宿主蛋白酶在流感病毒进入阶段的作用研究进展

李 博, 颜海燕, 李玉环*

(中国医学科学院、北京协和医学院医药生物技术研究所, 中国医学科学院抗病毒药物研究重点实验室, 北京 100050)

摘要: 流感病毒血凝素 (hemagglutinin, HA) 是病毒入侵宿主细胞的关键因素, 涉及病毒与靶细胞的结合及膜融合过程。宿主体内的蛋白酶对HA进行裂解和激活, 是病毒识别宿主细胞及启动膜融合的先决条件, 也是病毒感染宿主的必要条件。本文总结了II型跨膜丝氨酸蛋白酶、人类组织激肽释放酶及其他宿主蛋白酶对不同亚型流感病毒HA的蛋白水解激活作用, 并对其作为潜在抗病毒治疗靶点的可能性进行了探讨。

关键词: 血凝素; 宿主细胞蛋白酶; 流感病毒; 膜融合; 抗病毒

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Advances in host protease-mediated influenza virus entry

LI Bo, YAN Hai-yan, LI Yu-huan*

(*CAMS Key Laboratory of Antiviral Drug Research, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*)

Abstract: Influenza virus hemagglutinin (HA) is a key factor in the virus's invasion of host cells, involving the binding of the virus to target cells and the fusion of membranes. The proteolytic cleavage and activation of HA by host proteases are prerequisites for the virus to recognize host cells and initiate membrane fusion, and are also essential for viral infection of the host. This article summarizes the proteolytic activation of different subtypes of influenza virus HA by type II transmembrane serine proteases, human tissue kallikreins, and other host proteases, and discusses their potential as targets for antiviral therapy.

Key words: hemagglutinin; host cell protease; influenza virus; membrane fusion; antiviral

流感病毒属于正黏病毒科, 是具有分段、负义、单链RNA基因组的包膜病毒[1]。流感病毒每年造成约500万例严重感染病例, 导致250 000～500 000人死亡, 对人类健康构成严重威胁[2]。流感病毒根据其核蛋白和基质蛋白的不同, 可以被划分为甲、乙、丙和丁4种类型[3,4], 其中甲型和乙型流感病毒 (influenza A and B virus, IAV/IBV) 是人类季节性流感暴发的主要病原体。IAV/IBV表面包含3种包膜蛋白: 血凝素 (hemagglutinin, HA)、神经氨酸酶 (neuraminidase, NA) 及基质蛋白2 (matrix protein 2, M2)。在病毒颗粒内部存在8个病毒RNA片段, 它们以病毒核糖核蛋白复合物的形式存在, 每个病毒RNA片段都被核蛋白所包裹, 并与3种RNA聚合酶形成复合体[5,6]。IAV根据其表面糖蛋白HA和NA的抗原特征和基因序列的差异, 可以进一步细分为不同的亚型[7]。目前, 自然界中已发现有18种HA亚型 (H1～H18) 和11种NA亚型 (N1～N11)[8]。乙型流感病毒则主要分为B/Victoria和B/Yamagata两个谱系[9]。

流感病毒HA与宿主细胞表面唾液酸聚糖的特异性结合启动感染, 随后通过网格蛋白依赖性途径、网格蛋白和小窝蛋白非依赖性途径以及巨胞饮作用等多种内吞途径进入宿主细胞[10,11]。当病毒通过内吞作用进入宿主细胞后, 病毒包膜上的M2离子通道打开, H^+离子从内体腔室进入病毒粒子内部, 这一酸性环境触发

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*通讯作者 Tel: 86-10-63010984, E-mail: yuhuanlibj@126.com

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HA发生不可逆的构象变化, 导致病毒包膜与内体膜融合[11-13]。流感病毒的HA属于I类病毒融合蛋白, 其前体HA0在细胞内合成, 随后通过内质网、高尔基体以及囊泡分泌途径被运输到细胞质膜[14,15]。未经过裂解的HA0无法响应酸性环境的诱导发生构象变化从而促进膜融合。宿主细胞的蛋白酶可以将HA0裂解为通过二硫键连接的HA1和HA2亚基[16], 其中, HA1亚基的球状结构域携带着与宿主细胞表面唾液酸受体结合的位点, 而HA2亚基则包含驱动膜融合的融合肽片段[17]。因此, 流感病毒入侵宿主细胞的过程, 依赖于宿主蛋白酶对HA蛋白的裂解激活, 这是病毒成功侵入宿主细胞的关键步骤。

