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# 非经典蛋白分泌在病原体感染中的机制与作用

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**摘 要**:非经典蛋白分泌(unconventional protein secretion, UcPS)是指独立于内质网-高尔基体经典分泌通路的蛋白质释放方式,主要包括直接跨质膜转运、ABC转运体介导的外排、借助囊泡运输的分泌及高尔基体旁路途径。经非经典途径分泌的蛋白质可执行信号转导、免疫调控及与其胞内功能不同的“兼性”活性,参与炎症反应、神经退行性疾病及肿瘤等病理过程。近年来研究发现,UcPS在病原体感染中具有重要作用:病原体与宿主细胞均可利用该途径分泌效应因子或免疫分子,进而影响感染建立、免疫逃逸及宿主防御。UcPS的调控与多类感染性疾病的发生、进展密切相关。文中系统综述UcPS的类型及分子机制,重点探讨其在病原体-宿主互作中的功能及作用机制。

**关键词**:非经典蛋白分泌;病原体感染;病原体-宿主互作;免疫调节
**分类号**:(中图)Q51;R37 **文献标志码**:A

蛋白分泌是细胞将合成的蛋白精准递送至胞外或细胞膜的过程,对细胞通讯、免疫防御及酶释放等生命活动至关重要,是多细胞生物维持稳态与功能整合的分子基础[1-2]。在经典分泌途径中,分泌蛋白通常携带信号肽(signal peptide),该信号序列被信号识别颗粒(signal recognition particle, SRP)识别,引导多肽链通过SEC61易位子转位至内质网(endoplasmic reticulum, ER)腔。随后信号肽被切除,蛋白经历折叠与初步糖基化修饰,在ER出口位点(ER exit sites, ERES)被分选进入COPⅡ囊泡,转运至内质网-高尔基体中间区室(ER-Golgi intermediate compartment, ERGIC),再经COPⅠ囊泡递送至高尔基体(Golgi apparatus),进一步修饰后,通过囊泡转运至质膜后释放到胞外[3-5](图1)。

近年来研究发现,部分蛋白可不依赖经典ER-Golgi通路,通过非经典蛋白分泌(unconventional protein secretion, UcPS)途径释放。这类蛋白通常缺乏信号肽,其分泌机制主要包括3种模式(图1):直接跨质膜转运(Ⅰ型);ATP结合盒式蛋白(ATP-binding cassette, ABC)转运体介导的外排(Ⅱ型);囊泡运输途径(Ⅲ型)[6]。此外,某些含信号肽或跨膜结构域的蛋白在进入内质网后,也可绕过高尔基体直接到达细胞膜,该途径被称为高尔基体旁路分泌途径(Ⅳ型)[6](图1)。非经典分泌在酵母、植物、果蝇、哺乳动物等多种生物体内广泛存在,显示出进化保守性。蛋白通过非经典途径分泌的意义在于:部分蛋白需避免进入ER-Golgi腔内被修饰,以维持其活性[7-8];而部分蛋白在胞质中仍具有重要功能[9-10]。此外,在氧化应激、营养缺乏或病原体刺激等条件下,经典分泌途径功能可能受限,非经典分泌可作为代偿机制释放关键分子,以维持细胞稳态。

随着非经典分泌相关蛋白谱的扩展,其在炎症反应、神经退行性疾病及肿瘤微环境调控中的病理意义日益受到关注[11]。本文系统综述非经典分泌的分子机制,并重点探讨其在病原体感染过程中的双重作用:一方面,宿主通过非经典途径分泌细胞因子及效应分子,以增强抗感染防御反应;另一方

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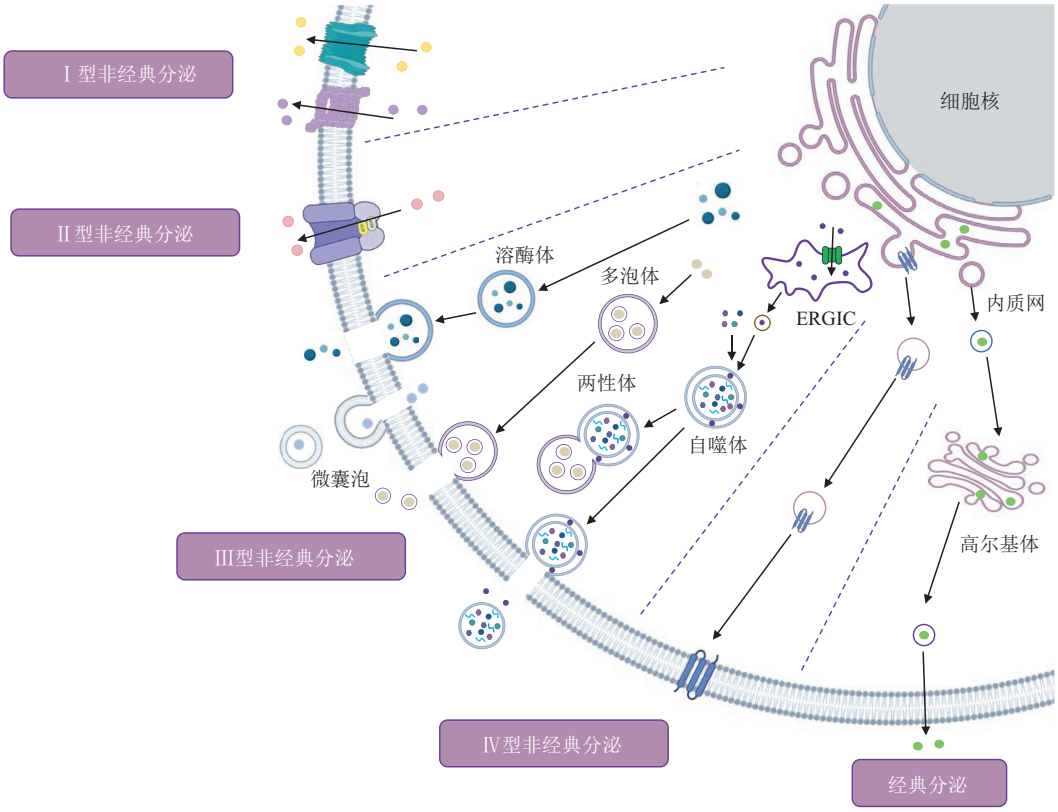



