·综 述·

病毒劫持 ESCRT 系统促进自身复制的研究进展

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摘 要：内吞体分选转运复合体(endosomal sorting complex required for transport, ESCRT)系统驱动细胞的不同生命进程，包括内体分选、细胞器生物发生、囊泡运输、维持质膜完整性、细胞质分裂期间的膜裂变、有丝分裂后的核膜重组、自噬过程中吞噬孔的封闭以及包膜病毒出芽等。越来越多的证据表明，ESCRT 系统能够被不同家族病毒劫持用于自身增殖。在病毒生命周期的不同阶段，病毒可以通过各种方式干扰或利用 ESCRT 系统介导的生理过程，最大限度地提高感染宿主的机会。此外，许多逆转录病毒和 RNA 病毒蛋白具有“晚期结构域”基序，可招募宿主 ESCRT 亚基蛋白帮助病毒内吞、运输、复制、出芽以及外排。因此，病毒“晚期结构域”基序和 ESCRT 亚基蛋白可能是病毒感染治疗中具有广泛应用前景的药物靶点。本文重点综述了 ESCRT 系统的组成及功能，ESCRT 亚基和病毒“晚期结构域”基序对病毒复制的影响以及 ESCRT 介导的抗病毒作用，以期为抗病毒药物的开发和利用提供参考。

关键词：病毒；劫持；内吞体分选转运复合体(ESCRT)系统；复制

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Virus hijacking ESCRT system to promote self-replication: a review

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Abstract: Endosomal sorting complex required for transport (ESCRT) system drives various cellular processes, including endosome sorting, organelle biogenesis, vesicle transport, maintenance of plasma membrane integrity, membrane fission during cytokinesis, nuclear membrane reformation after mitosis, closure of autophagic vacuoles, and enveloped virus budding. Increasing evidence suggests that the ESCRT system can be hijacked by different family viruses for their proliferation. At different stages of the virus life cycle, viruses can interfere with or exploit ESCRT-mediated physiological processes in various ways to maximize their chance of infecting the host. In addition, many retroviral and RNA viral proteins possess "late domain" motifs, which can recruit host ESCRT subunit proteins to assist in virus endocytosis, transport, replicate, budding and efflux. Therefore, the "late domain" motifs of viruses and ESCRT subunit proteins could serve as promising drug targets in antiviral therapy. This review focuses on the composition and functions of the ESCRT system, the effects of ESCRT subunits and virus "late domain" motifs on viral replication, and the antiviral effects mediated by the ESCRT system, aiming to provide a reference for the development and utilization of antiviral drugs.

Keywords: virus; hijacking; endosomal sorting complex required for transport (ESCRT) system; replication

内吞体分选转运复合体(endosomal sorting complex required for transport, ESCRT)由外周膜蛋白复合物 ESCRT-0、-I、-II、-III，以及 Vps4-VTA1 和 ALIX 同型二聚体等相关蛋白组成[1-5]，其形成了一种进化保守的膜重构机制。ESCRT 首次发现于酵母中，其在酵母液泡分选过程中货物分选和内体膜重构中发挥重要作用[6]。后续研究发现，ESCRT 参与了真核细胞的多种生命过程，包括介导胞质分裂[7]、质膜修复[8]、囊泡分裂[9]、有丝分裂后的核膜重组[10]、外泌体的生物发生[11]、内体溶酶体膜损伤修复[12-13]、线粒体生物发生[14]以及自噬过程中吞噬孔的封闭[15-16]。不仅如此，逆转录病毒出芽也需要 ESCRT 系统[17-18]。甚至，尿液中 ESCRT 亚基蛋白的减少也与病毒(SARS-CoV-2)的活跃复制密切相关[19]。ESCRT 这些功能的发挥与其亚复合体和相关辅助蛋白密不可分。

随着生物技术的飞速发展，越来越多的证据表明，ESCRT 作为真核细胞膜蛋白分选的重要分子机制，参与了包膜病毒复制生命周期的多个环节[20]。究其原因，病毒通过其编码的"晚期结构域"基序招募宿主 ESCRT 通路蛋白，促进病毒内吞、运输、复制、出芽以及外排[21-24]。因此，通过阻断 ESCRT 与病毒蛋白或泛素的相互

