2026, 66(1): 149-169
CSTR: 32112.14.j.AMS.20250587
DOI: 10.13343/j.cnki.wsxb.20250587

微生物学报
Acta Microbiologica Sinica
http://journals.im.ac.cn/actamicrocn

Review 综述

Numb 相关激酶的生理功能及其在病毒感染中的作用

李睿[1#]，蒋艳[1#]，游灵巧[1]，孙悦茵[1]，李佳慧[1]，王玉娥[1,2*]，张龙祥[1*]

1 西南大学 动物医学院，重庆
2 国家生猪技术创新中心，重庆

李睿, 蒋艳, 游灵巧, 孙悦茵, 李佳慧, 王玉娥, 张龙祥．Numb 相关激酶的生理功能及其在病毒感染中的作用[J]．微生物学报, 2026, 66(1): 149-169．
LI Rui, JIANG Yan, YOU Lingqiao, SUN Yueyin, LI Jiahui, WANG Yu'e, ZHANG Longxiang. Numb-associated kinases: physiological functions and roles in viral infection[J]. Acta Microbiologica Sinica, 2026, 66(1): 149-169.

摘　要：Numb 相关激酶(Numb-associated kinases, NAKs)家族是一类在进化上高度保守的丝氨酸/苏氨酸蛋白激酶，由衔接蛋白相关激酶 1 (adaptor-associated kinase 1, AAK1)、细胞周期蛋白 G 相关激酶(cyclin G-associated kinase, GAK)、骨形态发生蛋白 2 诱导激酶(bone morphogenetic protein 2-inducible kinase, BMP2K)和丝氨酸/苏氨酸激酶 16 (serine/threonine kinase 16, STK16)这 4 个成员构成。NAKs 广泛参与调控细胞的内吞、胞内运输、分化、自噬以及信号转导等基本生命活动。近年来，研究发现 NAKs 在多种病毒生命周期的不同阶段，包括入侵、组装、释放以及免疫逃逸等环节均发挥着关键作用。同时，已有针对 NAKs 的小分子抑制剂应用于相关生理性或病毒感染性疾病的临床研究与治疗。本文将系统梳理 NAKs 的主要生理功能及其在病毒感染中的作用，为病毒致病机制研究和以 NAKs 为靶点的新药开发提供参考依据。

关键词：Numb 相关激酶；生理功能；小分子抑制剂；病毒生命周期

资助项目：国家自然科学基金(32302852)；重庆市自然科学基金(CSTB2023NSCQ-MSX0366)；中央高校基本科研业务费专项资金(SWU-KQ22035)；西南大学大学生创新创业训练计划(S202510635265, X202510635250)；重庆市教委科学技术研究项目(KJQN202300224)
This work was supported by the National Natural Science Foundation of China (32302852), the Natural Science Foundation of Chongqing (CSTB2023NSCQ-MSX0366), the Fundamental Research Funds for the Central Universities (SWU-KQ22035), the Southwest University Training Program of Innovation and Entrepreneurship for Undergraduates Project (S202510635265, X202510635250), and the Science and Technology Research Program of Chongqing Municipal Education Commission (KJQN202300224).
[#]These authors contributed equally to this work.
*Corresponding authors. E-mail: ZHANG Longxiang, dyzlx015029@163.com; WANG Yu'e, vetyuewang@163.com
Received: 2025-07-29; Accepted: 2025-09-10; Published online: 2025-09-28

Numb-associated kinases: physiological functions and roles in viral infection

LI Rui[1#], JIANG Yan[1#], YOU Lingqiao[1], SUN Yueyin[1], LI Jiahui[1], WANG Yu'e[1,2*], ZHANG Longxiang[1*]

1 College of Veterinary Medicine, Southwest University, Chongqing, China
2 National Center of Technology Innovation for Pigs, Chongqing, China

Abstract: Numb-associated kinases (NAKs) are a family of evolutionarily conserved serine/threonine kinases, encompassing adaptor-associated kinase 1 (AAK1), cyclin G-associated kinase (GAK), bone morphogenetic protein 2-inducible kinase (BMP2K), and serine/threonine kinase 16 (STK16). NAKs are widely involved in various physiological processes, such as endocytosis, intracellular transport, cell differentiation, autophagy, and signal transduction. In recent years, studies have shown that NAKs play a key role in different life cycle stages including virus entry, assembly, release, and immune escape of various viruses. Furthermore, small-molecule inhibitors targeting NAKs have been applied in clinical research and treatment of related physiological or viral infectious diseases. This article systematically reviews the primary physiological functions of NAKs and their roles in viral infection, aiming to provide a theoretical foundation for elucidating the pathogenic mechanisms of viruses and developing novel therapeutic drugs targeting NAKs.

Keywords: Numb-associated kinases; physiological function; small-molecule inhibitors; virus life cycle

蛋白激酶是存在于生物体内的一大类酶，根据所涉及的蛋白质种类差异，主要分为酪氨酸激酶和丝氨酸/苏氨酸激酶(serine/threonine kinase, STK)两大类。Numb 是一种在进化上保守的多功能蛋白，在细胞命运决定中发挥关键作用，不仅参与细胞内吞、迁移、黏附、分裂等基本细胞活动，还参与蛋白泛素化修饰以及 Notch 等关键信号通路[1]。Numb 相关激酶(Numb-associated kinases, NAKs)因能磷酸化 Numb 蛋白而得名，是一类普遍存在于生物体中的丝氨酸/苏氨酸蛋白激酶，该家族现包括 4 个核心成员：(1) 衔接蛋白相关激酶 1 (adaptor-associated kinase 1, AAK1)；(2) 细胞周期蛋白 G 相关激酶(cyclin G-associated kinase, GAK)；(3) 骨形态发生蛋白 2 诱导激酶(bone morphogenetic protein 2-inducible kinase, BMP2K)，也称 BMP2 诱导激酶(BMP2-inducible kinase, BIKE)；(4) STK16，也称 MPSK1/PKL12/Krct/TSF-1[2] (图 1A)。结构上，NAKs 的 N 端激酶结构域在进化上高度保守，而 C 端的其他结构域差异较大，序列同源性低至 30% 以下[3] (图 1B)。这种"保守头部+多变尾部"的结构特征也决定了其底物的特异性及生理功能的多样性(图 1C，红色区域呈现的为 NAKs 保守的激酶结构域；NAKs 高变区分别以紫色、粉色、蓝色和绿色表示)。NAKs 通过催化底物蛋白丝氨酸/苏氨酸的磷酸化来发挥其调

✉ actamicro@im.ac.cn, ☏ 010-64807516

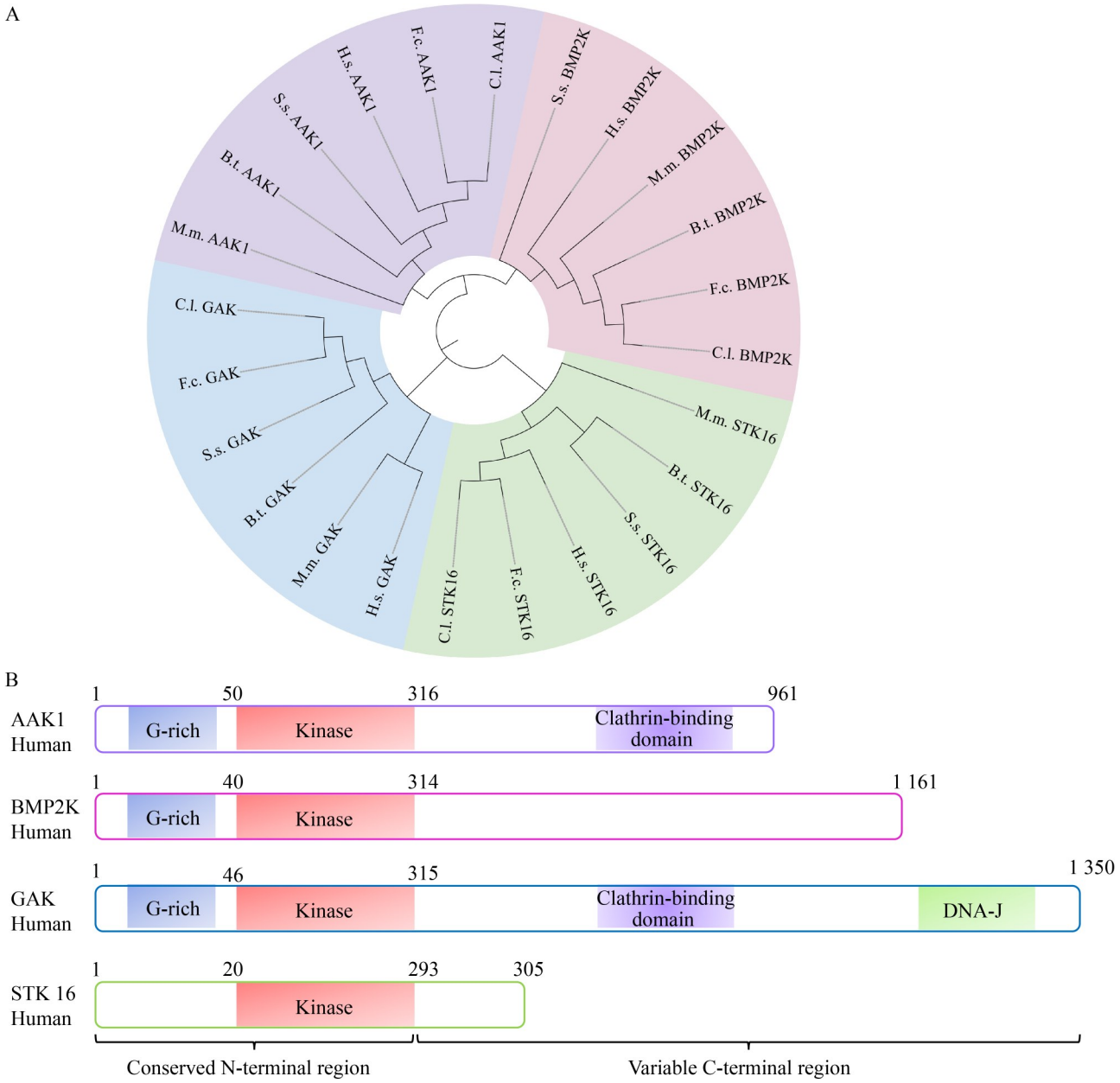
A
C.l. AAK1
F.c. AAK1
H.s. AAK1
S.s. AAK1
B.t. AAK1
M.m. AAK1
S.s. BMP2K
H.s. BMP2K
M.m. BMP2K
B.t. BMP2K
F.c. BMP2K
C.l. BMP2K
C.l. GAK
F.c. GAK
S.s. GAK
B.t. GAK
M.m. GAK
H.s. GAK
M.m. STK16
B.t. STK16
S.s. STK16
H.s. STK16
F.c. STK16
C.l. STK16
B
AAK1
Human
1
50
316
961
G-rich
Kinase
Clathrin-binding domain
BMP2K
Human
1
40
314
1 161
G-rich
Kinase
GAK
Human
1
46
315
1 350
G-rich
Kinase
Clathrin-binding domain
DNA-J
STK 16
Human
1
20
293
305
Kinase
Conserved N-terminal region
Variable C-terminal region
C
AAK1
BMP2K
GAK
STK16

图1 NAKs家族成员的系统发育树和三维结构示意图

Figure 1 Phylogenetic tree and 3D structural schematic of the NAKs family. A: Phylogenetic tree of the NAKs family generated using MEGA 7 software [H. s. AAK1: *Homo sapiens* AAK1 (Gene ID: 22848); H. s. GAK: *Homo sapiens* GAK (2580); H. s. BMP2K: *Homo sapiens* BMP2K (55589); H. s. STK16: *Homo sapiens* STK16 (8576); B.t. AAK1: *Bos taurus* AAK1 (532546); B.t. GAK: *Bos taurus* GAK (511296); B.t. BMP2K: *Bos taurus* BMP2K (505766); B.t. STK16: *Bos taurus* STK16 (521237); S. s. AAK1: *Sus scrofa* AAK1 (110255208); S. s. GAK: *Sus scrofa* GAK (100625047); S. s. BMP2K: *Sus scrofa* BMP2K (100624635); S. s. STK16: *Sus scrofa* STK16 (100153147); M.m. AAK1: *Mus musculus* AAK1 (269774); M.m. GAK: *Mus musculus* GAK (231580); M.m. BMP2K: *Mus musculus* BMP2K (140780); M.m. STK16: *Mus musculus* STK16 (20872); F.c. AAK1: *Felis catus* AAK1 (101094013); F. c. GAK: *Felis catus* GAK (101094018); F. c. BMP2K: *Felis catus* BMP2K (101094669); F.c. STK16: *Felis catus* STK16 (101095674); C.l. AAK1: *Canis lupus familiaris* AAK1 (474625); C.l. GAK: *Canis lupus familiaris* GAK (479133); C.l. BMP2K: *Canis lupus familiaris* BMP2K (487819); C.l. STK16: *Canis lupus familiaris* STK16 (488536)]; B: Domain organization of NAKs [The kinase (red) domain is located at the N-terminal. The length of the region downstream of the kinase domain is variable]; C: 3D structural representations of NAKs members predicted *via* AlphaFold 2 [AAK1 (UniProt ID: Q2M2I8; purple), BMP2K (Q9NSY1; pink), and GAK (O14976; blue) exhibit an N-terminal high G-region (yellow) followed by a kinase domain (red) with variable-length C-terminal regions, whereas STK16 (O75716; green) displays lower molecular weight with its structure primarily consisting of the kinase domain].