**图1 蛋白质分泌途径**

面,病原体则可"劫持"宿主的非经典分泌途径释放毒力因子,进而促进感染进程。

## 1 非经典蛋白分泌途径的分类与分子机制

### 1.1 直接跨质膜转运途径(Ⅰ型UcPS)

Ⅰ型非经典分泌是指缺乏信号肽的胞质蛋白直接跨越质膜释放至胞外的过程。在哺乳动物细胞中,该过程依赖质膜瞬时形成的亲水孔道,此孔道可由分泌蛋白自身寡聚化或其他成孔蛋白介导形成。代表性分泌蛋白包括成纤维细胞生长因子-2(FGF2)[12]、HIV转录反式激活蛋白(HIV-Tat)[13-14]、白细胞介素-1β(IL-1β)[15-16]、微管相关蛋白Tau[17-18]以及钙卫蛋白S100A8/A9[19]等。

对FGF2分泌机制的研究最为深入。首先,FGF2通过与$Na^+/K^+$-ATP酶(ATP1A1)结合被招募至质膜胞质侧;随后,在Tec激酶的作用下发生磷酸化,使其表面碱性氨基酸簇与质膜内叶的磷脂酰肌醇-4,5-二磷酸(PI(4,5)$P_2$)高亲和力结合,驱动FGF2寡聚化并垂直插入脂质双分子层,形成亲水性跨膜孔道,从而实现外排。释放后的FGF2被细胞表面的硫酸乙酰肝素蛋白聚糖(HSPG)捕获,介导局部旁分泌信号传递[12,20]。胆固醇正向调节该过程,通过增强FGF2与PI(4,5)$P_2$的结合及膜张力促进孔道形成[21]。HIV-Tat亦采用类似机制分泌。

另一个典型蛋白是IL-1β。但与FGF2不同,IL-1β无法通过自身寡聚形成孔道,其跨越质膜依赖于焦孔素D(Gasdermin D, GSDMD)[15-16]。炎性小体激活后,Caspase-1切割pro-IL-1β生成成熟的mIL-1β,并剪切GSDMD生成其N端片段(GSDMD-N)。GSDMD-N与PI(4,5)$P_2$结合后寡聚,形成孔径为10~20 nm的跨膜通道,介导mIL-1β外排。尽管GSDMD在质膜上成孔通常导致细胞焦亡[22],但Kagan J C实验室发现,在超活化巨噬细胞中,GSDMD-N孔道介导mIL-1β释放的同时,细胞仍能保持存活[15],这一现象部分归因于ESCRT复合物介导的膜修复机制[23]。这表明GSDMD介导的分泌是一个主动且受调控的过程。

### 1.2 ABC转运体介导的分泌途径(Ⅱ型UcPS)

Ⅱ型非经典分泌途径依赖ABC转运体介导蛋白质的跨膜外排。ABC转运体作为广泛存在于原核与真核生物中的跨膜蛋白超家族,通过ATP结合与水解驱动其构象变化,调控底物通道的开放与关闭,实现能量依赖的主动转运。该途径相关研究较少,目前仅有少数底物被鉴定,包括酿酒酵母的交配信息素α因子(mating hormone α-factor 1, MFA1)和利什曼原虫的亲水乙酰表面蛋白B[24-25]。

MFA1基因编码的前体肽缺乏N端信号肽，经C端CAAX基序异戊烯化、羧甲基化及蛋白酶切割后，最终生成12个氨基酸的成熟α因子。成熟α因子定位于质膜处，通过ABC转运体Ste6直接外排至胞外，完成细胞间信号传递[24]。哺乳动物中，热休克蛋白Hsp70的非经典分泌也与ABC转运体相关；热休克后Hsp70可从完整细胞释放，ABC转运体抑制剂格列苯脲可抑制其分泌[26]。

### 1.3　借助囊泡结构的分泌途径（Ⅲ型UcPS）

Ⅲ型非经典分泌通过将可溶性胞质蛋白选择性包裹进膜性细胞器，借助囊泡运输及膜融合过程实现其胞外释放。该途径涉及的膜结构包括晚期内体/多泡体（multivesicular bodies，MVBs）、分泌型溶酶体、分泌型自噬体、ERGIC以及微囊泡（microvesicles，MVs）等[20,27-28]。Ⅲ型非经典分泌的复杂性不仅体现在其涉及的细胞器种类多样，更在于其精细的调控网络。细胞可依据生理状态与环境信号，灵活启动特定分泌通路，促进目标蛋白释放[29-30]。例如，应激条件下，某些分泌蛋白可通过与特定分子伴侣或转运因子相互作用，被定向装载至相应囊泡中[28,31-32]。

**1.3.1**　*内吞-溶酶体系统介导的分泌*　晚期内体/多泡体（MVB）由早期内体成熟形成，内体膜内陷生成腔内小泡（intraluminal vesicles，ILVs）。胞质蛋白可通过3种模式进入ILVs：ESCRT-0/Ⅰ/Ⅱ/Ⅲ复合物介导的泛素依赖途径、ALIX-Syntenin参与的非泛素依赖途径以及腔内片段途径。这些ILVs有两种命运：①MVB与液泡或溶酶体融合后，ILVs被降解；②MVB与质膜融合后，ILVs以外泌体形式分泌到胞外[27]。目前调控MVB命运选择的信号机制尚不明确。

