细胞质中未折叠糖蛋白中糖链并介导其泛素化降解发挥作用，FBXO2是单纯疱疹病毒1型（herpes simplex virus-1，HSV-1）UL9的结合伴侣，HSV-1感染促进FBXO2在细胞核之间穿梭，使FBXO2与细胞核中磷酸化的UL9结合，将其输出至细胞质，导致其泛素化和通过26S蛋白酶体降解[33-34]；在EB病毒（EB virus，EBV）感染细胞后，FBXO2结合糖基化的糖蛋白gB，通过泛素蛋白酶体途径促进糖蛋白gB降解，从而减弱EBV的感染性[13]。

研究[32]显示：病毒不仅受宿主F-Box家族蛋白调节，也可反作用于F-Box蛋白，如PEDV的非结构蛋白2（non-structural protein 2，NSP2）通过K48连接的泛素蛋白酶体途径靶向FBXW7降解；EBV感染影响FBXO2的转录，增加细胞中FBXO2水平。

F-Box蛋白家族成员通过泛素蛋白酶体途径降解病毒蛋白或稳定宿主体内干扰素信号通路2种途径抑制病毒复制，部分病毒（PEDV和VSV等）感染后也可反作用于F-Box蛋白，调控F-Box的转录和翻译，从而影响病毒在细胞中的感染。

2.2 F-Box蛋白在病毒感染过程中的促进作用

FBXW1在HIV复制过程中不仅降解Vpu进而抑制HIV复制，还通过泛素蛋白酶体途径降解CD4[35-36]、骨髓基质细胞抗原2（bone marrow stromal antigen-2，BST-2）[37-38]和细胞间黏附分子1（intercellular cell adhesion molecule-1，ICAM-1）[39]等宿主限制性因子，促进HIV复制并促进HIV感染后p53介导的T淋巴细胞凋亡[40]。FBXW1还能够被裂谷热病毒（rift valley fever virus，RVFV）的非结构蛋白（nonstructural protein，NSs）招募，与FBW11通过泛素蛋白酶体系统靶向蛋白激酶R（protein kinase R，PKR）降解，破坏PKR介导的抗病毒作用[41-42]。另一种F-Box蛋白FBXO34能识别转录因子，全基因组成簇的规律间隔的短回文重复序列（clustered regularly interspaced short palindromic repeats，CRISPR）/Cas9文库筛选发现FBXO34是HIV的潜伏激活因子，通过促进核不均一核糖体蛋白泛素化降解，导致HIV-1 mRNA的翻译增强，使HIV-1处于激活状态[43]。

F-Box蛋白能够参与细胞信号转导。在感染病毒后，宿主细胞利用自身的天然免疫因子和信号通路抵御病毒，同时，病毒也可以利用天然免疫中的信号通路抑制免疫应答。丙型肝炎病毒（hepatitis C virus，HCV）5A蛋白与FBW2和调控细胞内质网钙离子（calcium ion，Ca^{2+}）转运的三磷酸肌醇受体Ⅲ型（inositol triphosphate receptor type Ⅲ，IP3R3）形成复合物，使IP3R3泛素化并降解，促进HCV感染[44]。RVFV感染宿主后，病毒的NSs蛋白与FBXO3形成SCF复合物，通过泛素蛋白酶体途径降解通用转录因子ⅡH（transcription factor ⅡH，TFⅡH）的p62亚基，从而抑制Ⅰ型干扰素反应[45]；与FBW7能够抑制IAV不同，FBXO6与核苷酸结合寡聚化结构域样受体X1（nucleotide-binding oligomerization domain-like receptor X1，NLRX1）相互作用，促进其K48连接的泛素化修饰的蛋白酶体降解，从而降低宿主对IAV的抗病毒反应[46]；干扰素λ受体1（interferon λ receptor 1，IFNLR1）在流感病毒PR8感染时会发生降解。研究者[47]使用生物素标记发现：F-Box和FBXO45与IFNLR1相互作用，并介导IFNLR1的多泛素化，降低IFNLR1蛋白的稳定性，抑制干扰素刺激

基因激活。

F-Box蛋白也能与宿主体内癌基因相互作用，调节病毒感染导致的相关疾病。卡波济肉瘤相关疱疹病毒（Kaposi's sarcoma-associated herpesvirus，KSHV）感染的早期阶段，KSHV编码的蛋白潜伏相关核抗原（latency-associated nuclear antigen，LANA）同有转录调节活性的Notch蛋白片段ICN竞争与FBXW7的结合抑制ICN的降解[48]，KSHV编码的病毒干扰素调节因子3（viral interferon regulatory factor-3，vIRF-3）与SKP2泛素连接酶结合，并将其招募至c-MYC调控的启动子上，刺激c-MYC的泛素化和转录活性，促进c-MYC诱导的KSHV相关淋巴瘤的发生[49]；腺病毒衍生的癌基因产物E1A与应答调节蛋白RR1/RBX1相互作用，抑制FBW7的泛素化降解，从而促进癌细胞增殖[50]；EBV核抗原（EBV nuclear antigen，EBNA）3C通过SKP2复合物，促进抑癌基因编码的RB蛋白视网膜母细胞瘤肿瘤抑制蛋白（retinoblastoma protein，RB protein）[51]和p27蛋白的泛素化降解[52]；人类T淋巴细胞白血病病毒1型（human T-lymphocyte leukemia virus-1，HTLV-1）编码的HBZ通过抑制抗凋亡蛋白HAX-1和FBXO25的结合，抑制HAX-2蛋白的多泛素化水平，并保持HAX-3蛋白的稳定性[53]。