控功能。目前已鉴定出多种“NAKs-底物”信号轴，为其功能研究奠定了基础。

研究证实，NAKs 在参与网格蛋白介导的内吞(clathrin-mediated endocytosis, CME)、调控细胞生长发育、参与细胞自噬体形成与成熟以及介导信号转导调控等生理过程中扮演着重要角色[2]。NAKs 功能异常与多种疾病的进展密切相关，如阿尔茨海默病(Alzheimer disease, AD)[4-5]、帕金森病(Parkinson’s disease, PD)[6-7]等神经系统疾病以及胃癌、乳腺癌等多种癌症[8-16]。值得关注的是，与其他蛋白激酶功能类似，NAKs 除了作为细胞生理功能研究的重要靶标外，还可被多种高危的人类或动物病毒利用以完成自身感染[17]，如丙型肝炎病毒(hepatitis C virus, HCV)[18-22]、登革热病毒(dengue virus, DENV)[19,23-31]、埃博拉病毒(Ebola virus, EBOV)[19,24,26]、狂犬病毒(rabies virus, RABV)[32-33]、甲型流感病毒(influenza A virus, IAV)[34-35]和新型冠状病毒(severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)[36-41]等。其中，NAKs 可同时参与 HCV、DENV、EBOV 的入侵、组装和释放，而仅参与 RABV 和 SARS-CoV-2 的入侵。鉴于其在生理性和病毒感染性疾病的发生发展中发挥关键作用，NAKs 已成为上述疾病的潜在药物开发靶点，如目前用于治疗神经性疼痛的小分子抑制剂舒尼替尼(sunitinib)和 LX-9211 已被美国食品药品监督管理局批准进入临床[42-43]。因此，本文将以 NAKs 激酶家族为切入点，系统梳理该激酶主要的生理功能及其在病毒感染中的作用，为病毒致病机制研究和靶向蛋白激酶的药物设计提供理论框架和策略参考。

1 NAKs 的生理功能

1.1 AAK1

AAK1 的生理功能主要涉及调控膜蛋白内吞、参与细胞命运决定、调节细胞信号转导以

及参与肿瘤和神经系统疾病的发生发展。

1.1.1 参与膜蛋白内吞

AAK1 因可磷酸化 Numb 蛋白的 T102 而被归类为 NAKs 家族[44]。早期研究发现，它能与衔接蛋白复合体 2 (adaptor protein complex 2, AP2)的 α 亚基结合并磷酸化 AP2 的 μ1 亚基(AP2 subunit mu-1, AP2M1)的 T156，因此得名衔接蛋白相关激酶 1[45-46]。在 CME 途径中，AP2M1 的磷酸化是启动网格蛋白装配的关键步骤，AAK1 通过这一机制调控血管内皮生长因子受体(vascular endothelial growth factor receptors, VEGFR)[47]、表皮生长因子受体(epidermal growth factor receptor, EGFR) [21,48]、转铁蛋白受体(transferrin receptor, TfR)[49]和低密度脂蛋白受体相关蛋白(low density lipoprotein receptor-related protein, LRP)[50]等多种膜蛋白内吞及后续分选，由此影响血管生成、炎症反应和细胞稳态。此外，AAK1 在细胞中的表达量受到精确调控，表达过高反而会抑制内吞[45,50]。

1.1.2 参与细胞命运决定

细胞命运决定涉及凋亡、焦亡和自噬等多条通路，AAK1 在其中发挥关键作用。(1) 凋亡：AAK1 介导肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)的内化，抑制癌细胞凋亡[8]；也可加剧白细胞介素(interleukin, IL)-1β 诱导的髓核细胞凋亡与七氟醚诱导的神经元凋亡[51-52]。(2) 焦亡：通过 CME 途径促进脂多糖(lipopolysaccharide, LPS)内化，激活 Caspase-11 触发细胞焦亡[53-54]。(3) 自噬：其微管相关蛋白轻链 3 (microtubule-associated protein light chain 3, LC3)相互作用区(LC3-interacting region, LIR)可与 LC3/自噬相关蛋白 8 (autophagy-related protein 8, ATG8)结合并被招募至主要组织相容性复合体 I 类分子(major histocompatibility complex class I molecules, MHC-I)定位的细胞膜处，进而促进 MHC-I 内化及溶酶体降解[9,34-35]；同时，也可通过磷酸化 AP2M1 加速 MHC-I 自噬清除[55-56]。

1.1.3 参与细胞信号转导

AAK1 通过磷酸化-内吞-降解/活化等方式精细调控以下信号通路。(1) 核因子 κB (nuclear factor kappa-B, NF-κB)通路：NF-κB 经典通路的激活依赖于核因子 κB 抑制因子 α (inhibitor of NF-κB, IκBα)的磷酸化及泛素化降解，解除对 p65/p50 二聚体的抑制，促使其入核启动靶基因转录。AAK1 可通过促进 IκBα 降解、催化 p65-S536 磷酸化及 p65-K310 乙酰化进一步增强 NF-κB 活性，从而介导炎症反应并提升细胞存活[53]。(2) Notch 通路：作为该通路的正调控因子，AAK1 可与 Notch 结合并使其内化并在早期内体中保持稳定，进而调控细胞的分化、增殖和凋亡[57-58]。(3) Wnt 通路：LRP6 是 Wnt 配体的共激活受体，AAK1 通过 CME 途径将 LRP6 内化，阻断其与 Wnt 配体结合，进而负调节 Wnt/β-catenin 信号通路的激活[59]。

1.1.4 AAK1 与肿瘤及神经系统疾病密切相关

在肿瘤中 AAK1 与 RalBP1 关联的 Eps 同源结构域蛋白(RalBP1-associated Eps domain-containing protein, REPS) 1/2、RalA 结合蛋白 1 (RalA-binding protein 1, RALBP1)等蛋白相互作用，诱导上皮-间充质转化与耐药[12]，与胃癌、卵巢癌等预后不良相关[60-62]。小分子抑制剂 Sunitinib (临床试验编号为 NCT00510640/NCT00299741)已被用于甲状腺癌和前列腺癌的临床治疗中。在神经系统疾病中 AAK1 参与神经营养因子内吞[63]、突触囊泡回收介导的痛觉传递[64]、神经元迁移与树突塑形[65-66]，并与 AD、PD、家族型肌萎缩性侧索硬化症及青少年

重度抑郁症等发病相关[4,67-69]。抑制剂 LX-9211 (临床试验编号为 NCT04662281/NCT04455633)在治疗带状疱疹后神经疼痛和糖尿病周围神经疼痛中有显著疗效[43,70]。除上述功能外，AAK1 还参与自然杀伤细胞的功能调节[71]、调控细胞内的整体翻译水平[72]以及脂质和活性氧的代谢[73]。

1.2 GAK

GAK 最初因与细胞周期蛋白 G 结合而被命名为细胞周期蛋白 G 相关激酶[74]，又因序列与辅助蛋白(auxilin)高度同源，也称 Auxilin 2[75]。该激酶在胞质和胞核均有分布，胞质 GAK 对网格蛋白解离和网格蛋白包被的囊泡(clathrin-coated vesicles, CCVs)组装至关重要。它可将热休克同源蛋白 70 (heat shock cognate protein 70, Hsc70)招募至 CCVs，利用 ATP 水解驱动网格蛋白晶格解离以完成“解包”；也可结合磷脂协助网格蛋白从囊泡上解离[76-77]。同时，GAK 还可介导网格蛋白与质膜及反式高尔基体网络(trans-Golgi network, TGN)结合[78]，在 CME、受体信号转导及 TGN-溶酶体运输中发挥重要作用[79-81]。值得注意的是，外源过表达 GAK 反而抑制 CME[82]。GAK 通常分别与 AP1 的 γ 亚基和 AP2 的 α 亚基结合并磷酸化其 μ 亚基[75,82]：与 AP1 结合促进 GAK 定位于 TGN，参与溶酶体酶分选[83]；与 AP2 结合则磷酸化 AP2M1-T156 参与 TfR、EGFR 等受体内吞[78]。此外，GAK 可磷酸化 Na^+/K^+-ATP 酶 α-亚基以调节细胞内的钠钾平衡[84]，与“突触”乙酰胆碱酯酶变体(N-terminally extended “synaptic” acetylcholinesterase variant, N-AChE-S)结合并抑制其诱导的细胞凋亡[5]，与 IL12 受体 β2 (interleukin 12 receptor β2, IL-12Rβ2)相互作用调节 IL12 信号[85]，并通过维持溶酶体稳态影响线粒体自噬[86-87]。

核内 GAK 与 cyclin G、蛋白质磷酸酶 2A (protein phosphatase 2A, PP2A)、雄激素受体(androgen receptor, AR)、网格蛋白重链(clathrin heavy chain, CHC)和微小染色体维持蛋白 3 (minichromosome maintenance protein 3, MCM3)等蛋白结合形成相应的复合物，在调节 PP2A 和 AR 的功能活性、维持中心体的成熟、染色体-微管连接及 DNA 复制许可中发挥重要作用[13,88-91]。功能异常时 GAK 通过磷酸化抑癌转录因子含反式激活结构域的 p63 亚型(transactivation domain-p63 isoform, TAp63)而抑制肿瘤形成[92]，也能与 α-核突触蛋白(α-synuclein)结合参与 PD 发生发展，并成为潜在治疗靶点[93-94]。

1.3 BMP2K

BMP2K 因最早报道可磷酸化骨形态发生蛋白 2 (bone morphogenic protein 2, BMP2)并促进成骨细胞分化而得名[95]，主要定位于胞质囊泡并以相分离液滴形态存在[96]。功能上，它与 AAK1/GAK 相似：通过 AP2M1 或 Numb 依赖的 CME 途径参与 EGFR、胰岛素受体底物 2 (insulin receptor substrate 2, IRS2)等膜蛋白内吞[97-101]；与非典型趋化因子受体 3 (atypical chemokine receptor 3, ACKR3)相互作用诱导后者磷酸化，参与非经典 G 蛋白偶联受体(G protein-coupled receptor, GPCR)信号转导[102]。值得注意的是，BMP2K 也可发生缓慢自磷酸化[95]。

BMP2K 与细胞的生长和分化密切相关，且呈细胞类型依赖的双向调控[103]。抑制成骨细胞分化：可通过影响碱性磷酸酶活性和骨钙素的表达抑制成骨细胞分化[95,104-105]。促进脂肪细胞分化：长链非编码 RNA 核富集转录本 1 (nuclear enriched abundant transcript 1, NEAT1)可调节 BMP2K 的表达，促进绵羊前体脂肪细胞分化[106-107]。促进红细胞成熟：通过调节蛋白转运相关蛋白分泌相关蛋白 16 同源物(secretory 16 homolog, SEC) A 和 SEC24B 的分布及 SEC31A 的表达参与红细胞成熟[108-111]。促进巨核细胞分

裂：与细胞周期蛋白依赖性激酶 2 (cyclin-dependent kinase 2, CDK2)结合，促进巨核细胞有丝分裂和分化[112]。此外，临床研究表明，BMP2K 与幽门螺杆菌性胃炎[113]、高度近视[114]、肥胖[115]、2 型糖尿病[116]和克氏锥虫感染[117]，以及白血病、癌症等多种疾病[100,118]发生发展密切相关。

1.4 STK16

STK16 因激酶结构域与 NAKs 成员相似也被归入本家族，但进化距离较远[119]。该蛋白的生物学特征先后由 Stairs、Kurioka、Ligos 和 Berson 等验证，并曾被命名为 Krct、EDPK、PKL12 和 MPSK1，最终被统一命名为 STK16[120]。目前研究提示其功能可归纳为“激酶+转录因子”双重角色。(1) 激酶活性：STK16 可磷酸化发育调控型 GTP 结合蛋白 1 (developmentally regulated GTP-binding protein 1, DRG1)、信号转导和转录激活因子 3 (signal transducer and activator of transcription 3, STAT3)、细胞性骨髓细胞瘤病癌基因(cellular myelocytomatosis concogene, c-MYC)、WD 重复结构域 1 (WD repeat domain 1, WDR1)和丝氨酸/苏氨酸蛋白激酶 1 (serine/threonine-protein kinase 1, AKT1)等底物，分别参与调控蛋白泛素化修饰[121]、Janus 激酶(janus kinase, JAK)/信号转导子和转录激活子 3 (signal transducer and activator of transcription 3, STAT3)介导的炎症及肿瘤发生[14]、c-MYC 稳定性与细胞周期[15]、肝细胞的极化与分泌[122]和细胞代谢及凋亡调控[16]。(2) 转录活性：STK16 可不依赖激酶活性直接结合 DNA[121]，发挥转录因子的作用；可识别转化生长因子-β (transforming growth factor-β, TGF-β)诱导的 C 型钠尿肽(C-type natriuretic peptide, CNP)和血管内皮生长因子(vascular endothelial growth factor, VEGF)基因近端启动子区中富含 GC 的调控序列，促进其转录[120]；也可通过转录因子 ETS 样蛋白 1 (ETS like-1 protein, ELK1)调控基因表达[123-124]。高尔基体定位的 STK16 在解聚后转位至核室区，可发挥转录因子功能[125]。此外，STK16 在细胞黏附和乳腺导管形态发生中也发挥重要作用[121,126]。STK16 的上述生理特性为后续深入研究其在平滑肌细胞收缩和极化肝细胞分泌等过程中的作用奠定基础[122,127]，其异常表达与乳腺癌[14]、结肠癌[15]和肺腺癌[16]等多种癌症密切相关。