1 参与流感病毒血凝素裂解的宿主蛋白酶

流感病毒HA蛋白的裂解位点由特定的氨基酸序列构成, 这一序列的差异性影响了其对宿主细胞中蛋白酶的敏感性。HA0在HA茎区暴露的肽环上的一个特定的精氨酸–甘氨酸肽键处被裂解, 而该肽环的序列和大小在各种病毒株之间表现出多样性。低致病性禽流感 (low pathogenic avian influenza virus, LPAIV) 和季节性人类流感病毒株通常具有一个精氨酸 (arginine, R) 构成的单碱基HA裂解位点, 少数情况下, 该位点由赖氨酸 (lysine, K) 组成。相比之下, 高致病性禽流感 (highly pathogenic avian influenza virus, HPAIV) 病毒则具有多碱基裂解位点R-X-R/K-R[18], 这种结构能够被广泛存在的弗林蛋白酶 (Furin) 或前蛋白转化酶5/6 (proprotein convertases 5/6, PC5/6) 等特异性识别并裂解[19,20]。

多碱基裂解位点主要分为两种类型: 第一种类型是通过连续插入多个碱性氨基酸 (如精氨酸、赖氨酸) 形成一个扩大的切割位点环, 这一特征是HPAIV所特有的, 并且能够被Furin所识别。第二种类型则通过用精氨酸或赖氨酸残基取代单个非碱性氨基酸, 形成二碱基或三碱基的切割基序, 如R-X-X-R或R-X-R-R, 这种裂解位点环的大小与单碱基环相似, 存在于LPAIV中的H9病毒分离株中[21]。

目前, 已鉴定出多种能够参与流感病毒HA裂解的宿主细胞蛋白酶, 包括胰蛋白酶[22]、II型跨膜丝氨酸蛋白酶 (type II transmembrane serine proteases, TTSPs)[23]、人类组织激肽释放酶相关肽酶 (Kallikrein-related peptidases, KLKs)[24]、Furin[20]、类胰蛋白酶Clara[25]、微纤溶酶[26]和因子Xa酶[27]等 (表1)[24,28-38]。由于IAV是季节性流感的主要病原体, 因此本文将从该角度出发, 针对人体中参与IAV HA裂解活化的宿主蛋白酶进行综述。

1.1 II型跨膜丝氨酸蛋白酶 丝氨酸蛋白酶主要存在于真核生物、原核生物及病毒中[39]。TTSPs属于丝氨酸蛋白酶家族成员[40], 主要表达于细胞膜上。在人类中, TTSPs家族包含17个成员, 如跨膜丝氨酸蛋白酶2 (transmembrane serine protease 2, TMPRSSS2)[41]、跨膜丝氨酸蛋白酶4 (transmembrane serine protease 4, TMPRSSS4)[42]、人气道胰蛋白酶样蛋白酶 (human airway trypsin-like protease, HAT/TMPRSS11D)[28]、鳞状细胞癌差异表达基因1 (differentially expressed in squamous cell carcinoma gene 1, DESC1)[34]、跨膜丝氨酸蛋白酶13 (transmembrane serine protease 13, TMPRSSS13/MSPL)[43]、跨膜丝氨酸蛋白酶matriptase

Table 1 Expression and cleavage sites of host proteases in human tissues. TMPRSS2: Transmembrane serine protease 2; TMPRSS4: Transmembrane serine protease 4; TMPRSS11D: Human airway trypsin-like protease; Matriptase: Transmembrane serine protease matriptase; TMPRSS13/MSPL: Transmembrane serine protease 13; DESC1: Differentially expressed in squamous cell carcinoma gene 1; KLK1: Tissue kallikrein-1; KLK5: Kallikrein related peptidase 5; KLK12: Kallikrein related peptidase 12; PC5/6: Proprotein convertases 5/6