F-Box蛋白不仅能够抑制病毒复制，还可被病毒蛋白招募，形成SCF复合物，调控干扰素上游因子或降解宿主限制性因子，从而促进病毒的复制以及病毒引起的其他疾病。宿主F-Box蛋白在病毒感染过程中的作用见表1。

3 病毒F-Box蛋白在病毒感染过程中的作用

病毒与宿主之间的军备竞赛促使病毒进化出多种方式逃避宿主抗病毒反应。病毒编码的F-Box蛋白也能够招募宿主的SKP1和Cullin1，形成SCF复合物，从而影响病毒感染。

VV编码的锚蛋白C端痘蛋白重复序列（pox protein repeats of ankyrin-C-terminal，PRANC）/F-Box蛋白已被证实能与Cullin蛋白相互作用，并介导底物特异性降解[4]。痘苗病毒（vaccinia virus，VACV）编码的含F-Box蛋白结构域的C9蛋白，能特异性识别干扰素诱导蛋白（interferon-induced proteins with tetratricopeptide repeats，IFITs），并通过蛋白酶体途径降解IFITs，从而影响宿主的抗病毒活性[54]；当VV感染宿主细胞后，RIPR3降解诱导因子（viral inducer of RIPK3 degradation，vIRD）促进K48连接的受体相互作用蛋白激酶3（receptor in teracting protein kinase 3，RIPK3）泛素化和降解，促进病毒复制[55]。FNIP通过其F-Box结构域与宿主Ras相关蛋白1b（Ras-related protein 1b，Rap1B）和Ras相关蛋白7A（Ras-related protein 7A，Rab7A）相互作用，并与SKP1和Cullin1结合形成SCF复合物，促进Rap1B和Rap7A的降解[56]；LEF-7也参与组装成SCF复合物，其F-Box蛋白结构域能够抑制病毒诱导的磷酸化宿主组蛋白变体H2AX关键区域，增强病毒晚期基因的释放，增加杆状病毒的复制[57]。

病毒编码的含F-Box蛋白结构域的锚蛋白也能参与信号转导，抑制NF-κB信号通路。鼠痘病毒（ectromelia virus，ECTV）编码4种含F-Box的锚蛋白[58-60]：EVM002、EVM005、EVM154和EVM165；ORFV编码5种锚蛋白[61]：ORF008、ORF123、ORF126、ORF128和ORF129。上述含F-Box蛋白结构域的锚蛋白对NF-κB信号通路均有抑制作用，与宿主F-Box蛋白共同参与形成SCF复合物，抑制肿瘤坏死因子α和白细胞介素1刺激的磷酸化IκB-α降解及p65核转位，抑制NF-κB的激活。

上述研究结果表明：在病毒感染过程中，DNA病毒能够编码部分包含F-Box结构域的蛋白，通过蛋白酶体途径降解宿主体内天然先天免疫因子或宿主限制性因子，从而促进病毒复制。病毒F-Box蛋白在病毒感染过程中的作用机制见表2。

4 总结与展望

在病毒与宿主的协同进化过程中，F-Box蛋白在调控病毒蛋白、宿主限制因子稳定性、干扰素和NF-κB等信号通路方面起重要作用。宿主F-Box新底物的鉴定和解析病毒F-Box蛋白能够提高研究者对于病毒发病机制及病毒与宿主相互作用的认识。特别是病毒F-Box蛋白能与宿主体内SCF复合物相互作用，为寻找能够拮抗病毒F-Box蛋白的宿主因子提供了新的方向，进而为发现其抗病毒的作用机制提供新思路。

F-Box蛋白相关药物逐渐被开发，在抗肿瘤活性方面取得良好效果，如FBXL2激活剂BC-1258能促进有丝分裂激酶B降解，导致致瘤细胞的四倍体、有丝分裂阻滞和凋亡，抑制胸腺裸小鼠的肿瘤形成[62]；SKP2抑制剂SZL P1-41可以抑制肿瘤生