传统上溶酶体被视为降解中心，但最新研究发现，其在Rab GTP酶、腔内pH及细胞器互作网络调控下可转化为“分泌型溶酶体”，释放水解酶和信号分子，参与免疫应答、胞外消化及膜修复等过程[33-35]。例如，脂肪酸结合蛋白4（fatty acid binding protein 4，FABP4）缺乏信号肽，经内体进入溶酶体后，最终通过溶酶体-质膜融合分泌[36]。该过程不依赖ESCRT，可能由分子伴侣介导的自噬（chaperone mediated autophagy，CMA）实现：Hsc70识别FABP4的KFERQ样基序，将其递送至溶酶体膜并通过LAMP2A复合物进入腔内[36-39]。

此外，某些错误折叠或易聚集的胞质蛋白（如α-突触核蛋白（α-synuclein）、微管相关蛋白Tau）可通过错误折叠相关蛋白分泌（misfolding-associated protein secretion，MAPS）途径外排[40]。该机制中，错误折叠蛋白先经UFM1修饰，再经USP19去泛素化后决定其分泌命运，随后由DNAJC5介导进入晚期内体/溶酶体，最终通过与质膜融合释放至胞外[40-42]。这一途径有助于清除毒性蛋白聚集物，维持细胞稳态。

**1.3.2**　*自噬体系统介导的分泌*　分泌型自噬（secretory autophagy）指通过自噬体向细胞外分泌物质的过程。该过程可在细胞应激（如饥饿、炎症、氧化应激）以及细胞内运输受阻时被触发[43]。当细胞应激且伴随溶酶体完整性受损时，自噬囊泡内的货物不再运往溶酶体降解，而是被重新导向质膜，将内容物分泌至细胞外环境。自噬体可直接与质膜融合，也可与MVB融合生成两性体（amphisome），再进一步与质膜融合完成外排[44]。该通路涉及多种自噬和内吞调节因子，包括自噬相关基因（Atg）蛋白、SNARE蛋白以及Ras相关蛋白（Rab）等。

以自噬介导的IL-1β分泌为例：在溶酶体损伤情况下，货物受体TRIM16识别IL-1β并与R-SNARE蛋白Sec22b互作，将其募集至LC3-Ⅱ阳性的自噬体膜。随后，Sec22b与质膜上的SNARE蛋白Syntaxin3/4、SNAP23及SNAP29相互作用，通过膜融合将IL-1β分泌至胞外[29]。自噬体亦可先与MVB融合：在HMGB1和Annexin A2的分泌过程中，蛋白首先被包裹至LC3阳性自噬体中，随后与CD63阳性MVB融合为两性体，最终与质膜融合释放。Rab11介导自噬体与MVB融合，Rab8A和Rab27调控两性体与质膜的融合[45-46]。

**1.3.3**　*ERGIC介导的蛋白跨膜转位与分泌*　ERGIC作为内质网与高尔基体之间的关键膜区室，除在经典蛋白质分泌中扮演枢纽角色外，近年研究进一步揭示了其在非经典分泌中的重要功能。定位于ERGIC的膜蛋白TMED10通过寡聚化形成蛋白转运体，介导IL-1β等多种无信号肽蛋白跨膜转运进入ERGIC腔，最终实现胞外释放。这条通路被称为TMED10介导的非经典分泌（TMED10-channelled UcPS，THU）[47]。在这一过程中，定位于ERGIC的小GTP酶Rab蛋白也发挥关键调控作用：Rab1促进TMED10寡聚化及分泌货物的跨膜转运；Rab2调控ERGIC的功能分区，通过与马达蛋白KIF5b协同作用，将TMED10从ERGIC经典分泌区分离，形成专门负责非经典分泌的功能区[48]。尽管非经典分泌货物蛋白如何从ERGIC绕过高尔基体目前尚不明确，但现有证据提示其可能与Atg8

修饰(Atg8ylation)密切相关[29,49-50]。ERGIC膜能够触发Atg8ylation[51],并产生Atg8ylation修饰的囊泡以促进自噬体形成[52]。因此,ERGIC介导的非经典分泌下游路径极可能导向分泌型自噬,同时也存在与内吞-溶酶体系统相耦联的可能。

**1.3.4** *微囊泡介导的分泌* 微囊泡(MVs)是细胞通过质膜直接向外"出芽"形成的胞外囊泡,直径约100~1 000 nm,可携带蛋白质、脂质及核酸等生物活性分子,参与细胞间通讯。与MVB-外泌体系统相比,MVs的生成更为迅速直接。例如,单核细胞可在数秒内通过MVs脱落瞬时释放成熟IL-1$\beta$,且该过程不依赖细胞死亡[53]。

目前的研究提出了几种MVs形成的模型。其一为"经典微囊泡"模型:在$Ca^{2+}$信号触发下,细胞骨架解聚,磷脂酰丝氨酸外翻,质膜向外隆起,随后经MLCK激活和肌动蛋白-肌球蛋白收缩,最终导致膜断裂并释放囊泡;该过程可由Arf6或RhoA-ROCK信号通路激活[10,27]。其二为ARMM(ARRDC1-mediated microvesicles)模型:通过ARRDC1将TSG101招募到质膜上,进而招募ESCRT-Ⅲ复合物,使质膜向外内陷,最终由Vps4介导膜断裂,完成囊泡脱落[27,54]。