1.5 NAKs 成员生理功能的区别与联系

NAKs 家族“保守头部+多变尾部”的结构特征，决定了其成员在生理功能上既存在相似性，也表现出显著差异性。相似性在于：(1) 除 STK16 外，所有 NAKs 成员均可通过磷酸化 AP2M1-T156 位点或与其他膜蛋白相互作用参与细胞的内吞作用；(2) GAK 与 STK16 进化亲缘关系较近，二者均参与转录调控并与细胞分裂过程相关；(3) 所有 4 个 NAKs 成员均参与调控细胞自噬、凋亡和分化等过程，与细胞命运决定密切相关。差异性在于：(1) AAK1：最初因其在神经递质内吞和突触囊泡回收中的作用被视为治疗神经性疼痛的靶点，后续研究揭示其还参与癌症相关受体内吞/循环及多种癌症信号通路调控，使其逐渐成为癌症治疗的潜在靶点；(2) GAK：研究焦点集中于其与 PD 等神经系统疾病发病机制的关联，同时其在调控细胞有丝分裂中的作用也备受关注；(3) BMP2K：虽与 AAK1 同源性最高，但其主要功能是调节细胞分化，并参与糖尿病发生和血细胞生成；(4) STK16：作为最新发现的成员，与其他 NAKs 亲缘关系最远，其功能主要与癌症的发生发展密切相关。为更清晰地阐明 NAKs 各成员间生理功能的异同点，对其底物、修饰位点以及主要生理/病理功能进行了系统总结(表 1)。

表1 NAKs的底物、修饰位点及其生理与病理功能

Table 1 Substrates, modification sites, and physiological/pathological functions of NAKs

NAKs members	Substrate proteins	Modification sites	Physiological functions	Related diseases
AAK1	AP2M1	T156	Regulation of CME[45]; endosomal pathway[46]; receptor-mediated endocytosis[46]; receptor endocytosis and recycling[21,47-50]; angiogenesis[47]; regulation of the Wnt signaling pathway[59]; coated vesicle cycle[128]; regulation of protein subcellular localization[129-130]; apoptosis[8,51-52]; clathrin-coated pit (CCP) formation and cargo sorting[131]; caspase-11-dependent pyroptosis[53-54]; macroautophagy/autophagy[9,34-35]	AD[4]; impairment of learning and memory[130]; vascular dementia[129]; colon adenocarcinoma[8]; breast cancer[9]; bladder urothelial carcinoma[10]; gastric cancer[11]
	Numb	T102	Regulation of the Notch signaling pathway[132]; coated pit maturation[44]	–
	Eps15	–	Coated pit maturation[44]	–
	IκBα	S536, K310	Regulation of the NF-κB signaling pathway[53]	Ischemic stroke[133]; pulmonary inflammatory[53]
	Notch 1	–	Regulation of the Notch signaling pathway[57]; promoted neural stem cell differentiation[58]	Ischemic stroke[58]
	REPS1/2, RALBP1	–	Epithelial-mesenchymal plasticity[12]; increased therapy resistance[12]	Hepatocellular carcinoma[12]
GAK	Hsc70	–	Coated pit maturation[134]	–
	Cyclin G	–	Regulation of cell-cycle[74]	–
	TAp63	T46, T281	Tumorigenesis[92]	–
	N-AChE-S	–	Apoptosis[5]	AD[5]
	IL12β a2	–	Cell signaling[85]	–
	AR	–	Cell signaling[13]	Prostate cancer[13]
	Vha44	S543	Lysosomal acidification[7]	PD[6-7]
	AP2M1	T156	Regulation of CME[135]; cell growth and centrosome duplication[136]; endosomal pathway[78]	–
	AP1	–	Receptor-mediated endocytosis[82]; golgi to lysosome transport[78,80]	–
	Atp1a3	T705	Resting membrane potential[84]	PD[84]
	Sipa1L1	T249	Brain developmental regulation[84]	–
	CHC	T606	Regulation of mitosis[89,137]	–
	PP2A	T104	Microtubule generation and outgrowth[91]	–
	LRRK2	–	Regulation of neuron projection development[138]	PD[138]
BMP2K	AP2M1	T156	Regulation of CME[98]	–
	CLINT1	T294	Sorting in TGN-endosome pathway[31]	–

(待续)

(续表1)

NAKs members	Substrate proteins	Modification sites	Physiological functions	Related diseases
	ACKR3	–	Regulation of the GPCR signaling pathway[102]	–
	CDK2	–	Polyploidization[112]; regulation of bone mineralization[107]	Osteoporosis[107]; megakaryoblastic leukemia[112]
STK16	DRG1	T100	Cellular growth[119]	–
	STAT3	S727	Drug resistance[14]	Triple-negative breast cancer[14]
	c-MYC	S452	Ubiquitin-proteasome pathway[15]	Colorectal cancer[15]
	WDR1	–	Hepatic secretion[122]	–
	AKT1	–	Regulation of AKT1 pathway[16]; cell proliferation and apoptosis[16]	Lung adenocarcinoma[16]
	CNP/VEGF	–	Regulation of the TGF-β signaling pathway[139]	–
	ELK1	–	Cell signaling[123]	Brain lower grade glioma[123]

– indicates that the kinase modification sites or the related diseases were not identified.

2 NAKs在病毒感染中的作用

前期研究证实宿主细胞蛋白激酶在病毒感染中发挥着重要作用，如PP2A[140]、EGFR[141]、TANK结合激酶1 (TANK-binding kinase-1, TBK1)[142]等宿主细胞蛋白激酶在猪繁殖与呼吸综合征病毒、猪流行性腹泻病毒以及鸭肠炎病毒感染过程中均发挥重要作用。随着对NAKs家族激酶活性研究的深入，近年来多项研究揭示该家族成员在病毒入侵、复制、组装、释放及免疫逃逸等过程中扮演着关键角色(图2)。NAKs与病毒生命周期的对应关系见表2。

2.1 AAK1

AAK1最主要的功能是参与病毒入侵。AAK1是磷酸化AP2M1的关键激酶，该修饰对AP2M1在CME途径中与货物蛋白结合至关重要。包括SARS-CoV-2[37-41,148]、EBOV[19]、DENV[23,25]、HCV[21]、RABV[32-33]和托斯卡纳病毒(Toscana virus, TOSV)[146]等在内的多种病毒，可利用AAK1介导的AP2M1磷酸化，经CME途径进入细胞。例如，在感染过程中DENV和RABV可上调宿主AAK1的mRNA和蛋白水平[23,33]，进而增强AP2M1磷酸化，促进病毒通过CME途径入侵细胞[25,32]。靶向AAK1 ATP口袋的抑制剂巴瑞克替尼(baricitinib)、吡咯[2,3-b]吡啶衍生物、SGC-AAK1-1衍生物及化合物(compounds 12、11f和nCorv-EMBS)均可降低AAK1活性，阻断AP2M1磷酸化，阻碍AP2M1与SARS-CoV-2受体血管紧张素转化酶2 (angiotensin-converting enzyme 2, ACE2)的结合，最终抑制病毒入侵[37-40,148]。此外，AAK1还通过非CME途径参与病毒入侵。如HCV除通过CME途径入侵细胞外，还可借助磷酸化衔接蛋白Numb-T102，经Numb依赖的内吞途径进入细胞；同时，AAK1也可通过增强HCV辅助受体EGFR的内化及再循环，帮助HCV建立有效感染[21]。

除了参与病毒入侵外，AAK1在病毒组装/释放、潜伏感染解除及免疫逃逸等环节也发挥多重作用。(1) 组装/释放：AAK1通过磷酸化AP2M1促进HCV核衣壳蛋白-AP2M1相互作用，并引导病毒颗粒转运至组装位点完成组装，抑制剂Sunitinib可有效抑制感染性病毒粒子的产生[19,33]。AAK1还可通过调节AP1和AP4的磷酸化影响其与HCV非结构蛋白2的结合，参与病毒释放及细胞间传播[20]。抑制AAK1活性或敲低其表达，可减弱AP2M1的磷酸化水平，进而抑制DENV和EBOV的释放[19,25]。在新城疫病毒(Newcastle disease virus, NDV)中AAK1

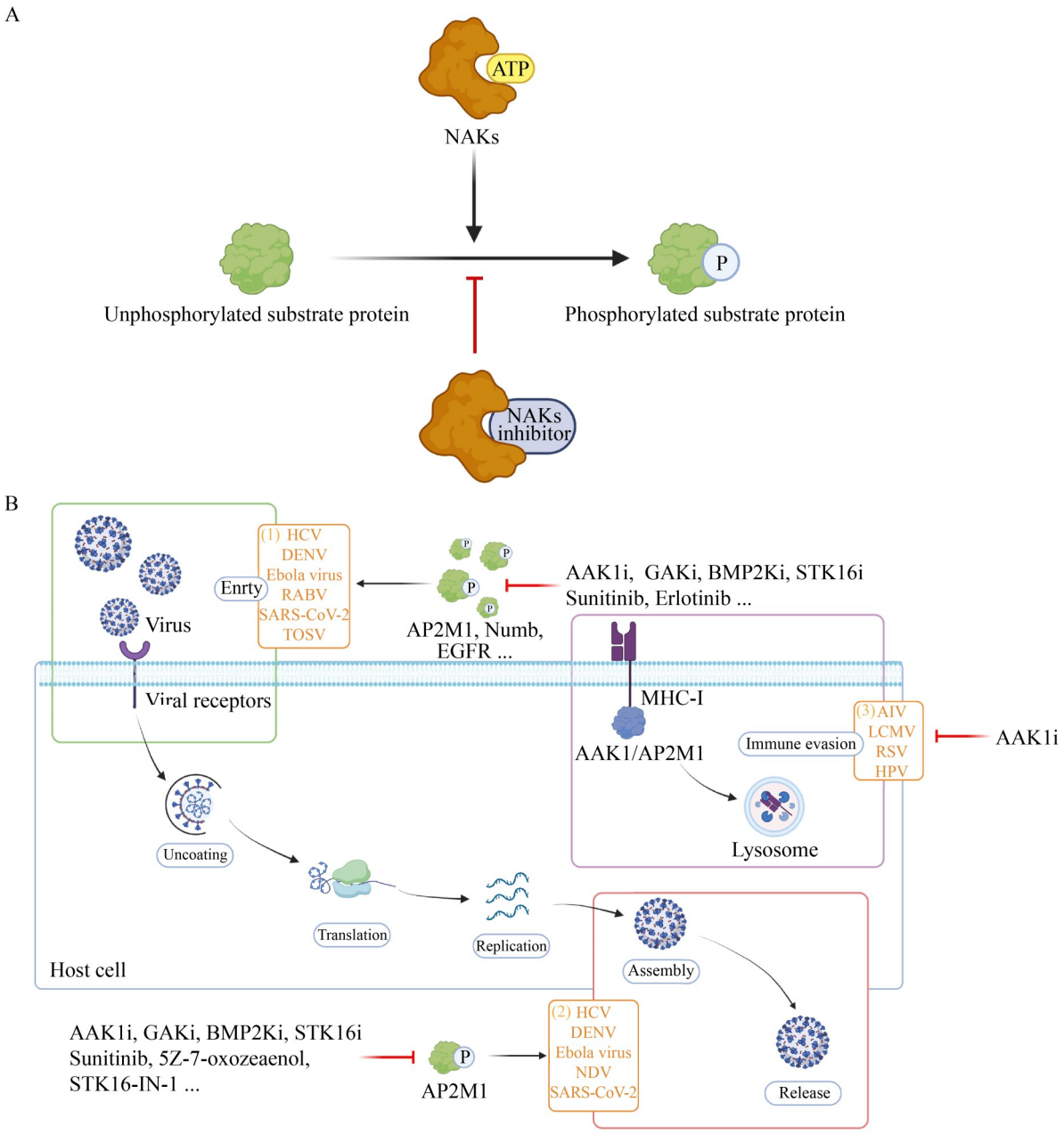

图2　NAKs及其抑制剂参与病毒生命周期模式图

Figure 2　Schematic diagram of NAKs and their inhibitors in the viral life cycle. A: Schematic diagram of NAK inhibitor mechanism [NAK inhibitors block the ATP-binding pocket, reducing ATP binding and preventing substrate phosphorylation]; B: Schematic of NAKs involvement in multiple stages of viral infection [(1) Inhibitors targeting NAKs (AAK1i, GAKi, BMP2Ki, and STK16i) mainly suppress viral entry through two mechanisms: (i) inhibition of NAKs kinase activity to attenuate phosphorylation of AP2M1 and Numb, and (ii) disruption of EGFR internalization; (2) NAKs inhibitors predominantly inhibit viral assembly/release by suppressing the phosphorylation of AP2M1; (3) AAKi assists viral immune evasion by downregulating the expression of MHC-I on the cell surface].