Protease	Cleavage site sequence	Expression in human tissue	Reference
TMPRSS2	R↓	Nasal epithelium, trachea, bronchus, lungs (type II lung cells), larynx, tonsils, myocardium, prostate, pancreas, liver, kidney, skin	[28]
TMPRSS4	R↓	Esophagus, lung, small intestine, stomach, colon, bladder, kidney	[29]
TMPRSS11D	R↓	Trachea, bronchus, esophagus, tongue, nasal epithelium, larynx, epiglottis, tonsil, skin, brain	[28]
Matriptase	R/K-X-X/S-R↓	Widely expressed in epithelial tissues: nasal epithelium, trachea, bronchus, salivary glands, esophagus, kidney, small intestine, stomach, prostate, skin, hair follicles	[30-32]
TMPRSS13/MSPL	R/K-K-K-R↓	Lung, brain, kidney, liver, spleen, prostate, pancreas, skin, small intestine, colon, testes, thymus	[33]
DESC1	R↓	Esophagus, prostate, salivary glands, skin, bladder	[34,35]
KLK1	R↓	Colon, kidney, pancreas, salivary glands, skin, small intestine	[36]
KLK5	R↓	Lungs, esophagus, skin, testicles, salivary glands	[24,37]
KLK12	R↓	Colon, duodenum, esophagus, prostate, salivary glands, skin, small intestine, testicles, stomach	[24]
Furin	R-X-R/K-R↓	Widely expressed in various tissue	[38]
PC5/6	R-X-R/K-R↓	Widely expressed in various tissue	[38]

(transmembrane serine protease matriptase, ST14/matriptase)[30]等。TTSPs家族成员具有相同的结构域, 包括N端细胞质结构域、疏水性跨膜结构域、茎区和C端细胞外丝氨酸蛋白酶结构域。C端结构域由催化三联体—组氨酸 (His)、天冬氨酸 (Asp) 和丝氨酸 (Ser) 构成, 它们是胰蛋白酶样丝氨酸蛋白酶催化活性的核心[44]。TTSPs的细胞外部分从茎区开始, 包含11个高度保守的结构域, 有助于TTSPs的激活和与底物的相互作用[23,44]。跨膜丝氨酸蛋白酶不仅可以调节各种肽激素、生长因子、酶、受体的功能[45], 还参与裂解活化一些包膜病毒, 如仙台病毒[46]和流感病毒[28]的表面糖蛋白配体, 启动病毒感染过程。

TTSPs通过裂解IAV HA, 在病毒进入阶段发挥重要作用。Böttcher等[28]证实人源的TMPRSS2和HAT体外能够促进3种血凝素亚型 (H1、H2和H3) 的IAV感染, 并在缺乏外源性胰蛋白酶的情况下, 支持MDCK细胞中IAV的多周期复制。进一步对HA裂解的亚细胞定位进行研究, 发现HA是被位于细胞膜上的TMPRSS2和HAT裂解, 而不是被释放到上清液中的可溶性蛋白酶裂解。其中, TMPRSS2只能裂解细胞内合成的IAV HA, 而HAT可以裂解细胞内合成及细胞表面吸附的IAV HA[47]。Matriptase选择性裂解流感病毒H1亚型中特定毒株的HA, 且支持人呼吸道上皮细胞中IAV的多周期复制, 但不能裂解H2及H3型IAV[31]。此外, 据报道TMPRSS2和HAT还可以激活所有的甲型H9N2毒株, Matriptase仅可激活部分毒株[32]。而人肺组织中表达的TTSPs其他家族成员MSPL和DESC1, 同样具有裂解H1、H2及H3型IAV HA的能力[35]。Laporte等[29]检测了18种人源TTSPs对于H1及H3亚型的HA的裂解作用, 结果同样显示TMPRSS2及HAT可裂解活化甲型H1N1及H3N2流感病毒的HA, TMPRSS4仅限于裂解活化H1N1型的HA, 然而TMPRSS3及TMPRSS6缺乏HA裂解能力, 或许是由于蛋白酶结构域空间呈现的不同所导致的。在TTSPs家族中, TMPRSS2和TMPRSS4不仅在结构域组成上具有高度的相似性, 而且在其蛋白酶结构域的序列上也展现出较高的一致性, 大约在43%～44%之间。因此, 它们对流感病毒HA裂解的特异性一致, 能够识别并切割HA0蛋白的单碱基切割位点, 从而激活流感病毒[48,49]。