### 1.4 高尔基体旁路分泌途径(Ⅳ型UcPS)

在内质网应激或机械拉伸等细胞应激条件下,部分含信号肽或跨膜结构域的蛋白可绕过经典ER-Golgi途径,直接由ER转运至质膜,该过程被归类为Ⅳ型非经典分泌[6]。典型的Ⅳ型UcPS底物包括囊性纤维化跨膜传导调节因子(cystic fibrosis transmembrane conductance regulator, CFTR)[55]和阴离子交换蛋白Pendrin[56]。二者的致病突变体CFTR-ΔF508和Pendrin-H723R易发生错误折叠并滞留于ER,在内质网应激激活IRE1$\alpha$-XBP1信号轴后,可通过两种途径选择性外排[57]:(1)GRASP55依赖途径:在静息状态下,GRASP55以二聚体形式锚定于高尔基体,内质网应激诱导其磷酸化后,GRASP55通过PDZ1结构域识别CFTR的PDZ基序,将其包装进非COPⅡ依赖性囊泡;(2)HSP70-DNAJC14通路:该复合物可招募未折叠的Pendrin及损伤相关分子HMGB1,并将其共同装载进囊泡[58]。随后,这些货物可能经由Rab8与Rab11等小GTP酶协助运输[59],并在SNARE复合物介导下实现囊泡与质膜融合,最终将目标蛋白定位至细胞膜,参与离子稳态维持。TMED家族蛋白同样参与Ⅳ型非经典分泌途径:TMED3负责识别滞留于内质网的膜蛋白,随后由TMED2/3/9/10复合体介导其转运过程[60-61]。

综上所述,非经典蛋白质分泌可根据货物特征、跨膜转运方式及最终定位分为4类途径(图1):Ⅰ型通过直接跨质膜转运实现蛋白外排;Ⅱ型依赖ABC转运体介导胞质蛋白的主动释放;Ⅲ型借助ERGIC、多泡体、自噬体及分泌型溶酶体等膜性细胞器完成选择性包装与分泌;Ⅳ型则使部分膜蛋白在应激状态下绕过高尔基体,直接由内质网转运并嵌入质膜。4种非经典分泌途径在分子机制上各具特征,但在细胞应激环境下往往并行协作,共同构成维持蛋白稳态与调控胞外信号传递的重要分泌系统。

## 2 非经典蛋白分泌途径在病原体感染中的双重角色

在应激条件下,非经典蛋白分泌系统常被激活,其中病原体感染是极为重要的诱因之一。随着研究的深入,其在感染过程中的双重作用日益明确:一方面,非经典分泌可促进警报素释放并增强抗原呈递,进而激活宿主免疫反应,提升对病原体的识别与清除能力;另一方面,病原体也可劫持该途径,以逃避免疫监视并促进自身复制与扩散。因此,深入探索非经典分泌途径在病原体感染中的作用,不仅有助于揭示宿主-病原体互作的分子机制,也将为新型抗感染策略的研发提供重要理论支撑。

### 2.1 非经典分泌介导的抗感染作用

在病原体感染过程中,宿主细胞会激活非经典分泌系统以抵御入侵。当模式识别受体(PRRs)识别病原体相关分子模式(PAMPs)后,下游信号通路被激活,促使干扰素、白细胞介素等先天免疫及炎症介质表达[62]。同时,炎性小体的激活进一步驱动IL-1$\beta$等非经典分泌炎症因子释放[15,63];此外,HMGB1也经非经典途径释放,作为损伤相关分子模式(DAMP)与晚期糖基化终产物受体(RAGE)等结合,增强促炎细胞因子信号[45,64]。这些非经典分泌因子有助于募集免疫细胞,引发强烈的炎症反应,从而有效对抗感染。

除可溶性炎症介质外,细胞内囊泡系统也参与抗病原体免疫应答。自噬作为真核细胞中高度保守的降解机制,不仅维持胞内稳态,还与先天免疫及炎症反应密切相关。它通过形成自噬体选择性包裹靶标(病毒颗粒或病原体),并与溶酶体融合实现内容物降解[65-66]。在病毒刺突蛋白被干扰素刺激基因(ISG)产物识别或细菌被Toll样受体(TLR)识别时,降解型自噬被激活,借助自噬体-溶酶体途径清除病原体[67-69]。自噬还参与抗原加工,协助启动

适应性免疫：宿主细胞可通过自噬将抗原递送至溶酶体，并装载至MHC Ⅱ类分子，从而激活$CD4^+$ T细胞[70]。例如，在树突状细胞中，自噬可处理HIV-1病毒的Gag蛋白，将其呈递于MHC Ⅱ分子，有效激活特异性$CD4^+$ T细胞应答[71]。此外，细菌感染还会显著促进外泌体等细胞外囊泡的分泌。这些囊泡能够携带抗菌肽、微生物抗原及功能性RNA，在细胞间传递信息，协同调控先天性及适应性免疫反应[72-74]。

综上所述，非经典分泌系统通过释放警报素与细胞因子、呈递抗原及介导细胞间通讯，将病原体感知、炎症放大与免疫调节等多个免疫环节紧密联结，构成关键的多维调控网络，在抗感染免疫中扮演核心角色。