表2 NAKs及其抑制剂影响的病毒生命周期

Table 2 The effects of NAKs and their inhibitors on the viral life cycle

NAKs members	Viruses	Substrate proteins of NAKs	Stage(s) of the viral life cycle involved	Inhibitors	References
AAK1	HPV	−	Immune evasion	−	[143]
	HCV	AP2M1, AP1-A	Entry, assembly, release	Sunitinib	[18-21]
		EGFR, Numb, AP2M1	Entry	Sunitinib	[21]
	DENV	AP2M1, AP1M1	Entry, release	Sunitinib, Erlotinib	[19,23-25]
	EBOV	AP2M1, AP1M1	Entry, release	Sunitinib, Erlotinib	[19,24]
	RABV	AP2M1	Entry	Sunitinib	[32-33]
	RSV	AP2M1	Immune evasion	−	[56]
	SARS-CoV-2	AP2M1	Entry	Baricitinib, 1,2,4a,5-tetrahydro-4H-benzo[b] [1,4]oxazino[4,3-d] [1,4]oxazine scaffold and its derivatives, novel compounds (compounds 12, 11f, and nCorv-EMBS), SGC-AAK1-1-based inhibitors	[36-41,144]
	NDV	AP1M1, AP2M1	Assembly/release	Sunitinib, Erlotinib	[145]
	TOSV	AP2M1	Entry	Sunitinib	[146]
	IAV	AP2M1	Immune evasion	−	[34-35]
	LCMV	AP2M1	Immune evasion	−	[34]
	PRV	Numb, Notch2	Activation	−	[132]
GAK	HCV	AP2M1, AP1-A	Entry, assembly, release	Sunitinib, isothiazolo[5,4-b]pyridine-based inhibitors	[18,20-22]
	DENV	−	−	Isothiazolo[4,3-b]pyridine-based inhibitors	[26-29]
	EBOV	−	−	Isothiazolo[4,3-b]pyridine-based inhibitors	[19,26]
	CHIKV	−	−	Isothiazolo[4,3-b]pyridine-based inhibitors	[26]
	SARS-CoV-2	AP2M1	Entry	RMC-242, Gefitinib, Baricitinib	[36,41]
	NDV	AP1M1, AP2M1	Assembly, release	Sunitinib, Erlotinib	[145]
	TOSV	AP2M1	Entry	Erlotinib	[146]
BMP2K	DENV	AP2M1, CLINT1	Entry, assembly/release	25A,5Z-7-oxozeaenol	[30-31]
	HIV-1	−	Replication	−	[147]
	SARS-CoV-2	−	Entry, assembly/release	Sunitinib, Erlotinib, RMC-76	[36]
	VEEV	−	−	5Z-7-oxozeaenol	[30]
STK16	SARS-CoV-2	−	Entry, assembly/release	STK16-IN-1	[36]

− indicates that the kinase substrate proteins were not identified or the relevant inhibitors were not used.

可磷酸化 AP1M1 和 AP2M1，调控 F 蛋白的胞内运输及质膜定位，进而影响病毒组装和释放[145]。(2) 潜伏感染解除：伪狂犬病毒(pseudorabies virus, PRV)感染下调 miR-155-5p 表达，解除其对 AAK1 的抑制，导致 AAK1 表达上调，进而激活 Numb/Notch2 信号通路，最终

促进病毒增殖[132]。(3) 免疫逃逸：IAV、淋巴细胞脉络丛脑膜炎病毒(lymphocytic choriomeningitis virus, LCMV) 和呼吸道合胞病毒(respiratory syncytial virus, RSV)等病毒感染导致细胞的巨自噬增强，LC3B/ATG8 表达增加引起 AAK1 过度被募集，进而促使 MHC-I 类分子内化与循环，使以上病毒得以逃避宿主免疫防御[34,56]。此外，AAK1 对于人乳头瘤病毒(human papillomavirus, HPV)感染所导致的癌细胞的存活也至关重要，可能与 AAK1 参与调节多种致癌信号通路以及调节致癌相关受体的内化和循环有关[143]。

2.2 GAK

GAK 和 AAK1 是最早被鉴定的 NAKs 成员，常在同一病毒感染中被并行研究。与 AAK1 类似，GAK 通过磷酸化 AP2M1 介导 CME，参与 HCV 入侵[21]以及病毒粒子的组装[18-20]；异噻唑[5,4-b]吡啶、异噻唑[4,3-b]吡啶及其衍生物可靶向 GAK ATP 口袋，阻断上述过程有效阻止 HCV 入侵和组装[22]。此外，GAK 还通过相似机制参与 TOSV 的入侵[146]以及协助 NDV 的组装/释放[145]。靶向 GAK 的抑制剂异噻唑[4,3-b]吡啶及其衍生物可有效抑制 DENV、EBOV 和基孔肯雅病毒(chikungunya virus, CHIKV)感染[26-29]，同时发现结构优化后的衍生物较先导化合物具有更高的靶向性、更低的 EC_{50}。GAK 抑制剂吉非替尼(gefitinib)、baricitinib 和 RMC-242 等对 SARS-CoV-2 依赖 CME 途径入侵宿主细胞具有显著抑制效果，推测其通过抑制 GAK-AP2M1 轴发挥作用[36,41]。

2.3 BMP2K 和 STK16

功能上，BMP2K 与 AAK1 和 GAK 相似，可磷酸化 AP2M1 参与 CME 途径依赖的病毒入侵。研究表明敲除或抑制 BMP2K (如新型化合物 25A、5Z-7-oxozeaenol)可有效抑制 DENV 入侵，回补 BMP2K 可恢复感染水平，提示其对病毒入侵至关重要[30]。同一抑制剂 5Z-7-oxozeaenol 也可有效抑制委内瑞拉马脑炎病毒(Venezuelan equine encephalitis virus, VEEV) 感染[30]。敲低 BMP2K 或使用 Sunitinib、Erlotinib 和 RMC-76 等 BMP2K 抑制剂均可抑制 SARS-CoV-2 的早期入侵和晚期感染[36]。此外，BMP2K 可磷酸化网格蛋白相互作用蛋白 1 (clathrin-interacting protein 1, CLINT1)，磷酸化后的 CLINT1 可与 DENV NS3 结合，参与病毒的组装/释放[31]；敲低 BMP2K 可抑制 HIV 的复制，回补后可以拯救这种抑制效果，证实 BMP2K 作为 HIV-1 复制所需的关键宿主因子[147]。

STK16 的研究起步较晚，但现有数据表明其同样抑制 SARS-CoV-2 感染，具体表现为 STK16 抑制剂 STK16-IN-1 在病毒的早期入侵和晚期感染阶段均呈剂量依赖性抗病毒效应[36]，提示 STK16 也可作为潜在抗病毒靶点。

3 总结与展望

NAKs 是一类进化保守的多功能丝氨酸/苏氨酸激酶，通过直接磷酸化或相互作用等机制调控内吞作用、胞内转运、细胞命运决定、细胞稳态维持和信号转导等关键生理过程。值得注意的是，多种病毒也“劫持” NAKs，利用其对 CME 关键蛋白的磷酸化或免疫逃逸调控作用完成自身的入侵、复制、组装和释放。然而，目前对于 NAKs 家族的生理功能认知尚不充分，如新成员 STK16 的生理功能仍存在诸多谜团。因此，未来的研究亟需：(1) 深入解析 NAKs 各成员如何协同调控多种信号通路；(2) 系统阐明 NAKs 在细胞发育、细胞命运决定以及在癌症、神经系统疾病和代谢疾病中的具体作用；(3) 在深入理解 NAKs 生理功能的基础上，揭示其作为“细胞枢纽”的全局性调控逻辑，为靶向干预或治疗相关疾病奠定理论基础。

在病毒感染领域，尤其是 NAKs 在病毒感染中的作用及其靶向抑制剂的开发和应用方面虽已取得诸多进展，但仍面临诸多问题。首先，NAKs 在病毒生命周期中的具体作用机制仍需深入阐明。其次，针对 NAKs 的小分子抑制剂的

开发、筛选及优化策略仍存在较大难度。病毒建立有效感染常需利用 NAKs 的生理功能，如某些病毒可借助 NAKs 介导的膜蛋白内吞和胞内转运过程完成宿主细胞入侵。然而，目前对 NAKs 家族成员的生理功能研究尚不充分，这也限制了对其在病毒感染中作用机制研究的深度。现阶段，抗病毒药物研发主要聚焦于两大方向：一是靶向病毒的直接抗病毒药物，通过作用于病毒生命周期中的关键环节(如病毒吸附/入侵、基因组转录/复制等)直接抑制或杀灭病毒，代表药物包括病毒吸附/入侵抑制剂、核苷/核苷酸类似物等；二是靶向宿主的间接抗病毒药物，通过作用于宿主细胞中病毒增殖所必需的因子(如病毒受体、宿主蛋白酶、激酶等)干扰病毒生命周期的某个或多个阶段，从而阻断有效感染。该策略的优势在于可能开发出广谱性强且不易诱发病毒耐药性的药物。事实上，鉴于 NAKs 在多种病毒生命周期的不同阶段发挥关键作用，靶向 NAKs 的广谱抗病毒抑制剂开发已受到广泛关注并已取得重要进展。例如，在 SARS-CoV-2 流行期间，NAKs 抑制剂 Baricitinib 被证实可缓解患者由感染引起的临床症状[40]；NAKs 抑制剂 Sunitinib 也被证实可有效抑制包括 HCV、DENV、EBOV、RABV、RSV、NDV、TOSV 以及 SARS-CoV-2 在内的多种病毒的不同感染阶段。然而，目前可用于抗病毒研究或临床治疗的 NAKs 抑制剂仍然有限。考虑到这类抑制剂显著的广谱抗病毒潜力和广阔的临床应用前景，亟需通过大规模筛选和开发新型药物来满足实际临床需求。

目前，靶向 NAKs 的抗病毒药物开发策略主要包括老药新用、现有抑制剂优化和新药开发 3 个方面。(1) 老药新用：典型案例如 Sunitinib，该药已从治疗神经性疼痛及癌症转向抗病毒应用。因此，通过高通量筛选已有 NAKs 抑制剂是否具有抗病毒活性显得至关重要。(2) 现有抑制剂优化：针对 Sunitinib、Baricitinib、异噻唑[4,3-b]吡啶等抑制剂存在的细胞毒性大、靶点不专一等问题亟需进行结构优化。例如，通过在异噻唑[4,3-b]吡啶支架的 3-苯基或 3-哌啶基部位引入羧酰胺残基可获得靶向 GAK 活性更强、半数抑制浓度(median inhibition concentration, IC_{50})更低的小分子化合物，该化合物已被证实可有效抑制 DENV 感染[28]；通过支架跳跃(scaffold hopping)策略优化鲁索利替尼(Ruxolitinib)和 Baricitinib，可获得靶向 AAK1 选择性更高、疗效更佳的抗病毒化合物[10]；将 SGC-AAK1-1 的 1H-吲哚唑支架与化合物 6 的药效团融合，得到的新型化合物 11f 细胞毒性更低且抗病毒效果与先导化合物相当[135]。(3) 新药开发：通过基于片段的药物开发(fragment-based drug discovery, FBDD)技术揭示片段 9595 的卤素键是与 AAK1 相互作用的关键位点[149]，这为开发靶向 AAK1 的新型抑制剂提供了方向；通过化学蛋白质组学(chemical proteomics)技术进行筛选也是重要的新药开发策略之一，如基于 TIM-063-kinobeads 的化学蛋白质组学筛选出 TIM-098a，该化合物可避免脱靶效应，并作为 AAK1 选择性更高、疗效更优的抗病毒候选物[135]。此外，还可以考虑多靶点联合策略以提高抗病毒效果，如 Mao 等[38]报道了一种同时靶向 AAK1 和组蛋白去乙酰化酶的新型化合物，能更有效地抑制 SARS-CoV-2 入侵细胞。

综上所述，未来针对 NAKs 的研究可重点聚焦于以下两方面：(1) 整合分子生物学、人工智能及多组学等技术手段，系统解析并绘制 NAKs-病毒相互作用的全局网络，为临床药物研发奠定理论基础；(2) 持续优化研发策略，开发具有选择性高、毒性低、疗效强的单一或组合抑制剂，并在人类/动物模型中系统评估其安全性与有效性。通过紧密衔接基础研究与临床疾病治疗需求，NAKs 有望成为治疗多种生理及病毒感染性疾病的理想靶标，其研究成果也将为深入解析病毒感染机制和推进蛋白激酶靶向药物研发提供重要参考。

作者贡献声明

李睿：图表绘制，稿件撰写与修改；蒋艳：文献检索与整理，稿件撰写与修改；游灵巧：数据收集与分析；孙悦茵：格式修改与校对；李佳慧：文献查漏补缺；王玉娥：文章框架构思与设计，提供资源，语言润色，监督管理；张龙祥：文章框架构思与设计，项目支持，稿件审阅与投稿，监督管理。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

参考文献

[1] GULINO A, Di MARCOTULLIO L, SCREPANTI I. The multiple functions of Numb[J]. Experimental Cell Research, 2010, 316(6): 900-906.