作用将显著抑制包膜病毒的产量[25-26]。同时，病毒蛋白与 ESCRT 亚基相互作用的环肽(cyclic peptides, CP)抑制剂也将是一个具有广泛应用前景的抗病毒策略[27-28]。更重要的是 ESCRT-III蛋白 CHMP3 在不影响胞质分裂的情况下阻止包膜病毒的出芽，其可成为 ESCRT 依赖性病毒出芽的广泛、有效的抑制剂[29-30]。因此，由于 ESCRT 系统功能多样性及其驱动不同的细胞进程决定了其在病毒复制不同生命周期中发挥重要作用。

1 ESCRT 的组成及功能

ESCRT 由 4 种不同的多聚复合体组成(ESCRT-0、-I、-II、-III)。4 种复合体彼此之间相互作用维持着 ESCRT 的拆分和循环利用。ESCRT-0 由 2 个亚基组成，即肝细胞生长因子调节的酪氨酸激酶底物(hepatocyte growth factor-regulated tyrosine kinase substrate, HRS, 也称为 HGS)和信号转导衔接分子 1/2 (signal transduction linker molecules, STAM1/2)；ESCRT-I 是一种茎形异源四聚体蛋白质复合物，包含 Vps23、Vps28 和 Vps37 亚基[3-4,31]。ESCRT-0 招募 ESCRT-I，启动多囊泡体(multivesicular body, MVB)依赖的货物分拣[32]，协调泛素化货物的聚集和内体膜的腔内出芽[33]。早在 2001 年，Katzmann 等[31]研究发现 ESCRT-I 通过 Vps23 (TSG101)中一个保守的 UBC 样域(类似于泛素结合酶 E2 的保守结构域)识别核内体中泛素化的货物并介导其分选进入 MVB 囊泡。另外，蛋白质组学分析显示，TSG101 还结合了一系列与细胞质分裂有关的蛋白，包括 CEP55、CD2AP、ROCK1 和 IQGAP1，与细胞质分裂调控密切相关[34]。因此，ESCRT-I 是将泛素化修饰与蛋白质分选和 MVB 通路相联系的桥梁，在 MVB 通路中发挥核心作用。

ESCRT-II是一个 Y 形复合体，由 VPS22 (也称为 EAP30)、VPS36 (也称为 EAP45)和 2 个 VPS25 分子(也称为 EAP20)组成[5]；ESCRT-III 是带电荷的多泡体蛋白 CHMP1−CHMP7 组成[35]。作为 ESCRT-III 的组装因子，ESCRT-I 和 ESCRT-II协同作用将 ESCRT-III募集到膜下发生出芽的位置[36]，随后 ESCRT-III级联聚合负责驱动完成出芽过程最后的膜变形和裂变[37]。另外，ESCRT-III (Snf7)寡聚物的长度控制了 MVB 囊泡的大小，而 ESCRT-II作为支架辅助 2 个 Snf7 寡聚物组装成复合体的核心，在 MVB 分选过程中介导货物的分拣和囊泡形成[38]。

1997 年，AAA 型 ATPase 酶 Vps4 被确定为 ESCRT 复合体的第 5 个亚基，其作用是将货物运送到液泡所必需的位置，并驱动 ESCRT 亚基进出 ESCRT-III进行动态交换，从而将亚基循环回细胞质，最终利用 ATP 水解的能量来驱动 ESCRT 依赖的膜裂变反应[39-40]。Vps4 及其底物 ESCRT-III似乎是执行膜脱落反应的关键成分[41]，但 Vps4 作为低聚物(六聚性很弱)，通常是六聚环或由 6 个或 12 个亚基组成的堆叠六聚环[42]，其包含 3 个不同的结构元件：(1) 结合 ESCRT-III蛋白尾部的 N 端 MIT 结构域；(2) 一个由大/小结构域组成的中心 ATP 酶盒，介导六聚化和 ATP 水解；(3) 在小的 ATPase 结构域内插入一个 β-结构域，结合 LIP5 (Vta1)，一个 ATPase 激活剂和 ESCRT-III结合蛋白[43]。

虽然每个 ESCRT 复合体亚基在货物分拣方面的作用已经相对明确，但货物如何从一个 ESCRT 亚复合体转移到下一个 ESCRT 亚复合体的机制依然不明。2017 年，Meister 等[44]研究发现内体分选泛素化货物过程中，可能通过 Flotillin-1 调节货物在 ESCRT-0 和 ESCRT-I 亚复合体之间的转移，而 Flotillin-1 主要与 ESCRT-0 和 ESCRT-I (HRS 和 TSG101)亚基相互作用，在