### 2.2　非经典分泌介导的促感染作用

**2.2.1**　*病毒*　许多无信号肽的胞质蛋白可通过非经典分泌途径释放，而在病毒感染过程中，该途经常被病毒“劫持”，由宿主的防御机制逆转为促进病毒复制与致病的重要工具（表1）。

首先，病毒利用UcPS途径分泌自身蛋白以增强感染能力。例如，HIV的转录反式激活因子Tat可通过Ⅰ型UcPS途径释放，其过程依赖$PI(4,5)P_2$介导的质膜寡聚成孔及HSPG参与[14,75]。胞外Tat（eTat）能上调$CD4^+$ T细胞表面HIV-1共受体CXCR4和CCR5的表达，促进病毒感染[76-77]；同时触发淋巴细胞、单核细胞和巨噬细胞产生IL-10等免疫抑制因子，形成免疫抑制微环境[77-78]。在SARS-CoV-2感染中，病毒3CL蛋白酶同样经Ⅰ型UcPS途径分泌至胞外，通过切割IFN-λ1削弱STAT1信号以逃避免疫反应；同时切割GSDMD使其失活以对抗细胞焦亡，从而兼顾病毒扩散与宿主细胞存活[79]（图2）。此外，在内质网应激条件下，SARS-CoV-2的S蛋白可被TMED3识别，并经由TMED2/3/9/10复合体介导，绕过高尔基体直接靶向质膜（图2）；沉默TMED复合体成员可使病毒滴度显著下降约90%[61]。SARS-CoV-2的ORF8蛋白可通过经典分泌和Ⅲ型UcPS途径分泌，非经典途径分泌的ORF8不发生糖基化，可与IL-17RA结合，激活NF-κB信号通路并加剧细胞因子风暴（图2），敲除ORF8可显著减轻动物肺部病变[7]。除上述病毒外，HIV的基质蛋白p17[80-81]、单纯疱疹病毒的VP22蛋白[82-83]、埃博拉病毒的基质蛋白VP40[84]、人类T细胞白血病病毒Ⅰ型（HTLV-Ⅰ）的Tax[85-86]、诺如病毒的NS1蛋白等[87-88]，也被证实可通过非经典分泌途径释放，参与病毒的致病过程。

**表1　通过非经典分泌途径释放的病毒蛋白**

| 病毒 | 蛋白质名称 | 分泌途径 | 生理意义 | 参考文献 |
|---|---|---|---|---|
| HIV | Tat | Ⅰ型 | 促进HIV潜伏库的建立与维持 | [13-14] |
| | p17 | Ⅰ型 | 诱导单核细胞的黏附和迁移，可能参与了HIV-1对免疫系统的干扰 | [80-81] |
| | ORF8 | Ⅲ型 | 促进细胞因子风暴 | [7,31] |
| SARS-CoV-2 | 3CL | Ⅰ型 | 促进病毒感染；限制宿主细胞死亡 | [79] |
| | S | Ⅳ型 | 诱导机体免疫反应 | [61] |
| Herpes virus | VP22 | 未知 | 可能影响病毒增殖 | [82-83] |
| Ebola virus | VP40 | 未知 | 可能影响免疫细胞 | [84] |
| HTLV-1 | Tax | Ⅲ型 | 刺激免疫系统引起过度炎症 | [85-86] |
| Norovirus | NS1 | Ⅰ型 | 抑制干扰素-λ（IFN-λ）介导的抗病毒免疫反应 | [87-88] |

其次，病毒劫持或重塑宿主膜系统以促进病毒粒子的分泌。一方面，病毒阻断自身被降解：塞内卡谷病毒（Seneca Valley Virus，SVV）的3C蛋白酶可切割自噬受体OPTN，削弱其功能；狂犬病毒（Rabies Virus）的M蛋白则阻止自噬体与溶酶体融合，从而促进病毒出芽[79,89-90]。另一方面，病毒利用内膜系统构建复制与释放平台：β-冠状病毒通过溶酶体排出病毒颗粒，该过程受Arl8b调控，并可被Rab7 GTPase竞争性抑制剂阻断[91-92]；SARS-CoV-2的ORF3a通过破坏溶酶体酸化抑制降解，借助关键残基Ser171与Trp193招募BORC-ARL8b复合体，协同SNARE机制驱动溶酶体向质膜运输，促进病毒释放[91,93-94]（图2）。病毒还可劫持微囊泡系统：HIV的Gag蛋白和埃博拉病毒的VP40通过模拟ESCRT结合位点，招募ESCRT蛋白形成微囊泡作为病毒释放载体[95-96]；HSV-1感染的少突胶质细胞亦可释放包裹完整病毒颗粒的微囊泡[97]。

最后,病毒通过重塑宿主细胞的非经典分泌通路,加剧炎症反应与重症进展。在SARS-CoV-2、SARS-CoV及MERS-CoV等重症感染中,炎症因子分泌失衡可诱发细胞因子风暴,导致多器官衰竭[63,98-99]。冠状病毒包膜蛋白E可通过激活TMED10介导的非经典分泌,促进IL-1β释放(图2),加剧肺部炎症[63]。同时,冠状病毒可激活炎性小体[100-101],活化的Caspase-1同时切割GSDMD及IL-1β前体,GSDMD-N端成孔进而介导mIL-1β跨膜释放。