[2] HUANG CX, JI CC, WANG J. Current thoughts on cellular functions of Numb-associated kinases[J]. Molecular Biology Reports, 2023, 50(5): 4645-4652.

[3] SMYTHE E, AYSCOUGH KR. The Ark1/Prk1 family of protein kinases. Regulators of endocytosis and the actin skeleton[J]. EMBO Reports, 2003, 4(3): 246-251.

[4] FU X, KE ML, YU WH, WANG X, XIAO Q, GU M, LÜ Y. Periodic variation of AAK1 in an $A\beta_{1\text{-}42}$-induced mouse model of Alzheimer's disease[J]. Journal of Molecular Neuroscience, 2018, 65(2): 179-189.

[5] TOIBER D, GREENBERG DS, SOREQ H. Pro-apoptotic protein-protein interactions of the extended N-AChE terminus[J]. Journal of Neural Transmission, 2009, 116(11): 1435-1442.

[6] DUMITRIU A, PACHECO CD, WILK JB, STRATHEARN KE, LATOURELLE JC, GOLDWURM S, PEZZOLI G, ROCHET JC, LINDQUIST S, MYERS RH. Cyclin-G-associated kinase modifies α-synuclein expression levels and toxicity in Parkinson's disease: results from the GenePD Study[J]. Human Molecular Genetics, 2011, 20(8): 1478-1487.

[7] ZHANG SP, WANG LF, YI SL, TSAI YT, CHENG YH, LIN YT, LIN CC, LEE YH, WANG HL, LI SH, WANG RQ, LIU Y, YAN W, LIU C, HE KW, HO MS. *Drosophila* Aux orchestrates the phosphorylation-dependent assembly of the lysosomal V-ATPase in glia and contributes to SNCA/α-synuclein degradation[J]. Autophagy, 2025, 21(5): 1039-1058.

[8] SO J, PASCULESCU A, DAI AY, WILLITON K, JAMES A, NGUYEN V, CREIXELL P, SCHOOF EM, SINCLAIR J, BARRIOS-RODILES M, GU J, KRIZUS A, WILLIAMS R, OLHOVSKY M, DENNIS JW, WRANA JL, LINDING RE, JORGENSEN C, PAWSON T, COLWILL K. Integrative analysis of kinase networks in TRAIL-induced apoptosis provides a source of potential targets for combination therapy[J]. Science Signaling, 2015, 8(371): rs3.

[9] LEONARDI M, PERNA E, TRONNOLONE S, COLECCHIA D, CHIARIELLO M. Activated kinase screening identifies the IKBKE oncogene as a positive regulator of autophagy[J]. Autophagy, 2019, 15(2): 312-326.

[10] LIN Q, LI J, WANG YP, ZANG J. Design, synthesis, and biological evaluation of novel ruxolitinib and baricitinib analogues for potential use against COVID-19[J]. Chemical Biology & Drug Design, 2023, 101(3): 760-771.

[11] SINGH S, PARTHASARATHI KTS, BHAT MY, GOPAL C, SHARMA J, PANDEY A. Profiling kinase activities for precision oncology in diffuse gastric cancer[J]. Omics, 2024, 28(2): 76-89.

[12] GOLKOWSKI M, LIUS A, SAPRE T, LAU HT, MORENO T, MALY DJ, ONG SE. Multiplexed kinase interactome profiling quantifies cellular network activity and plasticity[J]. Molecular Cell, 2023, 83(5): 803-818.e8.

[13] RAY MR, WAFA LA, CHENG H, SNOEK R, FAZLI L, GLEAVE M, RENNIE PS. Cyclin G-associated kinase: a novel androgen receptor-interacting transcriptional coactivator that is overexpressed in hormone refractory prostate cancer[J]. International Journal of Cancer, 2006, 118(5): 1108-1119.

[14] ZHU ZY, XIANG Q, LI SQ, CHEN C, SHI J. Serine/threonine kinase 16 phosphorylates STAT3 and confers a JAK2-Inhibition resistance phenotype in triple-negative breast cancer[J]. Biochemical Pharmacology, 2024, 225: 116268.

[15] LI P, LIU GS, WUSMAN LB, LI T. STK16 promoted colorectal cancer progress in a c-MYC signaling-dependent manner[J]. Molecular Medicine, 2024, 30(1): 50.

[16] WANG X, HUANG RH, LU ZY, WANG Z, CHEN XF, HUANG DY. Exosomes from M1-polarized macrophages promote apoptosis in lung adenocarcinoma *via* the miR-181a-5p/ETS1/STK16 axis[J]. Cancer Science, 2022, 113(3): 986-1001.

[17] 戚香, 蒋松伟, 袁滢惠, 许丽, 惠子, 叶向阳, 谢恬. 衔接子相关蛋白激酶 1 (AAK1)抑制剂抗病毒研究进展[J]. 药学学报, 2022, 57(7): 1991-2002.
QI X, JIANG SW, YUAN YH, XU L, HUI Z, YE XY, XIE T. Advances in antiviral research of adaptor-associated protein kinase 1 (AAK1) inhibitors[J]. Acta Pharmaceutica Sinica, 2022, 57(7): 1991-2002 (in Chinese).

[18] NEVEU G, BAROUCH-BENTOV R, ZIV-AV A, GERBER D, JACOB Y, EINAV S. Identification and targeting of an interaction between a tyrosine motif within hepatitis C virus core protein and AP2M1 essential for viral assembly[J]. PLoS Pathogens, 2012, 8(8): e1002845.

[19] BEKERMAN E, NEVEU G, SHULLA A, BRANNAN J, PU SY, WANG S, XIAO F, BAROUCH-BENTOV R, BAKKEN RR, MATEO R, GOVERO J, NAGAMINE CM, DIAMOND MS, de JONGHE S, HERDEWIJN P, DYE JM, RANDALL G, EINAV S. Anticancer kinase

inhibitors impair intracellular viral trafficking and exert broad-spectrum antiviral effects[J]. The Journal of Clinical Investigation, 2017, 127(4): 1338-1352.
[20] XIAO F, WANG S, BAROUCH-BENTOV R, NEVEU G, PU S, BEER M, SCHOR S, KUMAR S, NICOLAESCU V, LINDENBACH BD, RANDALL G, EINAV S. Interactions between the hepatitis C virus nonstructural 2 protein and host adaptor proteins 1 and 4 orchestrate virus release[J]. mBio, 2018, 9(2): e02233-17.
[21] NEVEU G, ZIV-AV A, BAROUCH-BENTOV R, BERKERMAN E, MULHOLLAND J, EINAV S. AP-2-associated protein kinase 1 and cyclin G-associated kinase regulate hepatitis C virus entry and are potential drug targets[J]. Journal of Virology, 2015, 89(8): 4387-4404.
[22] KOVACKOVA S, CHANG L, BEKERMAN E, NEVEU G, BAROUCH-BENTOV R, CHAIKUAD A, HEROVEN C, ŠÁLA M, de JONGHE S, KNAPP S, EINAV S, HERDEWIJN P. Selective inhibitors of cyclin G associated kinase (GAK) as anti-hepatitis C agents[J]. Journal of Medicinal Chemistry, 2015, 58(8): 3393-3410.
[23] PU SY, XIAO F, SCHOR S, BEKERMAN E, ZANINI F, BAROUCH-BENTOV R, NAGAMINE CM, EINAV S. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment[J]. Antiviral Research, 2018, 155: 67-75.
[24] BROMMAGE R, POWELL DR, VOGEL P. Predicting human disease mutations and identifying drug targets from mouse gene knockout phenotyping campaigns[J]. Disease Models & Mechanisms, 2019, 12(5): dmm038224.
[25] TONGMUANG N, YASAMUT U, NOISAKRAN S, SREEKANTH GP, YENCHITSOMANUS PT, LIMJINDAPORN T. Suppression of μ1 subunit of the adaptor protein complex 2 reduces dengue virus release[J]. Virus Genes, 2020, 56(1): 27-36.
[26] PU SY, WOUTERS R, SCHOR S, ROZENSKI J, BAROUCH-BENTOV R, PRUGAR LI, O'BRIEN CM, BRANNAN JM, DYE JM, HERDEWIJN P, de JONGHE S, EINAV S. Optimization of isothiazolo [4,3-b] pyridine-based inhibitors of cyclin G associated kinase (GAK) with broad-spectrum antiviral activity[J]. Journal of Medicinal Chemistry, 2018, 61(14): 6178-6192.
[27] WOUTERS R, PU SY, FROEYEN M, LESCRINIER E, EINAV S, HERDEWIJN P, de JONGHE S. Cyclin G-associated kinase (GAK) affinity and antiviral activity studies of a series of 3-C-substituted isothiazolo [4, 3-b] pyridines[J]. European Journal of Medicinal Chemistry, 2019, 163: 256-265.
[28] MARTINEZ-GUALDA B, SAUL S, FROEYEN M, SCHOLS D, HERDEWIJN P, EINAV S, de JONGHE S. Discovery of 3-phenyl-and 3-N-piperidinyl-isothiazolo [4, 3-b] pyridines as highly potent inhibitors of cyclin G-associated kinase[J]. European Journal of Medicinal Chemistry, 2021, 213: 113158.
[29] GERNINGHAUS J, ZHUBI R, KRÄMER A, KARIM M, TRAN DHN, JOERGER AC, SCHREIBER C, BERGER LM, BERGER BT, EHRET TAL, ELSON L, LENZ C, SAXENA K, MÜLLER S, EINAV S, KNAPP S, HANKE T. Back-pocket optimization of 2-aminopyrimidine-based macrocycles leads to potent dual EPHA2/GAK kinase inhibitors with antiviral activity[J]. Journal of Medicinal Chemistry, 2024, 67(15): 12534-12552.
[30] PU S, SCHOR S, KARIM M, SAUL S, ROBINSON M, KUMAR S, PRUGAR LI, DOROSKY DE, BRANNAN J, DYE JM, EINAV S. BIKE regulates dengue virus infection and is a cellular target for broad-spectrum antivirals[J]. Antiviral Research, 2020, 184: 104966.
[31] SCHOR S, PU S, NICOLAESCU V, AZARI S, KÕIVOMÄGI M, KARIM M, CASSONNET P, SAUL S, NEVEU G, YUEH A, DEMERET C, SKOTHEIM JM, JACOB Y, RANDALL G, EINAV S. The cargo adapter protein CLINT1 is phosphorylated by the Numb-associated kinase BIKE and mediates dengue virus infection[J]. Journal of Biological Chemistry, 2022, 298(6): 101956.
[32] WANG C, WANG JL, SHUAI L, MA X, ZHANG HL, LIU RQ, CHEN WY, WANG XJ, GE JY, WEN ZY, BU ZG. The serine/threonine kinase AP2-associated kinase 1 plays an important role in rabies virus entry[J]. Viruses, 2020, 12(1): 45.
[33] LUO J, ZHANG Y, WANG Y, LIU Q, CHEN LM, ZHANG BY, LUO YW, HUANG SL, GUO XF. Rhabdovirus infection is dependent on serine/threonine kinase AP2-associated kinase 1[J]. Life, 2020, 10(9): 170.
[34] LOI M, MÜLLER A, STEINBACH K, NIVEN J, BARREIRA Da SILVA R, PAUL P, LIGEON LA, CARUSO A, ALBRECHT RA, BECKER AC, ANNAHEIM N, NOWAG H, DENGJEL J, GARCÍA-SASTRE A, MERKLER D, MÜNZ C, GANNAGÉ M. Macroautophagy proteins control MHC class I levels on dendritic cells and shape anti-viral $CD8^+$ T cell responses[J]. Cell Reports, 2016, 15(5): 1076-1087.
[35] LOI M, LIGEON LA, MÜNZ C. MHC class I internalization *via* autophagy proteins[J]. Methods in Molecular Biology, 2019, 1880: 455-477.
[36] KARIM M, SAUL S, GHITA L, SAHOO MK, YE CJ, BHALLA N, LO CW, JIN J, PARK JG, MARTINEZ-GUALDA B, EAST MP, JOHNSON GL, PINSKY BA, MARTINEZ-SOBRIDO L, ASQUITH CRM, NARAYANAN A, de JONGHE S, EINAV S. Numb-associated kinases are required for SARS-CoV-2 infection and are cellular targets for antiviral strategies[J]. Antiviral Research, 2022, 204: 105367.
[37] MAO ND, XU YY, CHE H, YAO X, GAO Y, WANG CC, DENG HW, HUI Z, ZHANG H, YE XY. Design, synthesis and biological evaluation of novel 1, 2, 4a, 5-tetrahydro-4H-benzo [b] [1,4] oxazino [4,3-d] [1,4] oxazine-based AAK1 inhibitors with anti-viral property against SARS-CoV-2[J]. European Journal of Medicinal Chemistry, 2024, 268: 116232.
[38] MAO ND, XU YY, YAO X, GAO Y, HUI Z, CHE H, WANG CC, LU JS, YU J, HU SW, ZHANG H, YE XY.