表 1 宿主 F-Box 蛋白在病毒感染过程中的作用

Tab. 1 Role of host F-Box protein in process of viral infection

Virus classification	Virus	Host F-Box protein	Mechanism	Literature
RNA	HIV	FBXW1	Degradation of phosphorylated Vpu and inhibition of NF-κB activity; binds to phosphorylated Vpu, and degrades CD4, enhances BST-2 ubiquitination, inhibits p53 phosphorylation, and promotes T cell apoptosis. Degrade ICAM-1 and promote viral replication	[27,35-40]
		FBXO11	Inhibition of HIV-1 LTR activity and inhibition of latent HIV-1 activation	[20]
		FBXO1	Degradation of Vif protein through K48 linked ubiquitin chains, reducing infectivity of progeny virions	[23]
		FBXO34	Promotion of ubiquitination degradation of hnRNP U, enhance HIV translation, and keep it in an activated state	[43]
	VSV	FBXW7	Promotion of ubiquitination degradation of SHP2, destroy SHP2/c-Cbl complex that can degrade RIG-I, stabilize RIG-I, and increase antiviral response of host cells	[31]
		FBXO21	Promotion of polyubiquitination modification of ASK1 K29, enhance JNK and p38 signaling pathways, and promote production of pro-inflammatory cytokines and type Ⅰ interferon	[22]
	IAV	FBXW1	Decreasing of expression of NS1, thereby significantly reducing replication level of influenza virus	[28]
		FBXW7	Ubiquitination degrades SHP2 and inhibits influenza A virus replication	[30]
		FBXO45	Mediating the polyubiquitination of IFNLR1 and reducing its protein stability	[47]
		FBXO6	Interacting with NLRX1 to reduce host antiviral response to influenza virus	[46]
	PEDV	FBXW7	Inhibiting PEDV infection by enhancing expression of endogenous RIG-I and TBK1 and activating host interferon signaling pathway	[32]
	RVFV	FBXO3	NSs and FBXO3 are assembled into SCF complexes to degrade p62 and inhibit type Ⅰ interferon reaction	[45]
		FBXW11, FBXW1	NSs recruit FBXW11 and FBXW1, degradation of PKR, disruption of PKR-mediated antiviral effects	[41-42]
	HTLV-1	FBXO25	HBZ inhibits polyubiquitination of HAX-2 protein and promotes HAX-3 expression by inhibiting the binding of HAX-1 and FBXO25	[53]
DNA	HSV-1	FBXO2	HSV-1 infection promotes shuttling of NFB42 between cytosol and nucleus, FBXO2 interacts with UL9, this interaction mediates export of UL9 protein from the nucleus to the cytosol, leading to its ubiquitination and degradation via 26S proteasome	[33-34]
	EBV	FBXO2	Interacting and degrading glycoprotein gB, reducing EBV infectivity	[13]
	EBV	SKP2	3C recruits SKP2 to cyclinA complex to promote ubiquitination degradation of p27 and ubiquitination of EB protein	[51-52]
	HCV	FBXL2	NS5A protein forms complexes with IP3R3 and FBXL2, and promotes FBXL2 mediated degradation of IP3R3, promoting HBV infection	[44]
	KSHV	FBXW7	FBXW7 increases ubiquitination degradation of ICN, and LANA can compete with ICN to bind to FBXW7 and save degradation of ICN	[48]
		SKP2	vIRF-3 binds to SKP2 ubiquitin ligase, stimulates ubiquitination and transcriptional activity of c-Myc, and promotes tumorigenesis	[49]
	Adenovirus	FBW7	E1A interacts with RR1/RBX1 to inhibit FBW7 ubiquitination, reduce endogenous FBW7 degradation, and promote cancer cell proliferation	[50]

表2 病毒F-Box蛋白在病毒感染过程中的作用机制

Tab. 2 Role of viral F-Box protein in process of viral infection

Virus classification	Viral F-Box protein	Mechanism	Literature
ECTV	EVM00,EVM00, EVM15,EVM165	Interacting with SKP1, Cullin1, and ROC1 to form SCF complexes, exercising ubiquitination function and inhibiting TNF-α and IL-1β, stimulating IκB-a degradation and p65 nuclear translocation, inhibiting activation of NF-κB	[58-60]
VV	C9	Recognition of IFITs and degradation of IFITs through proteasome pathway affect antiviral activity of host	[54]
	vIRD	Promotion of RIPK3 ubiquitin degradation and promotion of viral replication	[55]
ORFV	ORF00,ORF12, ORF12,ORF128	Suppressing of degradation of p-IκBα protein, preventing nuclear translocation of p65, and inhibiting host activation of NF-κB signaling pathway	[61]
Megavirus	FNIP	Interacting with host Rap1B and Rap7A to form SCF complexes, promoting degradation of Rap1B and Rap7A	[56]
Baculovirus	LEF-7	Suppressing of key regions of phosphorylated H2AX, enhance release of late stage genes of virus, and increase virus replication	[57]

长[63-64]；靶向FBXO3的底物识别结构域ApaG的抑制剂BC-12155可阻止FBXO3与底物结合并导致底物降解[65]，也可阻止FBXO3依赖型的FBXL2泛素化增强，起到镇痛作用[66]。F-Box家族蛋白不仅能够抑制病毒复制，也能被病毒招募，降解宿主限制性因子，促进病毒感染。因此，将已有抑制剂应用于抗病毒领域以及开发阻断F-Box蛋白活性的小分子抑制剂或肽段，可以破坏病毒的生命周期并恢复宿主的抗病毒反应，为开发抗病毒疗法提供了新思路。

利益冲突声明：

所有作者声明不存在利益冲突。

作者贡献声明：

许明秀参与查阅、整理文献及撰写论文，桓晨参与论文选题、审阅和修改。

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