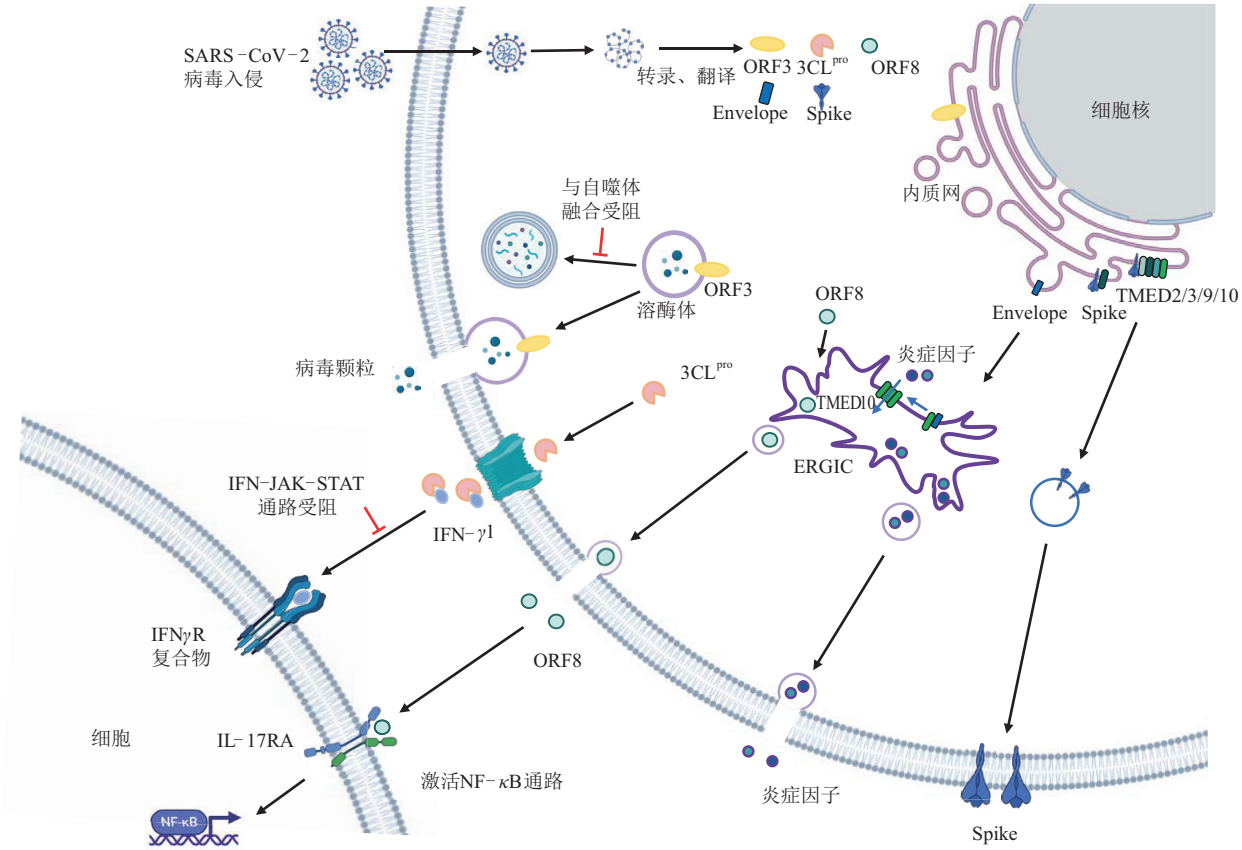



**图2 SARS-CoV-2通过非经典分泌途径介导的感染与过度炎症机制**

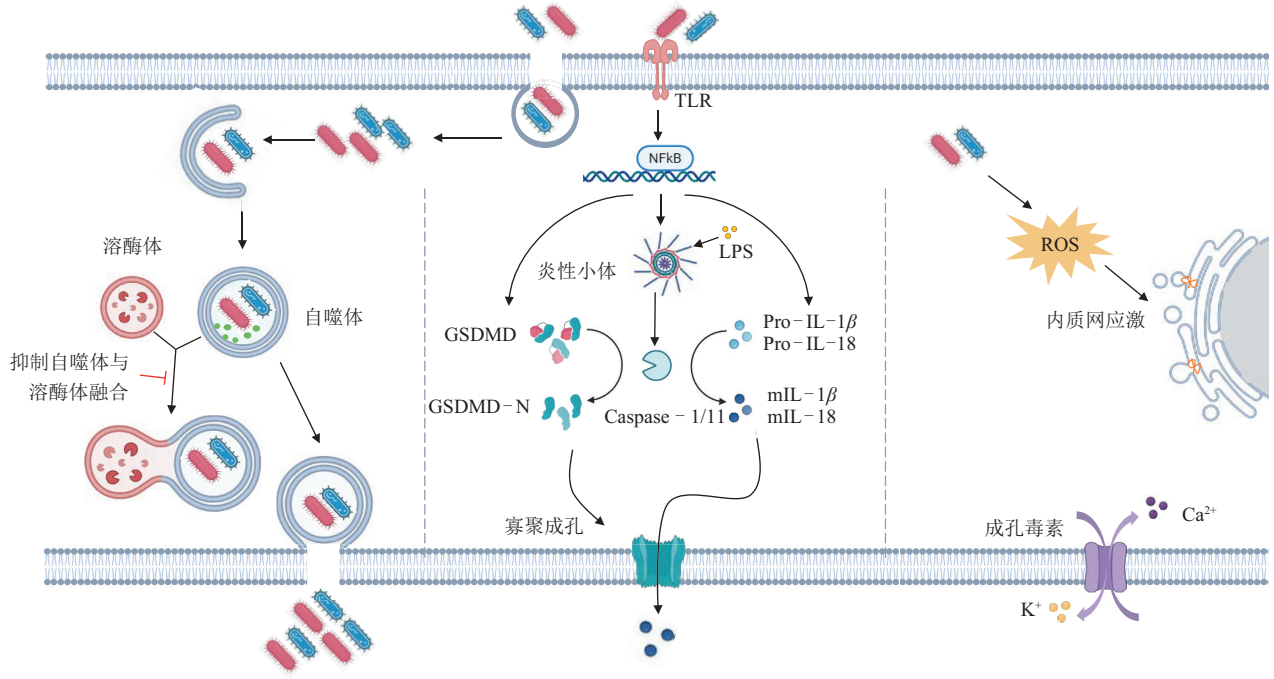
**2.2.2 细菌** 在宿主与病原菌的长期博弈中,细菌进化出多种策略,通过主动抑制降解型自噬、激活炎性小体及改变宿主细胞内微环境,调控宿主细胞非经典分泌系统,为自身生存与增殖创造有利条件(图3)。