Design, synthesis, and biological evaluation of novel AAK1/HDACs dual inhibitors against SARS-CoV-2 entry[J]. Bioorganic Chemistry, 2024, 153: 107973.
[39] HUI Z, DENG HW, XU YY, GAO Y, ZHAI CF, MAO ND, CHE H, LI Z, ZHANG YT, ZHANG H, XIE T, YE XY. Discovery and optimization of AAK1 inhibitors based on 1H-indazole scaffold for the potential treatment of SARS-CoV-2 infection[J/OL]. Molecular Diversity, 2025. DOI: 10.1007/s11030-025-11135-4.
[40] STEBBING J, KRISHNAN V, de BONO S, OTTAVIANI S, CASALINI G, RICHARDSON PJ, MONTEIL V, LAUSCHKE VM, MIRAZIMI A, YOUHANNA S, TAN YJ, BALDANTI F, SARASINI A, ROSS TERRES JA, NICKOLOFF BJ, HIGGS RE, ROCHA G, BYERS NL, SCHLICHTING DE, NIRULA A, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients[J]. EMBO Molecular Medicine, 2020, 12(8): e12697.
[41] HUANG J, ZHOU C, DENG JN, ZHOU JF. JAK inhibition as a new treatment strategy for patients with COVID-19[J]. Biochemical Pharmacology, 2022, 202: 115162.
[42] KOSTICH W, HAMMAN BD, LI YW, NAIDU S, DANDAPANI K, FENG JL, EASTON A, BOURIN C, BAKER K, ALLEN J, SAVELIEVA K, LOUIS JV, DOKANIA M, ELAVAZHAGAN S, VATTIKUNDALA P, SHARMA V, DAS ML, SHANKAR G, KUMAR A, HOLENARSIPUR VK, et al. Inhibition of AAK1 kinase as a novel therapeutic approach to treat neuropathic pain[J]. The Journal of Pharmacology and Experimental Therapeutics, 2016, 358(3): 371-386.
[43] UPSHAW WC, RICHEY JM, RAVI G, CHEN A, AHMADZADEH S, SHEKOOHI S, VISWANATH O, KAYE AD. An overview of the safety and efficacy of LX-9211 in treating neuropathic pain conditions[J]. Expert Opinion on Investigational Drugs, 2024, 33(8): 829-837.
[44] SORENSEN EB, CONNER SD. AAK1 regulates Numb function at an early step in clathrin-mediated endocytosis[J]. Traffic, 2008, 9(10): 1791-1800.
[45] CONNER SD, SCHMID SL. Identification of an adaptor-associated kinase, AAK1, as a regulator of clathrin-mediated endocytosis[J]. The Journal of Cell Biology, 2002, 156(5): 921-929.
[46] RICOTTA D, CONNER SD, SCHMID SL, von FIGURA K, HONING S. Phosphorylation of the AP2 mu subunit by AAK1 mediates high affinity binding to membrane protein sorting signals[J]. The Journal of Cell Biology, 2002, 156(5): 791-795.
[47] ABHINAND CS, GALIPON J, MORI M, RAMESH P, PRASAD TSK, RAJU R, SUDHAKARAN PR, TOMITA M. Temporal phosphoproteomic analysis of VEGF-A signaling in HUVECs: an insight into early signaling events associated with angiogenesis[J]. Journal of Cell Communication and Signaling, 2023, 17(3): 1067-1079.
[48] RAZZAQ A, DISOMA C, ZHOU YZ, TAO SY, CHEN ZP, LIU SX, ZHENG R, ZHANG YX, LIAO YJ, CHEN X, LIU SJ, DONG ZJ, XU LT, DENG X, LI SN, XIA ZX. Targeting epidermal growth factor receptor signalling pathway: a promising therapeutic option for COVID-19[J]. Reviews in Medical Virology, 2024, 34(1): e2500.
[49] HENDERSON DM, CONNER SD. A novel AAK1 splice variant functions at multiple steps of the endocytic pathway[J]. Molecular Biology of the Cell, 2007, 18(7): 2698-2706.
[50] CONNER SD, SCHMID SL. Differential requirements for AP-2 in clathrin-mediated endocytosis[J]. The Journal of Cell Biology, 2003, 162(5): 773-779.
[51] WANG Z, LIU B, MA XY, WANG Y, HAN WF, XIANG LB. lncRNA ZFAS1 promotes intervertebral disc degeneration by upregulating AAK1[J]. Open Medicine, 2022, 17(1): 1973-1986.
[52] CHEN YY, GAO X, PEI H. miRNA-384-3p alleviates sevoflurane-induced nerve injury by inhibiting Aak1 kinase in neonatal rats[J]. Brain and Behavior, 2022, 12(7): e2556.
[53] LIAN J, ZHU XX, DU J, HUANG BJ, ZHAO FT, MA CY, GUO R, ZHANG YX, JI LK, YAHAYA BH, LIN JT. Extracellular vesicle-transmitted miR-671-5p alleviates lung inflammation and injury by regulating the AAK1/NF- κB axis[J]. Molecular Therapy, 2023, 31(5): 1365-1382.
[54] YUAN C, AI KL, XIANG MH, XIE CL, ZHAO MY, WU M, LI HL, WU YR, CAO YQ, LI C, ZHONG YJ, PEI XM, LAW HKW, GAO LQ, XIAO QC, YANG XY. Novel 1-hydroxy phenothiazinium-based derivative protects against bacterial sepsis by inhibiting AAK1-mediated LPS internalization and caspase-11 signaling[J]. Cell Death & Disease, 2022, 13: 722.
[55] LOI M, GANNAGÉ M, MÜNZ C. ATGs help MHC class II, but inhibit MHC class I antigen presentation[J]. Autophagy, 2016, 12(9): 1681-1682.
[56] OH DS, PARK JH, JUNG HE, KIM HJ, LEE HK. Autophagic protein ATG5 controls antiviral immunity *via* glycolytic reprogramming of dendritic cells against respiratory syncytial virus infection[J]. Autophagy, 2021, 17(9): 2111-2127.
[57] GUPTA-ROSSI N, ORTICA S, MEAS-YEDID V, HEUSS S, MORETTI J, OLIVO-MARIN JC, ISRAËL A. The adaptor-associated kinase 1, AAK1, is a positive regulator of the Notch pathway[J]. Journal of Biological Chemistry, 2011, 286(21): 18720-18730.
[58] SONG YY, SHI RB, LIU YJ, CUI FZ, HAN L, WANG CD, CHEN TT, LI ZW, ZHANG ZJ, TANG YH, YANG GY, GUAN YT. M2 microglia extracellular vesicle miR-124 regulates neural stem cell differentiation in ischemic stroke *via* AAK1/NOTCH[J]. Stroke, 2023, 54(10): 2629-2639.
[59] AGAJANIAN MJ, WALKER MP, AXTMAN AD, RUELA-DE-SOUSA RR, SERAFIN DS, RABINOWITZ AD, GRAHAM DM, RYAN MB, TAMIR T, NAKAMICHI Y, GAMMONS MV, BENNETT JM, COUÑAGO RM, DREWRY DH, ELKINS JM,

GILEADI C, GILEADI O, GODOI PH, KAPADIA N, MÜLLER S, et al. WNT activates the AAK1 kinase to promote clathrin-mediated endocytosis of LRP6 and establish a negative feedback loop[J]. Cell Reports, 2019, 26(1): 79-93.e8.

[60] 王崴, 王鹤潼, 刘勋, 朱利民, 林婷婷. 睑板腺癌细胞过表达THBS1后的蛋白质组学研究[J]. 中华眼科杂志, 2025, 61(5): 376-383.
WANG W, WANG HT, LIU X, ZHU LM, LIN TT. Proteomic analysis of meibomian gland carcinoma cells after overexpression of thrombospondin 1[J]. Chinese Journal of Ophthalmology, 2025, 61(5): 376-383 (in Chinese).

[61] ZHANG ZH, HUANG YQ, LI S, HONG L. Comprehensive analysis based on glycolytic and glutaminolytic pathways signature for predicting prognosis and immunotherapy in ovarian cancer[J]. Journal of Cancer, 2024, 15(2): 383-400.

[62] LI C, WAN ZQ, DENG QL, LI ZG, WANG YL. Exploring the shared gene signatures and molecular mechanisms between bladder urothelial carcinoma and metabolic syndrome[J]. Archivos Espanoles de Urologia, 2023, 76(8): 605-621.

[63] KUAI LT, ONG SE, MADISON JM, WANG X, DUVALL JR, LEWIS TA, LUCE CJ, CONNER SD, PEARLMAN DA, WOOD JL, SCHREIBER SL, CARR SA, SCOLNICK EM, HAGGARTY SJ. AAK1 identified as an inhibitor of neuregulin-1/ErbB4-dependent neurotrophic factor signaling using integrative chemical genomics and proteomics[J]. Chemistry & Biology, 2011, 18(7): 891-906.

[64] TONELLO R, ANDERSON WB, DAVIDSON S, ESCRIOU V, YANG L, SCHMIDT BL, IMLACH WL, BUNNETT NW. The contribution of endocytosis to sensitization of nociceptors and synaptic transmission in nociceptive circuits[J]. Pain, 2023, 164(6): 1355-1374.

[65] SHEHATA SN, DEAK M, COLLODET C, SPIEGL SF, GELEY S, SUMPTON D, SAKAMOTO K. Identification of novel PCTAIRE-1/CDK16 substrates using a chemical genetic screen[J]. Cellular Signalling, 2019, 59: 53-61.

[66] LÉGER H, SANTANA E, LEU NA, SMITH ET, BELTRAN WA, AGUIRRE GD, LUCA FC. Ndr kinases regulate retinal interneuron proliferation and homeostasis[J]. Scientific Reports, 2018, 8: 12544.

[67] LATOURELLE JC, PANKRATZ N, DUMITRIU A, WILK JB, GOLDWURM S, PEZZOLI G, MARIANI CB, DESTEFANO AL, HALTER C, GUSELLA JF, NICHOLS WC, MYERS RH, FOROUD T. Genomewide association study for onset age in Parkinson disease[J]. BMC Medical Genetics, 2009, 10: 98.

[68] SHI BX, CONNER SD, LIU J. Dysfunction of endocytic kinase AAK1 in ALS[J]. International Journal of Molecular Sciences, 2014, 15(12): 22918-22932.

[69] XU YF, ZHANG R, DU XZ, HUANG YX, GAO Y, WEN YJ, QIAO D, SUN N, LIU ZF. Identification of aberrant plasma vesicles containing AAK1 and CCDC18-AS1 in adolescents with major depressive disorder and preliminary exploration of treatment efficacy[J]. Genomics, 2025, 117(2): 110993.

[70] LI JP, LI Y, LIU LF, JIANG W, JIA YM, YANG J, LI L, ZHANG XJ, SU JT, KAUSHIK S. Discovery and evaluation of HW161023 as a potent and orally active AAK1 inhibitor[J]. Bioorganic & Medicinal Chemistry Letters, 2024, 114: 130012.

[71] KÖNIG S, NIMTZ M, SCHEITER M, LJUNGGREN HG, BRYCESON YT, JÄNSCH L. Kinome analysis of receptor-induced phosphorylation in human natural killer cells[J]. PLoS One, 2012, 7(1): e29672.

[72] 姜贵先, 胡荣贵, 吴皓. AAK1相互作用蛋白的筛选及其调控细胞内整体翻译水平的研究[J]. 上海交通大学学报(医学版), 2023, 43(7): 821-828.
JIANG GX, HU RG, WU H. Screening of AAK1 interaction proteins and its role in regulating global translation level in cells[J]. Journal of Shanghai Jiao Tong University (Medical Science), 2023, 43(7): 821-828 (in Chinese).

[73] KIM Y, LEE SB, CHO M, CHOE S, JANG M. Indian almond (*Terminalia catappa* Linn.) leaf extract extends lifespan by improving lipid metabolism and antioxidant activity dependent on AMPK signaling pathway in *Caenorhabditis elegans* under high-glucose-diet conditions[J]. Antioxidants, 2023, 13(1): 14.

[74] KANAOKA Y, KIMURA SH, OKAZAKI I, IKEDA M, NOJIMA H. GAK: a cyclin G associated kinase contains a tensin/auxilin-like domain[J]. FEBS Letters, 1997, 402(1): 73-80.