ESCRT-0/HRS 进行货物识别和分拣中发挥作用。此外，越来越多的证据表明，ESCRT 积极参与不同类型的自噬过程降解胞质成分[16]，其亚基可以直接与关键的自噬相关蛋白(ATGs)相互作用，在胞吞和自噬通路之间建立更紧密的联系[44-46]，例如，ESCRT 相关蛋白 PDCD6IP/Alix 与 ATG12-ATG3 具有很强的相互作用，这种相互作用促进了基础自噬通量和晚期核内体功能[47]，而在基础自噬过程中，自噬调节因子与 ESCRT 亚基相互作用促进了核内体成熟，在最终与溶酶体融合之前，这种内体成熟的激活将促进自噬体和 MVB 的融合[48]。

2 病毒复制依赖于宿主 ESCRT 系统

越来越多的研究表明，ESCRT 及其相关蛋白在包括艾滋病毒在内的许多 RNA 病毒的组装和释放过程中发挥重要作用[23,49-51]。例如，逆转录病毒[52]、梅森辉瑞猴病毒(Mason Pfizer monkey virus, MPMV)[53]、埃博拉病毒(Ebola virus, EBOV)[54-55]和马尔堡病毒(Marburg virus, MARV)等都依赖于ESCRT系统实现病毒粒子有效外排和释放[56]。病毒编码的“晚期结构域”基序，可招募宿主 ESCRT 通路蛋白促进病毒入侵、复制、组装和出芽[21-24]，而干扰或敲除 ESCRT 某些亚基蛋白将显著抑制病毒增殖[17,57-58]。大多数包膜病毒家族已经学会利用ESCRT组件，以促进包封和获得 ESCRT-III以驱动终端分裂事件[59]。目前，ESCRT 亚基蛋白中，HRS、TSG101、Alix 和 Vps4 是被病毒劫持促进自身复制的明星分子(表 1)。一般来说，病毒通过招募一个或多个早期 ESCRT 组件，特别是 ESCRT 亚基蛋白 TSG101 和 Alix，进而与 ESCRT-III结合[60]。

TSG101 是胚胎和成体组织细胞生长、增殖和存活所必需的[61]，其主要功能是识别泛素化产物，在细胞液泡蛋白分选(vacuolar protein sorting, VPS)途径中发挥重要作用[62]，因此，TSG101 能帮助包膜晚期病毒蛋白通过内体分选到质膜组装[63]。同时，许多病毒结构前体多聚蛋白 Gag 中的晚期结构域 PTAP 基序通过招募 TSG101 帮助病毒在组装位点出芽[64]。TSG101 还能通过与 Hrs 和 Alix 的选择性相互作用，能将受体分选和溶酶体靶向与病毒衣壳释放过程联系起来[65]。另外，TSG101 也是 HSV-1 病毒 VP1/2 蛋白泛素特异性蛋白酶结构域活性的底物，其与 VP1/2 (1-767)相互作用并调节其泛素化，从而影响其在细胞内的分布，这是疱疹病毒去泛素化酶的第一个细胞底物[66-67]。后续研究表明，TSG101 被 RNA 干扰敲除后对细胞增殖影响较小，但可以有效地阻断 HIV 感染后的出芽过程[17]。

Alix 是一种 k63 选择性的多聚泛素链结合蛋白，由 Bro1 结构域、中心 V 结构域以及富脯氨酸区(PRR) 3 个部分组成[68]。Bro1 结构域位于 Alix 蛋白 N 端，负责与 CHMP4 (ESCRT-III)结合；中心 V 结构域与逆转录病毒 Gag 蛋白 YPXnL 基序和一些 MVB 货物结合[69]；脯氨酸区(PRR)位于蛋白 C 端，可以对上游结构域折叠并自动抑制配体结合[70]。Bro1 结构域的 Patch 2 与富含脯氨酸结构域的 TSG101 对接位点之间的分子内相互作用将 Alix 锁定在封闭构象内，使 Alix 无法与宿主 CHMP4 以及逆转录病毒 Gag 蛋白相互作用，这预示着解除 Alix 的自抑制分子内相互作用是 Alix 参与逆转录病毒出芽的关键步骤[71-74]，同时，在细胞中表达 Alix 蛋白的 Bro1 结构域足以挽救缺乏典型 L-结构域的 FIV 突变体出芽[75]。Alix 的 V 结构域与 Ub 在体内直接相互作用可以影响逆转录病毒粒子释放，出芽以及外源蛋白的分泌[76-81]，且偏向于 3 个以上 Ub 组成的泛素链[82-83]。据报道，在逆转录病