除人源的TTSPs之外, 鼠源的TMPRSS13和跨膜丝氨酸蛋白酶1 (transmembrane serine protease 1, TMPRSSS1/Hepsin) 在体外也可以有效地裂解H3亚型的HA[50]。在体内研究中, Hatesuer等[51]发现, 在*Tmprss2*基因敲除 (*Tmprss2*$^{-/-}$) 小鼠模型中, 甲型H1N1流感病毒的传播受到了显著抑制, 肺部病变程度明显降低。*Tmprss2*$^{-/-}$小鼠感染重组H2亚型病毒后, 仅检测到肺部轻微的组织损伤和免疫细胞浸润[52]。可见, TMPRSS2对H1及H2亚型流感病毒在小鼠中的传播和致病性至关重要。在另一项研究中, *Tmprss2*$^{-/-}$小鼠感染甲型H3N2流感病毒, 其复制仅部分受到抑制, 而*Tmprss2*$^{-/-}$、*Tmprss4*$^{-/-}$双敲除小鼠感染后其死亡率显著减少, 体重减轻情况明显好转, 表明TMPRSS2和TMPRSS4对于小鼠中甲型H3N2流感病毒的复制发挥协同调控作用[53]。TTSPs在人类和小鼠中对不同亚型的HA裂解能力存在差异。Bestle等[54]研究了人类和小鼠气道细胞中的TMPRSS2在不同亚型流感病毒中的激活和多周期复制作用, 发现人类气道上皮细胞Calu-3中的TMPRSS2能够裂解H1～H8、H10、H11、H14和H15亚型的流感病毒HA, 而小鼠气道细胞中的TMPRSS2则能够裂解H1、H2、H7和H10亚型的流感病毒HA。并且, 小鼠气道细胞中的H3亚型及Calu-3细胞中的H16亚型流感病毒的激活不依赖于TMPRSS2的活性。

TTSPs不仅裂解活化具有单碱基位点的HA, 还可以裂解具有多碱基氨基酸裂解位点的HPAIV HA。TMPRSS2是甲型H7N9流感病毒小鼠嗜肺性和致病性所必需的宿主因子, TMPRSS2敲除显著抑制流感病毒在小鼠气管、支气管和肺外植体中的复制[55]。此外, MSPL及其剪接变体TMPRSS13位于细胞质膜中, 具有识别裂解R-X-K/R-R和K-X-K/R-R两种基序的HPAIV HA的能力[33]。

1.2　组织激肽释放酶　激肽释放酶同样属于丝氨酸蛋白酶, 根据其理化性质、功能、底物和体内分布不同, 分为两大类: 参与血浆激肽形成的血浆激肽释放酶[56]和参与组织激肽形成的组织激肽释放酶家族[57]。该家族由人类组织激肽释放酶 (tissue kallikrein-1, KLK1) 和14种激肽释放酶相关肽酶 (KLK2～15) 组成[58-61]。KLKs在皮肤、中枢神经系统、胰腺、乳房、前列腺、肾脏等多种组织中表达水平不同[62]。尽管KLKs在结构上具有高度的同源性, 但它们的蛋白水解活性不同。KLK3、KLK7和KLK9具有糜蛋白酶样活性, KLK1、KLK10、KLK11和KLK4具有糜蛋白酶和胰蛋白酶样双重活性, 而其他组织型KLKs具有胰蛋白酶样活性。

KLKs已被确定为流感病毒感染的关键调控因子, 大多数KLKs在呼吸道上皮细胞和气道黏膜中产生[63,64]。气道上皮细胞既是流感病毒的靶细胞, 也是KLKs合成的场所。人呼吸道分泌的KLK5和KLK12具有裂解和激活H1、H2和H3亚型HA的能力。然而, 不同KLKs对不同流感亚型HA的裂解效率存在差异,

其中KLK5能有效裂解H1和H3亚型HA, 而KLK12可裂解H1和H2亚型HA[24]。Magnen团队[37]发现IAV感染可导致人呼吸道上皮细胞中KLK1和KLK5的表达水平增加, 并且人源KLK1和KLK5体外可以裂解部分H1和H3亚型的重组HA, 但只有KLK5促进体内外H3N2型流感病毒的感染。随后, 他们进一步证实小鼠同源蛋白酶KLK5在体内外均不能激活流感病毒[65]。流感病毒感染导致小鼠肺部KLK1的水平升高, 而人激肽释放酶结合蛋白 (human kallistatin, SERPINA4) 的表达水平下降, SERPINA4与KLK1形成复合物并抑制KLK1活性, 在IAV感染前增加小鼠肺部SERPINA4的表达, 可抑制甲型H1N1 (A/WSN/1933) 流感病毒对小鼠的攻击[36]。此外, 另一项研究表明, 鼠源KLK1不仅不能促进甲型H3N2流感病毒的感染, 还在感染的早期阶段发挥抗病毒的作用[66]。