[75] KOROLCHUK VI, BANTING G. CK2 and GAK/auxilin2 are major protein kinases in clathrin-coated vesicles[J]. Traffic, 2002, 3(6): 428-439.

[76] GREENER T, ZHAO XH, NOJIMA H, EISENBERG E, GREENE LE. Role of cyclin G-associated kinase in uncoating clathrin-coated vesicles from non-neuronal cells[J]. Journal of Biological Chemistry, 2000, 275(2): 1365-1370.

[77] LEE DW, WU XF, EISENBERG E, GREENE LE. Recruitment dynamics of GAK and auxilin to clathrin-coated pits during endocytosis[J]. Journal of Cell Science, 2006, 119(Pt 17): 3502-3512.

[78] LEE DW, ZHAO XH, ZHANG F, EISENBERG E, GREENE LE. Depletion of GAK/auxilin 2 inhibits receptor-mediated endocytosis and recruitment of both clathrin and clathrin adaptors[J]. Journal of Cell Science, 2005, 118(Pt 18): 4311-4321.

[79] HENRY KR, D'HONDT K, CHANG JS, NIX DA, COPE MJTV, CHAN CSM, DRUBIN DG, LEMMON SK. The actin-regulating kinase Prk1p negatively regulates Scd5p, a suppressor of clathrin deficiency, in actin organization and endocytosis[J]. Current Biology, 2003, 13(17): 1564-1569.

[80] ZHANG CX, ENGQVIST-GOLDSTEIN ÅEY, CARRENO S, OWEN DJ, SMYTHE E, DRUBIN DG. Multiple roles for cyclin G-associated kinase in clathrin-mediated sorting events[J]. Traffic, 2005, 6(12): 1103-1113.

[81] ZHANG L, GJOERUP O, ROBERTS TM. The serine/threonine kinase cyclin G-associated kinase regulates epidermal growth factor receptor signaling[J]. Proceedings of the National Academy of Sciences of the United States of America, 2004, 101(28): 10296-10301.

[82] UMEDA A, MEYERHOLZ A, UNGEWICKELL E. Identification of the universal cofactor (auxilin 2) in clathrin coat dissociation[J]. European Journal of Cell Biology, 2000, 79(5): 336-342.

[83] KAMETAKA S, MORIYAMA K, BURGOS PV, EISENBERG E, GREENE LE, MATTERA R, BONIFACINO JS. Canonical interaction of cyclin G associated kinase with adaptor protein 1 regulates lysosomal enzyme sorting[J]. Molecular Biology of the Cell, 2007, 18(8): 2991-3001.

[84] LIN AW, GILL KK, CASTAÑEDA MS, MATUCCI I, EDER N, CLAXTON S, FLYNN H, SNIJDERS AP, GEORGE R, ULTANIR SK. Chemical genetic identification of GAK substrates reveals its role in regulating Na^+/K^+-ATPase[J]. Life Science Alliance, 2018, 1(6): e201800118.

[85] LIN Y, TANG YJ, ZONG HL, GU JX, DENG WW, WANG C, SUN B. Cyclin G associated kinase interacts with interleukin 12 receptor beta2 and suppresses interleukin 12 induced IFN-gamma production[J]. FEBS Letters, 2007, 581(26): 5151-5157.

[86] MIYAZAKI M, HIRAMOTO M, TAKANO N, KOKUBA H, TAKEMURA J, TOKUHISA M, HINO H, KAZAMA H, MIYAZAWA K. Targeted disruption of GAK stagnates autophagic flux by disturbing lysosomal dynamics[J]. International Journal of Molecular Medicine, 2021, 48(4): 195.

[87] MUNSON MJ, MATHAI BJ, NG MYW, TRACHSEL-MONCHO L, deLa BALLINA LR, SCHULTZ SW, AMAN Y, LYSTAD AH, SINGH S, SINGH S, WESCHE J, FANG EF, SIMONSEN A. GAK and PRKCD are positive regulators of PRKN-independent mitophagy[J]. Nature Communications, 2021, 12: 6101.

[88] SATO J, SHIMIZU H, KASAMA T, YABUTA N, NOJIMA H. GAK, a regulator of clathrin-mediated membrane trafficking, localizes not only in the cytoplasm but also in the nucleus[J]. Genes to Cells, 2009, 14(5): 627-641.

[89] SHIMIZU H, NAGAMORI I, YABUTA N, NOJIMA H. GAK, a regulator of clathrin-mediated membrane traffic, also controls centrosome integrity and chromosome congression[J]. Journal of Cell Science, 2009, 122(Pt 17): 3145-3152.

[90] TANENBAUM ME, VALLENIUS T, GEERS EF, GREENE L, MÄKELÄ TP, MEDEMA RH. Cyclin G-associated kinase promotes microtubule outgrowth from chromosomes during spindle assembly[J]. Chromosoma, 2010, 119(4): 415-424.

[91] NAITO Y, SHIMIZU H, KASAMA T, SATO J, TABARA H, OKAMOTO A, YABUTA N, NOJIMA H. Cyclin G-associated kinase regulates protein phosphatase 2A by phosphorylation of its B'γ subunit[J]. Cell Cycle, 2012, 11(3): 604-616.

[92] YABUTA N, OTA C, SASAKURA T, NAITO Y, OKUZAKI D, FUKUSHIMA K, NOJIMA H. Late cornified envelope 1C (LCE1C), a transcriptional target of TAp63 phosphorylated at T46/T281, interacts with PRMT5[J]. Scientific Reports, 2018, 8: 4892.

[93] 康新江, 王昌河, 程序, 王变变, 秦宇豪, 安傲梅, 沈文鑫, 杨凯凯 . 细胞周期蛋白 G 相关激酶(GAK)对多巴胺神经元胞吞作用的调节机制及其导致帕金森病的病理机制[Z]. 西南医科大学, 西安交通大学 . 2023-10-27.
KANG XJ, WANG CH, CHENG X, WANG BB, QIN YH, AN AM, SHEN WX, YANG KK. The regulatory mechanism of cyclin G-associated kinase (GAK) on endocytosis in dopamine neurons and its resulting pathological mechanisms in Parkinson's disease[Z]. Southwest Medical University, Xi'an Jiaotong University. 2023-10-27 (in Chinese).

[94] 何淑君 . 果蝇帕金森氏病模型中网格脱包被分子 GAK/auxilin 介导渐进性运动障碍和多巴胺能神经元凋亡[J]. 科学新闻, 2018, 20(4): 129.
HE SJ. Auxilin underlies progressive locomotor deficits and dopaminergic neuron loss in a *Drosophila* model of Parkinson's disease[J]. Science News, 2018, 20(4): 129 (in Chinese).

[95] KEARNS AE, DONOHUE MM, SANYAL B, DEMAY MB. Cloning and characterization of a novel protein kinase that impairs osteoblast differentiation *in vitro*[J]. The Journal of Biological Chemistry, 2001, 276(45): 42213-42218.

[96] BORNER GHH, ANTROBUS R, HIRST J, BHUMBRA GS, KOZIK P, JACKSON LP, SAHLENDER DA, ROBINSON MS. Multivariate proteomic profiling identifies novel accessory proteins of coated vesicles[J]. The Journal of Cell Biology, 2012, 197(1): 141-160.

[97] SONG XL, LI ML, WU WG, DANG W, GAO Y, BIAN R, BAO RF, HU YP, HONG DF, GU J, LIU YB. Regulation of BMP2K in AP2M1-mediated EGFR internalization during the development of gallbladder cancer[J]. Signal Transduction and Targeted Therapy, 2020, 5: 154.

[98] RAMESH ST, NAVYASREE KV, SAH S, ASHOK AB, QATHOON N, MOHANTY S, SWAIN RK, UMASANKAR PK. BMP2K phosphorylates AP-2 and regulates clathrin-mediated endocytosis[J]. Traffic, 2021, 22(11): 377-396.

[99] BREHME M, HANTSCHEL O, COLINGE J, KAUPE I, PLANYAVSKY M, KÖCHER T, MECHTLER K, BENNETT KL, SUPERTI-FURGA G. Charting the molecular network of the drug target Bcr-Abl[J]. Proceedings of the National Academy of Sciences of the United States of America, 2009, 106(18): 7414-7419.

[100] MERCADO-MATOS J, JANUSIS J, ZHU S, CHEN SS, SHAW LM. Identification of a novel invasion-promoting region in insulin receptor substrate 2[J]. Molecular and Cellular Biology, 2018, 38(14): e00590-17.

[101] KRIEGER JR, TAYLOR P, GAJADHAR AS, GUHA A, MORAN MF, McGLADE CJ. Identification and

selected reaction monitoring (SRM) quantification of endocytosis factors associated with Numb[J]. Molecular & Cellular Proteomics, 2013, 12(2): 499-514.
[102] HICKS C, GARDNER J, EIGER DS, CAMARDA ND, PHAM U, DHAR S, RODRIGUEZ H, CHUNDI A, RAJAGOPAL S. ACKR3 proximity labeling identifies novel G protein-and β-arrestin-independent GPCR interacting proteins[J/OL]. bioRxiv, 2024. DOI: 2024.01.27.577545.
[103] HIRABAYASHI S, OHKI K, NAKABAYASHI K, ICHIKAWA H, MOMOZAWA Y, OKAMURA K, YAGUCHI A, TERADA K, SAITO Y, YOSHIMI A, OGATA-KAWATA H, SAKAMOTO H, KATO M, FUJIMURA J, HINO M, KINOSHITA A, KAKUDA H, KUROSAWA H, KATO K, KAJIWARA R, et al. $ZNF_3$84-related fusion genes define a subgroup of childhood B-cell precursor acute lymphoblastic leukemia with a characteristic immunotype[J]. Haematologica, 2017, 102(1): 118-129.
[104] ALOTAIBI RN, HOWE BJ, MORENO URIBE LM, SANCHEZ C, DELEYIANNIS FWB, PADILLA C, POLETTA FA, ORIOLI IM, BUXÓ CJ, WEHBY GL, VIEIRA AR, MURRAY J, VALENCIA-RAMÍREZ C, RESTREPO MUÑETON CP, LONG RE, SHAFFER JR, REIS SE, WEINBERG SM, NEISWANGER K, McNEIL DW, et al. Genetic analyses of enamel hypoplasia in multiethnic cohorts[J]. Human Heredity, 2022, 87(2): 34-50.
[105] 卫柄邑, 谢艳, 吴晓龙, 邢伟鹏, 王娜, 宁桃丽. lncRNA H19促进胎盘间充质干细胞成骨分化的相关研究[J]. 组织工程与重建外科, 2024, 20(6): 665-671.
WEI BY, XIE Y, WU XL, XING WP, WANG N, NING TL. Study on lncRNA H19 promoting osteogenic differentiation of placenta-derived mesenchymal stem cells[J]. Journal of Tissue Engineering and Reconstructive Surgery, 2024, 20(6): 665-671 (in Chinese).
[106] LI JR, SUN LM, SUN JZ, JIANG HZ. Genome-wide association research on the reproductive traits of Qianhua Mutton Merino sheep[J]. Animal Bioscience, 2024, 37(9): 1535-1547.
[107] ZHANG HG, XU RY, LI B, XIN ZL, LING ZJ, ZHU WW, LI X, ZHANG P, FU Y, CHEN JY, LIU LK, CHENG J, JIANG HB. LncRNA NEAT1 controls the lineage fates of BMSCs during skeletal aging by impairing mitochondrial function and pluripotency maintenance[J]. Cell Death & Differentiation, 2021, 29(2): 351-365.
[108] SU AI, WILTSHIRE T, BATALOV S, LAPP H, CHING KA, BLOCK D, ZHANG J, SODEN R, HAYAKAWA M, KREIMAN G, COOKE MP, WALKER JR, HOGENESCH JB. A gene atlas of the mouse and human protein-encoding transcriptomes[J]. Proceedings of the National Academy of Sciences of the United States of America, 2004, 101(16): 6062-6067.
[109] PERUCCA S, di PALMA A, PICCALUGA PP, GEMELLI C, ZORATTI E, BASSI G, GIACOPUZZI E, LOJACONO A, BORSANI G, TAGLIAFICO E, SCUPOLI MT, BERNARDI S, ZANAGLIO C, CATTINA F, CANCELLI V, MALAGOLA M, KRAMPERA M, MARINI M, ALMICI C, FERRARI S, et al. Mesenchymal stromal cells (MSCs) induce *ex vivo* proliferation and erythroid commitment of cord blood haematopoietic stem cells (CB-$CD34^+$ cells)[J]. PLoS One, 2017, 12(2): e0172430.
[110] POTTS MB, KIM HS, FISHER KW, HU YC, CARRASCO YP, BULUT GB, OU YH, HERRERA-HERRERA ML, CUBILLOS F, MENDIRATTA S, XIAO GH, HOFREE M, IDEKER T, XIE Y, HUANG LJ, LEWIS RE, MacMILLAN JB, WHITE MA. Using functional signature ontology (FUSION) to identify mechanisms of action for natural products[J]. Science Signaling, 2013, 6(297): ra90.
[111] CENDROWSKI J, KACZMAREK M, MAZUR M, KUZMICZ-KOWALSKA K, JASTRZEBSKI K, BREWINSKA-OLCHOWIK M, KOMINEK A, PIWOCKA K, MIACZYNSKA M. Splicing variation of BMP2K balances abundance of COPII assemblies and autophagic degradation in erythroid cells[J]. eLife, 2020, 9: e58504.
[112] WANG MM, ZHANG T, ZHANG XC, JIANG Z, PENG M, HUANG Z. BMP2K dysregulation promotes abnormal megakaryopoiesis in acute megakaryoblastic leukemia[J]. Cell & Bioscience, 2020, 10: 57.
[113] ZHOU XM, ZHU YM, LIU JY, LIU JD. Effects of *Helicobacter pylori* infection on the development of chronic gastritis[J]. The Turkish Journal of Gastroenterology, 2023, 34(7): 700-713.
[114] LIU HP, LIN YJ, LIN WY, WAN L, SHEU JJ, LIN HJ, TSAI Y, TSAI CH, TSAI FJ. A novel genetic variant of BMP2K contributes to high myopia[J]. Journal of Clinical Laboratory Analysis, 2009, 23(6): 362-367.
[115] CHEN JH, MENG YH, ZHOU JH, ZHUO M, LING F, ZHANG Y, DU HL, WANG XN. Identifying candidate genes for type 2 diabetes mellitus and obesity through gene expression profiling in multiple tissues or cells[J]. Journal of Diabetes Research, 2013, 2013(1): 970435.
[116] LOKMAN FE, SEMAN NA, ISMAIL AA, YAACOB NA, MUSTAFA N, KHIR ASM, HUSSEIN Z, WAN MOHAMUD WN. Gene expression profiling in ethnic Malays with type 2 diabetes mellitus, with and without diabetic nephropathy[J]. Journal of Nephrology, 2011, 24(6): 778-789.
[117] GRAEFE SEB, STREICHERT T, BUDDE BS, NÜRNBERG P, STEEG C, MÜLLER-MYHSOK B, FLEISCHER B. Genes from Chagas susceptibility loci that are differentially expressed in *T. cruzi*-resistant mice are candidates accounting for impaired immunity[J]. PLoS One, 2006, 1(1): e57.
[118] PANDZIC T, LARSSON J, HE LQ, KUNDU S, BAN K, AKHTAR-ALI M, HELLSTRÖM AR, SCHUH A, CLIFFORD R, BLAKEMORE SJ, STREFFORD JC, BAUMANN T, LOPEZ-GUILLERMO A, CAMPO E, LJUNGSTRÖM V, MANSOURI L, ROSENQUIST R, SJÖBLOM T, HELLSTRÖM M. Transposon mutagenesis reveals fludarabine resistance mechanisms in chronic lymphocytic leukemia[J]. Clinical Cancer Research, 2016, 22(24): 6217-6227.