毒通过 Alix 劫持宿主 ESCRT 系统的过程中，CHMP4 蛋白 C 端残基特异性结合 Alix 蛋白 Bro1 结构域，并通过 Alix 结合的病毒蛋白招募到细胞膜上一个共同位置促进病毒出芽[84-88]。有趣的是，一些猴免疫缺陷病毒(SIV) Gag 蛋白缺乏这一共识序列，但仍能结合 Alix[89]，同时，Alix 还能以一种独立于 ESCRT 的方式调节乙型肝炎病毒(hepatitis B virus, HBV)裸露衣壳颗粒的外排[90]，对于 HBV 而言，裸核衣壳释放可能有助于感染的传播。将 HBV 来源的核衣壳蛋白转染到细胞系后，衣壳被证明能够启动生产性感染，这表明如果将它们传递到细胞中，它们是具有“传染性的”[91]。虽然，HBV 裸衣壳释放不需要 ESCRT-I、ESCRT-III和 Vps4，Alix 对 HBV 的生产、衣壳组装和出芽也是可有可无的，但它对裸衣壳排出是必不可少的，过量 Alix 也能促进 HBV 裸衣壳释放[90]。这意味着 HBV 已经进化出不同的策略从受感染的细胞出芽，裸衣壳的非常规排出可能为研究 Alix 如何在没有 ESCRT 的情况下促进粒子出芽提供了一个模型系统[90]。

虽然已知大多数的 RNA 病毒会劫持 ESCRT 途径来完成出芽过程，但大型复杂的包膜 DNA 病毒，特别是虹膜病毒的出芽却很少被研究。Mi 等[92]研究初步表明 ESCRT 途径参与了虎纹蛙病毒 TFV 的释放，TFV 的 VP031L、VP065L 和 VP093L 分别与 Alix、TSG101 和 Nedd4 相互作用。Alix、TSG101 和 Nedd4 的共同消耗导致细胞外病毒粒子的产生显著减少，这是首次观察到虹膜病毒通过病毒蛋白与宿主蛋白之间的 3 种相互作用途径获得 ESCRT 通路，为包膜 DNA 病毒的出芽机制提供了参考。

表 1 ESCRT 亚基参与病毒各个生命周期

Table 1 ESCRT subunits participate in various virus life cycles

ESCRT	Participate in the virus lifecycle
Hrs	Macropinocytosis: KSHV[93]; Transcription and capsid secretion: HBV [94]
(ESCRT-0)	Replication: CHIKV[95] HTLV-2[96]; Assembly and budding: HCV[97] HIV-1[98]
TSG101	Egress and transmission:
(ESCRT-I)	HEV[99] MPMV[53] PFV[100] EBOV [54-55] MARV[56] HBV[101]
	PPRV[102] JUNV[103] NV[104] HML-2[105] FIV[75]
	Transport: IAV[106]; Virion formation: PRRSV[107]
	Budding and Release: HIV[34, 108-113]; RNA replication: CSFV[20-21]
Alix	Release: HEV[99] HIV-1[114] YFV[24]
	Budding: MOPV[73] HIV[87-88] BFV[115] SIV[89] EIAV[88]
	Replication fitness: HIV-1C[116]
	Assembly: HAV[117]
	Replication: HSV-1[118] DENV[119] Flaviviruses[120]
Vps4	Budding: HIV[121]; Budding and Egress: EBOV[122-126]
	Assembly: HPV[127-128]; Egress and transmission: VACV[129]
ESCRT	CHMP4A (ESCRT-III): Viral replication and assembly (Flaviviruses)[120]
(other subunits)	Eap20 (ESCRT-II): Release (HIV-1 gag)[130]
	STAM-1 (ESCRT-0): Entry (DENV)[131]
	CHMP4C (ESCRT-III): Envelopment (HSV1)[132]
	EAP20 (ESCRT-II): Replication (HSV1)[133]
	VPS/VTA1 (ESCRT-III): Envelopment (HCV)[95]
	EAP20 (ESCRT-II): RNA transport (HBV)[134]