首先,多种病原菌能够主动抑制宿主的降解型自噬,以维持其胞内生存。以沙门氏菌(*Salmonella*)和结核分枝杆菌(*Mycobacterium tuberculosis*)为代表的胞内病原菌,通过向宿主细胞质注入效应蛋白靶向自噬通路:沙门氏菌分泌的SopF蛋白可修饰自噬体膜上的V-ATP酶,阻断自噬体与溶酶体的识别与对接,有效抑制二者融合[102];结核分枝杆菌产生的脂质磷酸酶SapM则通过水解PI3P,阻碍自噬体与溶酶体融合[103]。此类对降解型自噬的抑制不仅为细菌提供了安全的胞内复制环境,也可能促进细菌的释放与扩散。

其次,部分细菌能够诱导宿主启动非经典分泌通路,释放炎症介质。例如,金黄色葡萄球菌(*Staphylococcus aureus*)和福氏志贺氏菌(*Shigella flexneri*)通过其病原相关分子模式或毒素激活炎性小体,促进IL-1β、IL-18的成熟及Gasdermin D(GSDMD)切割[104-106]。GSDMD在细胞膜上成孔,介导这些炎症因子快速释放,引发强烈炎症反应[107]。该反应虽有助于宿主初期防御,但过度炎症可导致组织损伤与免疫资源耗竭,反而有利于细菌扩散与持续感染。

最后,细菌感染所致的宿主细胞内微环境改变,也会间接干扰非经典分泌。细菌毒素或孔道蛋白常引起细胞膜通透性变化,导致钾离子外流、钙离子内流等离子动态失衡[108-111]。钙离子作为关键第二信使,可调控囊泡运输、细胞骨架重排及信号通路激活,进而影响非经典分泌过程中膜泡与质膜的融合效率;同时,细菌感染引发的内质网应激与氧化应激等反应,也可能系统性改变非经典分泌途径的活性。

**2.2.3 寄生虫** 寄生虫不仅能够干扰宿主细胞的非经典分泌系统,还可主动分泌自身缺乏信号肽的蛋白,协同促进感染的建立与进展(表2)。




（a）　抑制宿主细胞降解型自噬　　（b）　激活宿主细胞炎症小体　　（c）　改变宿主细胞内微环境

**图 3　细菌调控宿主非经典分泌通路的策略与效应**

**表 2　寄生虫中的非经典分泌蛋白及其功能**

| 寄生虫 | 蛋白质名称 | 分泌途径 | 功能转变 | 生理意义 | 参考文献 |
|---|---|---|---|---|---|
| 贾第虫属、内阿米巴属 | 烯醇化酶（Enolase） | 未知 | 糖酵解酶→毒力因子 | 作为毒力因子，定位于寄生虫表面，介导宿主黏附与定植，促进持续感染 | [117,119] |
| 滴虫属 | 磷酸丙糖异构酶（TvTIM） | 未知 | 糖酵解酶→毒力因子 | | [120] |
| 内阿米巴属、锥虫属、滴虫属、疟原虫属 | 甘油醛-3-磷酸脱氢酶（GAPDH） | 未知 | 糖酵解酶→毒力因子 | | [120-123] |
| 疟原虫属 | 延伸因子-1α（TEF-1α） | Ⅲ型 | 延伸因子→毒力因子 | 抑制 T 细胞介导的免疫应答 | [124] |
| 利什曼原虫属 | 亲水酰化表面蛋白 B（HASPB） | Ⅱ型 | 寄生虫传播→毒力因子 | 参与宿主适应与侵袭过程 | [25,125-127] |

寄生虫感染可激活炎性小体并调节细胞外囊泡的分泌。例如，弓形虫感染可以激活宿主细胞的 NLRP1 和 NLRP3 炎性小体，导致 IL-1$\beta$ 和 IL-18 的分泌以及细胞焦亡[112]；而在疟原虫感染中，受侵染的红细胞会释放富含 miRNA-Argonaute 2 蛋白复合物的细胞外囊泡，这些由宿主与寄生虫成分共同构成的囊泡可被内皮细胞摄取，通过 miRNA 介导的基因表达调控影响血管功能，此过程与严重脑型疟疾的病理机制密切相关[113]。

虽然对其分泌机制尚不完全清楚，但目前已鉴定出多种寄生虫的非经典分泌蛋白，包括烯醇化酶（Enolase）、磷酸丙糖异构酶（TvTIM）、甘油醛-3-磷酸脱氢酶（Glyceraldehyde-3-Phosphate Dehydrogenase，GAPDH）、延伸因子-1α（TEF-1α）及亲水酰化表面蛋白 B（HASPB）等[114-115]。这些分泌因子与寄生虫的毒力、宿主定植及免疫逃逸密切相关。

糖酵解酶可通过非经典分泌实现功能转变，由代谢酶转化为毒力因子。烯醇化酶、TvTIM 和 GAPDH 等糖酵解酶可在感染过程中被转运至虫体表面，赋予其新的致病功能。例如，疟原虫动合子表面的烯醇化酶可作为配体识别蚊中肠受体，并协同捕获宿主纤溶酶原，显著增强其侵袭能力[116]；溶组织内阿米巴（*Entamoeba histolytica*）的胞外烯醇化酶则作为毒力因子，协同 Dnmt2 介导的表观调控加剧组织损伤[117-118]；而在贾第鞭毛虫（*Giardia lamblia*）中，该酶能激活纤溶酶原并诱导上皮细胞坏死样死亡[119]。类似地，TvTIM 可定位于滴虫表面，直