[119] ESWARAN J, BERNAD A, LIGOS JM, GUINEA B, DEBRECZENI JÉ, SOBOTT F, PARKER SA, NAJMANOVICH R, TURK BE, KNAPP S. Structure of the human protein kinase MPSK1 reveals an atypical activation loop architecture[J]. Structure, 2008, 16(1): 115-124.

[120] GUINEA B, LIGOS JM, LAÍN de LERA T, MARTÍN-CABALLERO J, FLORES J, GONZALEZ deLa PEÑA M, GARCÍA-CASTRO J, BERNAD A. Nucleocytoplasmic shuttling of STK16 (PKL12), a Golgi-resident serine/threonine kinase involved in VEGF expression regulation[J]. Experimental Cell Research, 2006, 312(2): 135-144.

[121] STAIRS DB, NOTARFRANCESCO KL, CHODOSH LA. The serine/threonine kinase, krct, affects endbud morphogenesis during murine mammary gland development[J]. Transgenic Research, 2005, 14(6): 919-940.

[122] LÓPEZ-CORAL A, STRIZ AC, TUMA PL. A serine/threonine kinase 16-based phospho-proteomics screen identifies WD repeat protein-1 as a regulator of constitutive secretion[J]. Scientific Reports, 2018, 8: 13049.

[123] LI J, WANG Y, MENG XL, LIANG H. Modulation of transcriptional activity in brain lower grade glioma by alternative splicing[J]. PeerJ, 2018, 6: e4686.

[124] SELLITTI DF, KOLES N, MENDONÇA MC. Regulation of C-type natriuretic peptide expression[J]. Peptides, 2011, 32(9): 1964-1971.

[125] LIU JJ, YANG XX, LI BH, WANG JJ, WANG WC, LIU J, LIU QS, ZHANG X. STK16 regulates actin dynamics to control Golgi organization and cell cycle[J]. Scientific Reports, 2017, 7: 44607.

[126] LIGOS JM, de LERA TL, HINDERLICH S, GUINEA B, SÁNCHEZ L, ROCA R, VALENCIA A, BERNAD A. Functional interaction between the Ser/Thr kinase PKL12 and N-acetylglucosamine kinase, a prominent enzyme implicated in the salvage pathway for GlcNAc recycling[J]. The Journal of Biological Chemistry, 2002, 277(8): 6333-6343.

[127] LI BS, WANG XL, RUTZ B, WANG RX, TAMALUNAS A, STRITTMATTER F, WAIDELICH R, STIEF CG, HENNENBERG M. The STK16 inhibitor STK16-IN-1 inhibits non-adrenergic and non-neurogenic smooth muscle contractions in the human prostate and the human male detrusor[J]. Naunyn-Schmiedeberg's Archives of Pharmacology, 2020, 393(5): 829-842.

[128] FLETT A, SEMERDJIEVA S, JACKSON AP, SMYTHE E. Regulation of the clathrin-coated vesicle cycle by reversible phosphorylation[J]. Biochemical Society Symposium, 2005(72): 65-70.

[129] LI CJ, LU Y, ZHOU M, ZONG XG, LI C, XU XL, GUO LJ, LU Q. Activation of GABAB receptors ameliorates cognitive impairment *via* restoring the balance of HCN1/HCN2 surface expression in the hippocampal CA1 area in rats with chronic cerebral hypoperfusion[J]. Molecular Neurobiology, 2014, 50(2): 704-720.

[130] ZHOU M, LUO P, LU Y, LI CJ, WANG DS, LU Q, XU XL, HE Z, GUO LJ. Imbalance of HCN1 and HCN2 expression in hippocampal CA1 area impairs spatial learning and memory in rats with chronic morphine exposure[J]. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2015, 56: 207-214.

[131] KADLECOVA Z, SPIELMAN SJ, LOERKE D, MOHANAKRISHNAN A, REED DK, SCHMID SL. Regulation of clathrin-mediated endocytosis by hierarchical allosteric activation of AP2[J]. The Journal of Cell Biology, 2017, 216(1): 167-179.

[132] WANG NX, YANG F, QIU ZY, ZHANG L, ZOU DQ, TANG YR, ZHANG RH, SUN CL, LIU P, QI KX, WANG JY, HE H, GAN L. Curcumin prevents dexamethasone-induced activation of the pseudorabies virus in rat pheochromocytoma cells through the miR-155-5p-Aak1-Numb/Notch2 signalling axis[J]. Veterinary Research, 2025, 56(1): 86.

[133] SHEN BX, LIU N, DAI YW. Exosomes derived from umbilical cord mesenchymal stem cells ameliorate ischemic brain injury in mice by regulating AAK1 *via* miR-664a-5p[J/OL]. International Journal of Neuroscience, 2024. DOI: https://doi.org/10.1080/00207454.2024.2441120.

[134] HE ZP, ZUO PY, XU PL, YUAN HZ, BHAVE M, WEI XY, YANG ZY, HAN L, SCHMID SL, CHEN ZM. Dynamic early recruitment of GAK-Hsc70 regulates coated pit maturation[J]. Proceedings of the National Academy of Sciences of the United States of America, 2025, 122(22): e2503738122.

[135] YOSHIDA A, OHTSUKA S, MATSUMOTO F, MIYAGAWA T, OKINO R, IKEDA Y, TADA N, GOTOH A, MAGARI M, HATANO N, MORISHITA R, SATOH A, SUNATSUKI Y, NILSSON UJ, ISHIKAWA T, TOKUMITSU H. Development of a novel AAK1 inhibitor *via* kinobeads-based screening[J]. Scientific Reports, 2024, 14: 6723.

[136] OLSZEWSKI MB, CHANDRIS P, PARK BC, EISENBERG E, GREENE LE. Disruption of clathrin-mediated trafficking causes centrosome overduplication and senescence[J]. Traffic, 2014, 15(1): 60-77.

[137] YABUNO Y, UCHIHASHI T, SASAKURA T, SHIMIZU H, NAITO Y, FUKUSHIMA K, OTA K, KOGO M, NOJIMA H, YABUTA N. Clathrin heavy chain phosphorylated at T606 plays a role in proper cell division[J]. Cell Cycle, 2019, 18(16): 1976-1994.

[138] BEILINA A, RUDENKO IN, KAGANOVICH A, CIVIERO L, CHAU H, KALIA SK, KALIA LV, LOBBESTAEL E, CHIA R, NDUKWE K, DING JH, NALLS MA, International Parkinson's Disease Genomics Consortium, North American Brain Expression Consortium, OLSZEWSKI M, HAUSER DN, KUMARAN R, LOZANO AM, BAEKELANDT V, GREENE LE, et al. Unbiased screen for interactors of leucine-rich repeat kinase 2 supports a common pathway for sporadic and familial Parkinson disease[J]. Proceedings of the National Academy of Sciences of the United States of America, 2014, 111(7): 2626-2631.

[139] OHTA S, TAKEUCHI M, DEGUCHI M, TSUJI T, GAHARA Y, NAGATA K. A novel transcriptional factor with Ser/Thr kinase activity involved in the transforming growth factor (TGF)-beta signalling pathway[J]. The Biochemical Journal, 2000, 350(Pt 2): 395-404.
[140] XU JY, ZHANG L, XU YF, ZHANG H, GAO JX, WANG Q, TIAN ZJ, XUAN L, CHEN HY, WANG Y. PP2A facilitates porcine reproductive and respiratory syndrome virus replication by deactivating irf3 and limiting type I interferon production[J]. Viruses, 2019, 11(10): 948.
[141] YANG LJ, XU JY, GUO LJ, GUO TJ, ZHANG L, FENG L, CHEN HY, WANG Y. Porcine epidemic diarrhea virus-induced epidermal growth factor receptor activation impairs the antiviral activity of type I interferon[J]. Journal of Virology, 2018, 92(8): e02095-17.
[142] WANG DF, HUO H, WERID GM, IBRAHIM YM, TANG LJ, WANG Y, CHEN HY. TBK1 mediates innate antiviral immune response against duck enteritis virus[J]. Viruses, 2022, 14(5): 1008.
[143] BALDWIN A, LI WL, GRACE M, PEARLBERG J, HARLOW E, MÜNGER K, GRUENEBERG DA. Kinase requirements in human cells: II. Genetic interaction screens identify kinase requirements following HPV16 E7 expression in cancer cells[J]. Proceedings of the National Academy of Sciences of the United States of America, 2008, 105(43): 16478-16483.
[145] BU YW, TENG QY, FENG DL, LIANG R, WANG HR, ZHANG XH, LI X, JIA WF, XUE J, ZHAO Y, ZHANG GZ. Adaptor complex-mediated trafficking of Newcastle disease virus fusion protein is regulated by the YLMY motif of its cytoplasmic tail[J]. Virulence, 2022, 13(1): 1849-1867.
[146] MOALEM Y, KATZ R, SUBRAMANIAM AG, MALIS Y, YAFFE Y, BORENSTEIN-AUERBACH N, TADMOR K, RAVED R, MAOZ BM, YOO JS, LUSTIG Y, LUXENBURG C, PERLSON E, EINAV S, SKLAN EH. Numb-associated kinases regulate sandfly-borne Toscana virus entry[J]. Emerging Microbes & Infections, 2024, 13(1): 2382237.
[147] ZHOU HL, XU M, HUANG Q, GATES AT, ZHANG XD, CASTLE JC, STEC E, FERRER M, STRULOVICI B, HAZUDA DJ, ESPESETH AS. Genome-scale RNAi screen for host factors required for HIV replication[J]. Cell Host & Microbe, 2008, 4(5): 495-504.
[148] NAYARISSERI A, KHANDELWAL R, MADHAVI M, SELVARAJ C, PANWAR U, SHARMA K, HUSSAIN T, SINGH SK. Shape-based machine learning models for the potential novel COVID-19 protease inhibitors assisted by molecular dynamics simulation[J]. Current Topics in Medicinal Chemistry, 2020, 20(24): 2146-2167.
[149] DAMMANN M, KRAMER M, ZIMMERMANN MO, BOECKLER FM. Quadruple target evaluation of diversity-optimized halogen-enriched fragments (HEFLibs) reveals substantial ligand efficiency for AP2-associated protein kinase 1 (AAK1)[J]. Frontiers in Chemistry, 2022, 9: 815567.