3 病毒晚期结构域与 ESCRT 相互作用

“晚期(late, L)结构域”是包膜病毒编码的短肽序列，以促进新生病毒从受感染细胞中最终分离[135]。有囊膜的 RNA 病毒自身不能合成出芽所需要的大部分元件，需要劫持宿主的 ESCRT 途径完成病毒粒子的出芽[136-137]。因此，病毒编码的“晚期(L)结构域”基序招募 ESCRT 介导病毒组装和出芽过程中的膜分裂，这些短肽序列的突变或缺失将导致未成熟病毒粒子在质膜上的积累[58,138]。晚期结构域首次在逆转录病毒 Gag 结构前体中被发现[139]，逆转录病毒 Gag 蛋白泛素化募集 ESCRT 系统完成出芽的作用机制是有囊膜 RNA 病毒出芽研究的经典模型[52]。逆转录病毒以及其他很多病毒，包括沙粒病毒、丝状病毒、黄病毒和弹状病毒等，都利用晚期结构域(late domain)募集 NEDD4 家族泛素连接酶E3，完成Gag蛋白或其他同工蛋白的泛素化[136]。随后在许多其他包膜 RNA 病毒的结构蛋白中被检测到晚期结构域的存在[140-141]，例如，HIV-1 的 Gag^{p6} 蛋白[142-144]、埃博拉病毒 EBOV 基质蛋白 VP40[122-125]、戊型肝炎病毒 HEV 的 ORF3 蛋白[145]、胡宁病毒(Junin virus, JUNV) Z 蛋白[103]、马尔堡病毒 MARV 的 NP 核蛋白[146]、马传染性贫血病毒 EIAV 的 Gag 蛋白[147]。晚期结构域是一种线性氨基酸基序，迄今为止已经确定了3类L结构域基序(PT/SAP、YPXnL/LXXLF 和 PPxY)，即使最近有人提出其他基序也可以作为 L 结构域[141]。晚期结构域可与液泡分选(VPS4A 和 TSG101)和内吞途径(Nedd4)中的宿主蛋白相互作用[124]，且在不同的逆转录病毒中发现了 3 个晚期结构域一致基序，即 PTAP、PPPY 和 LYPXL，它们已被证明分别与细胞蛋白 TSG101、Nedd4 和 AP2 或 AIP 相互作用[148]，提示这些途径对病毒出芽至关重要。目前，小鼠乳腺肿瘤病毒(mouse mammary tumor virus, MMTV)使用的晚期(L)结构域序列仍未确定，Coren 等[149]研究发现，PLPPV 提供了 MMTV-L 结构域的功能代表了第 4 种逆转录病毒 L 结构域，使 MMTV Gag 蛋白能够协同细胞出芽途径进行释放。马传染性贫血病毒 EIAV 是迄今为止所研究的包膜病毒中特殊的一种病毒，EIAV 利用 Gag 中的一个新的基序 YPDL 作为晚期结构域，但 EIAV Gag 释放对 TSG101 缺失不敏感，而且 EIAV 颗粒中不含显著水平的 TSG101[147]。另外，丙型肝炎病毒(hepatitis C virus, HCV)在缺乏明确的晚期结构域基序的情况下，HCV 的 NS2 蛋白中 k63 连接的聚泛素化赖氨酸残基与 HRS 泛素相互作用基序结合以促进组装[95]。相比之下，马传染性贫血病毒(EIAV)的 YPDL L 结构域显然是独特的，它能够分别与 AP-2 接头蛋白复合体的 mu2 亚基和 Alix 蛋白相互作用[150]。