1.3 其他参与流感病毒激活的宿主蛋白酶 除了TTSPs家族和KLKs家族之外, 其他类型的宿主蛋白酶对于IAV HA的裂解活化同样至关重要。膜联蛋白II在甲型H1N1流感病毒 (A/WSN/1933) 的复制过程中介导纤溶酶原的激活, 从而增强病毒在小鼠体内的致病性和嗜神经性[67]。膜联蛋白II同样促进甲型H9N2流感病毒HA蛋白的裂解[68]。类胰蛋白酶Clara被证明可以裂解血凝素并以剂量依赖的方式激活IAV[25]。微纤溶酶可以促进甲型H1N1 (A/WSN/1933)、H3N2 (A/Aichi/2/68) 及H7N7 (A/seal/Massachusetts/1/81) 流感病毒的传染性[26]。因子Xa样蛋白酶则可以在鸡胚中裂解IAV HA0[69]。另一项研究中, Harbig等[50]采用RNA测序技术探究小鼠下气道组织、原代II型肺泡上皮细胞和小鼠肺细胞系MLE-15的蛋白酶表达情况, 结果证实H3型流感病毒HA还可以被鼠源的丝氨酸蛋白酶prostasin激活, 但不能被人源的prostasin裂解激活。Furin和PC5/6是枯草杆菌蛋白酶样丝氨酸蛋白酶家族成员, 在脊椎动物和无脊椎动物细胞中广泛表达, 它们多数位于反面高尔基体网状结构 (*trans*-Golgi network, TGN) 中, 并通过内体系统循环到质膜并返回TGN。它们能够催化TGN及转迁细胞区室中受体、激素、酶原生长因子和细胞表面蛋白的生理激活过程, 并且具有识别流感病毒HA裂解位点的共有序列R-X-K/R-R的能力[19,20,38]。

2 宿主蛋白酶抑制剂在抗流感病毒中的应用

流感病毒HA的裂解激活是流感病毒复制周期中由宿主细胞蛋白酶驱动的重要步骤, 是病毒包膜与内体膜融合及随后流感病毒基因组释放到细胞质的必要条件。随着研究的深入, TTSPs和KLKs等宿主蛋白酶在体内激活流感病毒复制的作用被逐渐揭示, HA裂解位点的氨基酸序列因IAV HA亚型而不同, 但对于每种IAV亚型都高度保守[70]。因此, 开发靶向宿主蛋白酶活性位点的抑制剂, 为广谱抗病毒药物的研发提供了一种新的策略。

Aprotinin是一种从牛肺中纯化的58个氨基酸组成的多肽, 它能够与胰蛋白酶、糜蛋白酶、纤溶酶、激肽释放酶等多种酶发生相互作用从而调节酶的活性。Camostat作为一种广谱丝氨酸蛋白酶抑制剂, 已被证实能有效抑制TMPRSS2的活性。根据文献报道, aprotinin和camostat均能抑制流感病毒在细胞及小鼠中的复制[71,72]。雾化aprotinin (在俄罗斯获批的治疗方法) 被证明可以缩短流感或副流感病毒感染者的症状持续时间[71]。然而, 由于aprotinin是从牛肺中分离出来的, 其反复使用可能增加患者发生超敏反应和过敏反应的风险。丝氨酸蛋白酶抑制剂的安全性很大程度上取决于其与酶的结合是否可逆。Camostat作为一种不可逆的共价结合剂, 在临床治疗其他疾病方面已有应用, 但是仍存在潜在的不良反应[73]。