接介导寄生虫与宿主细胞的黏附,并通过多种UcPS途径实现分泌[120]。GAPDH也通过非经典途径分泌并锚定于锥虫、疟原虫、滴虫及阿米巴等多种寄生虫表面,参与宿主黏附与持续感染[120-123]。鉴于其关键作用,这类糖酵解酶已成为潜在的抗寄生虫药物靶点。例如,与哺乳动物同源蛋白差异显著的疟原虫GAPDH,因其低交叉反应性而被视为极具前景的亚单位疫苗候选抗原[123]。

除糖酵解酶外,其他非经典分泌蛋白在免疫调节与宿主侵袭中发挥着重要作用。翻译延伸因子-1α(TEF-1α)可借助细胞外囊泡(EVs)分泌至宿主微环境,显著抑制T细胞免疫应答;其缺失会导致疟原虫丧失免疫逃逸能力并被宿主迅速清除[124]。以重组TEF-1α作为免疫原可诱导持久且高特异性的保护性免疫,提示其在疟疾亚单位疫苗开发中的重要价值[124]。此外,亲水酰化表面蛋白B(HASPB)为利什曼原虫特有,其N端乙酰化后可能依赖ABC转运体完成跨膜转运。在感染阶段,HASPB定位于质膜外表面的点状区域,参与宿主适应与侵袭过程,是目前利什曼病疫苗研究中的重要候选抗原[25,125-127]。

## 3 结语与展望

非经典蛋白质分泌是细胞在应激条件下介导无信号肽蛋白分泌或绕过高尔基体途径的关键机制,对维持细胞稳态与应激应答具有核心作用。近年来,非经典分泌领域的研究取得了显著进展,不仅鉴定出大量相关分泌蛋白,还揭示了其受应激类型、细胞器功能及信号通路共同调控的复杂网络。例如,白细胞介素-1β(IL-1β)的分泌可在炎症或饥饿等不同应激状态下,在Ⅰ型与Ⅲ型非经典分泌途径间灵活切换;自噬体和溶酶体也能够在不同信号引导下实现从降解功能向分泌功能的转变。这些发现表明,不同非经典分泌机制之间不仅存在交叉,更构成了一个高度动态的调控体系。深入解析相关蛋白及膜性细胞器的作用机制,将有助于实现对非经典分泌通路的精准调控,进而为疾病干预提供更具选择性的策略。

在宿主与病原体之间长达数百万年的分子军备竞赛中,哺乳动物细胞进化出复杂的免疫防御网络,而病原体则演化出多种策略,以规避、抑制甚至劫持这些防御机制。在这一过程中,非经典分泌表现出显著的“双刃剑”特性:一方面参与宿主的抗感染免疫防御,另一方面也常被病原体劫持,以促进其侵袭与免疫逃逸。例如,病毒可利用非经典分泌增强自身复制与扩散能力,细菌通过分泌效应蛋白或重塑宿主细胞内环境,以创造生存优势,寄生虫则借助自身非经典分泌蛋白介导宿主黏附、组织破坏或免疫抑制。这些研究共同表明,非经典分泌在宿主-病原体互作中处于核心调控地位,其功能导向取决于特定蛋白与信号通路的相互作用模式。因此,筛选并验证关键的非经典分泌蛋白,不仅可为新型抗感染药物的研发提供潜在靶点,也为亚单位疫苗的设计与开发开辟新方向。

然而,非经典分泌的基础研究与临床转化仍面临诸多挑战。首先,该类蛋白通常缺乏传统信号肽或分泌基序,难以通过常规序列分析工具(如BLAST或HMMer)进行有效识别与预测。其次,多数非经典分泌蛋白具有多种分泌途径,在不同细胞类型或病理微环境中可能呈现异质性分泌模式,增加了研究复杂性。此外,非经典分泌蛋白在细胞内、外常执行不同功能,这种“一蛋白多功能”特性进一步加大了对其生物学功能进行实质解析的难度。

未来关于非经典分泌与病原体感染的研究应聚焦以下方向:系统解析不同感染性疾病中的蛋白分泌组特征及非经典分泌的具体作用机制;阐明不同病原体动态调控非经典分泌的分子机制;探索针对非经典分泌通路或关键蛋白的特异性靶向干预策略。通过上述研究,有望深化对非经典分泌分子机制的理解,为感染性疾病、肿瘤、自身免疫疾病等多种疾病的精准治疗提供新思路与新策略。

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# The Mechanisms and Functions of Unconventional Protein Secretion in Pathogen Infection

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**Abstract:** Unconventional protein secretion (UcPS) refers to the release of proteins that occurs independently of the classical endoplasmic reticulum-Golgi secretory pathway. This process primarily involves direct translocate across the plasma membrane, export mediated by ABC transporters, vesicle-mediated secretion and the Golgi-bypass pathway. Proteins secreted via UcPS can engage in signal transduction, immune regulation and "moonlighting" activities that differ from their functions within the cell. These proteins participate in various pathological processes, including inflammatory responses, neurodegenerative diseases and tumors. Recent studies have demonstrated that UcPS plays an important role in pathogen infections, with both pathogens and host cells utilizing this pathway to secrete effector molecules or immune factors, thereby affecting infection establishment, immune evasion and host defense. The regulation of UcPS is closely linked to the onset and progression of various infectious diseases. This article systematically reviews the types and molecular mechanisms of UcPS, emphasizing its functions and mechanisms in pathogen-host interactions.

**Key words:** unconventional protein secretion; pathogen infection; pathogen-host interaction; immune regulation

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