目前，虽然许多病毒复制依赖于宿主 ESCRT 系统出芽，然而流感病毒的出芽被认为是独立于 ESCRT 的，Rossman 等[151]发现流感病毒 M2 蛋白介导了出芽的最后步骤，绕过了对宿主 ESCRT 蛋白的需要。另外，副黏病毒 M 蛋白介导出芽的机制与逆转录病毒 Gag 蛋白类似[52]。然而，副黏病毒通常缺少标准的病毒晚期结构域，这就使 M 蛋白出芽机制的研究陷入了瓶颈。尽管目前在新城疫病毒(newcastle disease virus, NDV)和副流感病毒(parainfluenza virus 5, PIV5)中发现了一种晚期结构域类似序列 FPIV，敲除后影响病毒增殖[152]。但是，该序列与常见晚期结构域同源性差异较大，并且没有数据支持证实其对 E3 存在募集作用。缺少标准的病毒晚期结构域的情况下，副黏病毒 M 蛋白如何被泛素化，是否同样募集宿主 ESCRT 系统仍不清楚。目前，副黏病毒 M 蛋白尚未有与出

芽直接相关的泛素化位点的报道，本实验室前期研究发现，副黏病毒NDV的M蛋白存在多个泛素化位点[153]，并且首次鉴定了其中一个位于M蛋白NLS的泛素化位点K247[153-155]，而且NDV的M蛋白泛素化修饰水平影响病毒粒子释放[153]，但NEDD4家族E3是否参与副黏病毒M蛋白的泛素化修饰过程仍不清楚。虽然副黏病毒M蛋白缺少PPxY结构或者其他经典的晚期结构域，但是仍然依赖ESCRT系统进行出芽，其机制仍不明晰(图1)[156]。

4 基于ESCRT系统的抗病毒作用

基于现有文献报道(表2)，目前还未能发现不同种类的病毒其晚期结构域基序各自的特点，还有很多病毒尚未能确定其晚期结构域基序。但研究发现，PSAP基序(表2)是多种不同种类病毒的晚期结构域基序之一，这也提示了