在抗击SARS-CoV-2的过程中, 科学家们也开发了一些针对TMPRSS2等TTSPs家族成员的抑制剂。Shapira团队[74]设计了一系列拟肽四肽化合物, 发现其对TMPRSS2和相关TTSP有良好的抑制活性, 其中N-0385具有良好的抗COVID-19作用, 被认为是一种具有很高潜力的抗病毒候选药物。通过利用matriptase的晶体结构构建了TMPRSS2的同源模型, 发现N-0385能够与TMPRSS2的催化三联体中的Ser441形成共价键, 从而形成紧密结合的抑制模式。在另一项研究中, Li等[75]发现一种来自链霉菌1647的代谢产物—假四肽omicsynin B4, 它通过抑制TMPRSS2及组织蛋白酶L的活性阻断冠状病毒的感染途径, 并且显示出对流感病毒的良好抑制活性。IAV HA与SARS-CoV-2刺突蛋白在激活机制上具有相似性, 两者都需要宿主细胞表达的蛋白酶来裂解病毒表面蛋白的同源三聚体蛋白, 从而促进病毒进入宿主细胞, 因此这些抑制剂在抗流感病毒治疗中同样具有治疗潜力。但是, 宿主蛋白酶抑制剂作为一种潜在的抗病毒策略, 仍处于研究和开发阶段, 尚未成为主流的临床治疗手段。随着研究的深入, 未来可能会有更多针对宿主蛋白酶的抑制剂进入临床应用 (表2)[71,74-87]。

3 总结与展望

流感病毒的大流行对人类健康及全球经济发展造成重要影响, 尽管疫苗与抗病毒药物的出现在一定程度上抑制了流感病毒的传播, 但是随着病毒的不断变异, 需要更有效的抗流感病毒策略[88]。目前, 针对流感

Table 2　The host protease inhibitors. Serpin E1: Plasminogen activator inhibitor-1; Serpin A1: Alpha1-antitrypsin, alpha1-proteinase inhibitor; Serpin C1: Serine protease inhibitor C1; *α*/*β* -SNAP: Alpha/beta soluble *N*-ethylmaleimide-sensitive factor attachment protein; GBP2/5: Guanylate binding protein 2/5; MARCH8: Membrane-associated ring-CH-type finger 8; SPINK6: Serine proteinase inhibitor Kazal-type 6; BAPA: Benzylsulfonyl-*D*-arginine-proline-4-amidinobenzylamide

Protease inhibitor	Protease	Reference
Aprotinin	HAT, TMPRSS2, TMPRSS4, plasmin, mini plasmin	[71]
N-0385	TMPRSS2, DESC, matriptase	[74]
Omicsynin B4	TMPRSS2	[75]
Serpin E1	HAT, TMPRSS2	[76]
Serpin A1	TMPRSS2	[77]
Serpin C1	TMPRSS2	[78]
α-SNAP, *β*-SNAP	Furin	[79]
GBP2, GBP5	Furin	[80]
MARCH8	Furin	[81]
SPINK6	HAT, KLK5	[82,83]
BAPA	HAT, TMPRSS2	[84]
Camostat	Serine protease inhibitors	[85]
Nafamostat	Serine protease inhibitors	[86]
Abz-Arg-Gln-Asp-Arg (Lys)-H	HAT	[87]

病毒复制过程中的关键靶点, 如流感病毒HA、流感病毒RNA依赖的RNA聚合酶、神经氨酸酶等的抑制剂都得到了极大的发展, 它们在流感病毒吸附、复制及释放等不同阶段有效抑制流感病毒复制。然而, 随着耐药株的出现和药物不良反应问题, 研发新型抗流感病毒药物显得尤为迫切[89,90]。

宿主蛋白酶对流感病毒的结合及膜融合至关重要, TTSPs和KLKs等宿主蛋白酶通过识别特异性的HA裂解位点在LPAIV和HPAIV的激活中起到关键作用, 它们的活性位点区域具有高度的结构同源性, 其中包含催化三联体His57、Asp102和Ser195。除了催化结构域之外, 还存在一些结构多样性的外部位点, 在底物结合和识别中发挥关键作用[70]。并且, HA裂解位点的突变对蛋白酶抑制剂产生耐药性的可能性较小, 因此靶向HA裂解活化的宿主蛋白酶可以作为广谱抗病毒药物研发新路径, 最大程度地减少耐药突变体暴发的可能性。

宿主蛋白酶不仅影响流感病毒复制过程, 还广泛参与调控其他生理活动。因此, 在设计和应用宿主蛋白酶抑制剂时, 需要格外谨慎, 避免可能引发的不良反应。此外, 宿主蛋白酶在流感病毒感染中发挥的作用具有高度选择性, 人和小鼠之间蛋白酶的功能也存在差异, 这提示了研究者利用小鼠作为模型动物探究蛋白酶抑制剂在预防和治疗流感病毒传播方面具有局限性。这种认识有助于研究者更深入地理解宿主蛋白酶在流感病毒复制中的具体作用机制, 并为开发更安全、更有效的抗流感病毒策略提供科学依据。

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