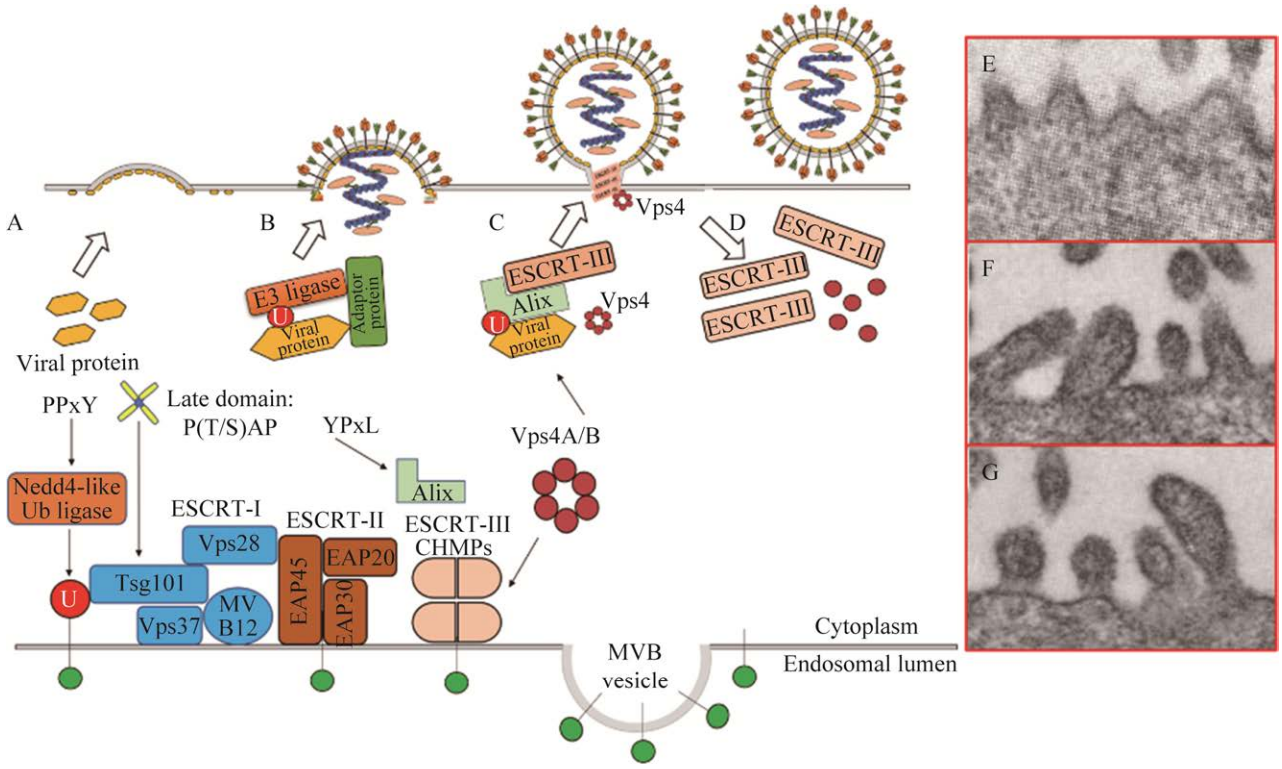

图1 囊膜RNA病毒蛋白泛素化修饰和晚期结构域募集宿主ESCRT系统出芽的模式图 A：病毒蛋白附着于细胞膜后多聚化启动出芽. B：病毒蛋白由E3泛素连接酶介导完成泛素化修饰. C：泛素化的病毒蛋白募集ESCRT-III/Vps4完成出芽. D：ESCRT系统解离、循环再利用；NDV不同出芽时期电镜图片摘自文献[156]. E：出芽泡形成. F：囊泡开始包裹各种组分. G：出芽泡颈部收缩，即将与细胞膜分离

Figure 1 Schematic diagram of ubiquitination modification of envelope RNA viral protein and recruitment of host ESCRT system budding mode by late domain. A: The viral protein is attached to the cell membrane and then polymerized to start budding. B: The ubiquitination of viral protein is mediated by E3 ubiquitin ligase. C: Ubiquitinated viral protein recruited ESCRT-III/Vps4 to complete budding. D: ESCRT system dissociation and recycling; Electron microscopy images of NDV at different budding stages were extracted from literature. E: Formation of budding vesicles. F: The vesicles begin to envelop various components. G: The neck of the budding vesicle contracts and is about to separate from the cell membrane.

表 2　不同病毒的晚期结构域基序

Table 2　Late domain motifs of different viruses

Serial No.	Virus	Species	Late domain
1	HIV-1	Lentivirus	PTAP; YPXnL, LYPX(n)L[142-144]
2	HIV-2	Lentivirus	PTAPP[109]
3	HTLV-1	Deltaretrovirus	PPxY, PSAP[157]
4	HML-2	Betaretrovirus-like	YPXnL, PTAP, PPxY[105]
5	PFV	Spumavirus	PSAP; PPPI; YEIL[100]
6	RSV	Alpharetrovirus	PPxY; YPXnL; PPPY; LYPSL[158]
7	EIAV	Lentivirus	YPXnL, YPDL[147]
8	FIV	Lentivirus	PSAP; LXXL[159]
9	MMTV	Betaretrovirus	PSAP; PLPPV[149]
10	MLV	Gammaretrovirus	PSAP; YPXnL; PPxY[140]
11	PERV	Gammaretrovirus	PPxY; P(F/S)AP[160]
12	M-PMV	Betaretrovirus	YPXnL; PPxY; PSAP[140]
13	EBOV	Ebolavirus	PPxY, PTAP, PPEY[122-125]
14	MARV	Marburgvirus	PSAP, PPPY[161-162]
15	HEV	Hepevirus	PSAP[145,163]
16	JUNV	Arenaviruses	PTAP[103]
17	BFV	Spumavirus	PLPI;YGPL[115]

病毒 PSAP 基序可作为抗毒病毒药物开发的一个有效靶点。另外，抑制病毒释放是一种有效的抗病毒药物开发策略，在 ESCRT 系统中，TSG101 (ESCRT-I)在促进不同包膜病毒高效出芽方面起着公认的重要作用。因此，基于 ESCRT 系统 TSG101 为靶点的抗病毒药物的开发和利用具有广阔前景[62,108]。病毒蛋白 Gag 与 TSG101 的相互作用是 HIV-1 复制周期中至关重要的一步，这种相互作用促使 ESCRT 启动病毒组装/出芽，使其成为抗病毒治疗的潜在靶点[164]，特别是 HIV 保守的晚期结构域基序 PTAP 位于 Gag 的 p6 区域，在 ESCRT 进入病毒出芽位点的过程中发挥核心作用[27,165]。理论上，阻断这种关键的 TSG101-p6 相互作用可以防止病毒出芽，并为新的靶向抗逆转录病毒疗法提供基础。最近的发现支持了这一观点，即抑制 HIV 出芽可以通过干扰 TSG101-Gag 相互作用的环肽来实现[143,166]。鉴于此，Goila 等[167]过表达 TSG101 的 N 端与 Gag 结合的结构域(TSG-5′)来阻断病毒 L 结构域与 TSG101 结合抑制 HIV-1 的出芽，开发类似 TSG-5′的抑制剂，可在不破坏核内体分选的情况下靶向 HIV-1[167]；Demirov 等[26]也采用过表达 TSG101 的 N 端结构域的策略阻断了晚期结构域功能抑制了 HIV-1 的出芽，表明 TSG101 衍生物可以通过阻断病毒出芽，作为 HIV-1 复制的有效和特异性抑制剂；另外，p6 中 PTAP 基序的重复在蛋白酶抑制剂治疗的情况下提高 Gag 的处理效率，从而增强病毒的耐药性，从而在病毒复制中具有选择性优势。这些发现强调了 PTAP 重复和蛋白酶突变在抗逆转录病毒治疗耐药发展中的相互关联作用[165]。

除了 HIV 病毒外，基于 ESCRT 系统 TSG101 为靶点的抗病毒策略对于其他病毒同样有效，例如，Anang 等[28]证实了另外一种环肽(CP11)抑制 ORF3-TSG101 的相互作用使基因 1 型和基因 3 型戊型肝炎病毒 HEV 的释放减少了约 90%；Lu 等[103]利用一种新的化合物 0013 阻断胡宁病毒 Z 蛋白晚期(L)结构域基序 PTAP 与 TSG101

相互作用显著抑制病毒外排；而以吡唑为基础的化合物也可以通过中断细胞 TSG101 与成熟病毒的相互作用，阻止细胞释放粒子的出芽过程来对抗多种包膜病毒[168]，Wan 等[102]研究发现抑制 TSG101 表达可阻断感染性小反刍兽疫病毒 PPRV 的 RNA 分选进入外泌体，成为阻断 PPRV 通过外泌体途径释放和传播的一种有效策略；Mannemuddhu 等[25]发现了一种质子泵抑制剂 tenatoprazole 阻断泛素与 TSG101 的相互作用，可抑制包括疱疹病毒 EBV 在内的几种包膜病毒的产量，另外，埃博拉病毒 EBOV 可以使用独立于 TSG101 使用 Vps (vacuolar protein sorting) 蛋白出芽，且 VPS4 也是线状病毒治疗的潜在靶点[169]。上述这些通过抑制病毒和宿主蛋白之间特定相互作用的小分子疗法可能在抗病毒治疗中具有普遍适用性。

虽然一些逆转录病毒的释放被蛋白酶体抑制剂破坏，但马传染性贫血病毒 EIAV 的出芽不受这些药物的影响，这突出了逆转录病毒 EIAV 的 L 结构域对宿主因子利用具有不同之处，EIAV 对蛋白酶体抑制剂的不敏感性是由 L 结构域本身决定的，与宿主因子无关[135]。而针对其他 ESCRT 亚基蛋白，Rheinemann 等[29]发现了来自猴子和老鼠的 ESCRT-III蛋白 CHMP3 的逆转座子的独立进化，RetroCHMP3 在不阻止胞质分裂的情况下阻止包膜病毒的出芽，其可成为 ESCRT 依赖性病毒出芽的广泛、有效的抑制剂。值得注意的是，retroCHMP3 蛋白修饰 ESCRT 活性，而不针对病毒蛋白本身，比其他直接抑制病毒复制的抗病毒蛋白更能抵抗病毒的反适应，同时，这些 retroCHMP3 蛋白已经进化到在脱落过程中免除了细胞 ESCRT 功能，因此可以专门对抗病毒对 ESCRT 途径的劫持[30]。

5 结论

病毒是专门寄生于细胞内的病原体，它们通过晚期结构域基序招募宿主 ESCRT 系统来最大限度地促进病毒内吞、运输、复制、出芽以及外排[21-24]。ESCRT 系统是一把双刃剑；其广泛参与多种细胞生理过程，对于细胞正常功能的发挥具有重要作用，然而，其容易被病毒劫持利用成为促进病毒复制的“帮凶”，因此，在不影响 ESCRT 系统正常生理功能的前提下，开发抑制病毒晚期结构域基序与 ESCRT 亚基蛋白之间特定相互作用的小分子抑制剂可能是一种有效的抗病毒策略。

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