2025, 65(11): 4827-4841
CSTR: 32112.14.j.AMS.20250357
DOI: 10.13343/j.cnki.wsxb.20250357

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

Review 综述

胞内寄生病原调控宿主细胞凋亡研究进展

冉茂双[1,2]，包佳玲[1,2]，潘国庆[1,2*]

1 西南大学，资源昆虫高效养殖与利用全国重点实验室，重庆
2 西南大学，微孢子虫感染与防控重庆市重点实验室，重庆

冉茂双, 包佳玲, 潘国庆. 胞内寄生病原调控宿主细胞凋亡研究进展[J]. 微生物学报, 2025, 65(11): 4827-4841.
RAN Maoshuang, BAO Jialing, PAN Guoqing. Research progress in the regulation of host cell apoptosis by intracellular pathogens[J]. Acta Microbiologica Sinica, 2025, 65(11): 4827-4841.

摘　要：在多细胞生物中细胞死亡始终处于动态变化的过程。其中，细胞凋亡作为调节性细胞死亡的重要形式主要有内源性和外源性2条通路。在病原感染过程中，宿主细胞可通过细胞凋亡清除被感染的细胞；而病原体也进化出多种策略来调控宿主细胞凋亡，包括利用效应蛋白调控细胞信号通路、凋亡相关基因的表达、凋亡通路关键蛋白以及半胱氨酸蛋白水解酶(cysteinyl aspartate specific proteinase, Caspase)家族蛋白酶活性等。本文对病毒、胞内细菌、胞内寄生真菌以及寄生虫等胞内寄生病原调控宿主细胞凋亡的分子机制与策略进行了综述，以期为进一步探索病原体与宿主之间复杂的相互作用机制提供参考。

关键词：细胞凋亡；胞内寄生病原；宿主细胞；调控机制

Research progress in the regulation of host cell apoptosis by intracellular pathogens

RAN Maoshuang[1,2], BAO Jialing[1,2], PAN Guoqing[1,2*]

1 State Key Laboratory of Resource Insects, Southwest University, Chongqing, China
2 Chongqing Key Laboratory of Microsporidia Infection and Control, Southwest University, Chongqing, China

Abstract: In multicellular organisms, cell death is perpetually in a dynamic process. Apoptosis as a

资助项目：国家自然科学基金(32272942, 32272944)；重庆市现代农业产业技术体系(COMAITS202311)；中央高校基本科研业务费专项资金(SWU-XDJH202322)；重庆市博士后特别资助项目(2023CQBSHTB3030)
This work was supported by the National Natural Science Foundation of China (32272942, 32272944), the Chongqing Modern Agricultural Industry Technology System (COMAITS202311), the Fundamental Research Funds for the Central Universities (SWU-XDJH202322), and the Special Funding for Chongqing Postdoctoral Research Project (2023CQBSHTB3030).
*Corresponding author. Tel: +86-23-68251683, E-mail: pan_guoqing@yeah.net
Received: 2025-04-29; Accepted: 2025-07-09; Published online: 2025-08-11

pivotal form of regulated cell death, mainly encompasses two pathways: the intrinsic pathway and the extrinsic pathway. During the pathogen infection, host cells are capable of eliminating the infected cells through apoptosis. On the other hand, pathogens have evolved a multitude of strategies to regulate host cell apoptosis. These strategies involve the use of effector proteins to modulate cellular signaling pathways, the regulation of the expression of apoptosis-related genes, the control of key proteins within the apoptosis pathway, and the modulation of the activity of proteases in the Caspase family. This article provides a comprehensive review of the molecular mechanisms and strategies by which intracellular pathogens, such as viruses, bacteria, parasitic fungi, and parasites, regulate host cell apoptosis. The aim is to offer valuable references for further exploration of the intricate interaction mechanisms between pathogens and hosts.
Keywords: apoptosis; intracellular pathogens; host cells; regulatory mechanisms

细胞死亡在多细胞生物中时刻都在发生，通过消除受损或衰老的细胞来维持发育过程中的形态发生和机体稳态，还可通过清除被感染的细胞来限制病原体传播[1]。细胞可能因意外细胞死亡(accidental cell death, ACD)或调节性细胞死亡(regulated cell death, RCD)而死亡[2]。ACD是一个不受控制的细胞死亡过程，由意外伤害刺激触发，且超出了细胞的可调节能力，最终导致细胞死亡[3]。RCD涉及效应分子参与的信号级联反应，具有独特的生化特征、形态特征和免疫学后果；其中，发生在生理条件下的RCD也被称为程序性细胞死亡(programmed cell death, PCD)[4]。细胞死亡命名委员会制定了从形态学、生化和功能角度定义和解释细胞死亡的指南，目前已定义超过15种细胞死亡类型；例如，细胞凋亡(apoptosis)被定义为由半胱氨酸蛋白水解酶(cysteinyl aspartate specific proteinase, Caspase, 包括起始和效应Caspase)介导的RCD，只有当细胞决定死亡时才会激活效应Caspase，一旦激活细胞死亡不可逆转，最多只能被延迟[5]。其他类型的细胞死亡包括坏死性凋亡(necroptosis)、细胞焦亡(pyroptosis)、铁死亡(ferroptosis)、自噬(autophagy)、坏死(necrosis)、泛凋亡(panoptosis)、铜死亡(cuproptosis)以及细胞内碱化死亡(alkaliptosis)等[6]。

在病原微生物与宿主的博弈过程中宿主细胞经调节性细胞死亡后被吞噬细胞吞噬，从而清除被病原体感染的细胞，消除病原体的“生存环境(living niche)”[7]。然而，随着宿主与病原体相互作用的不断进化，病原体也获得了多种策略来精细调控宿主细胞凋亡。近年来，生命科学研究的进步极大地拓展了病原-宿主相互作用研究的广度和深度，但仍有很多病原操纵宿主细胞的分子机制有待解析。本综述总结了细胞凋亡通路及胞内病原微生物调控宿主细胞凋亡的主要策略，以期为解析胞内病原体通过调控宿主细胞凋亡以促进自身感染和复制的机制提供参考。

1 细胞凋亡通路

1.1 内源性凋亡通路

内源性凋亡通路又称线粒体凋亡通路，主要是因为该通路的启动信号源自细胞内部的线粒体。当细胞受到DNA损伤、缺氧、代谢应激等刺激时，线粒体外膜透化(mitochondrial outer membrane permeabilization, MOMP)，导致线粒体膜间腔中的蛋白质(如细胞色素C等)被释放到细胞质中，与凋亡蛋白激活因子1 (apoptotic protease activating factor 1, Apaf1)结合并形成凋亡小体，进而激活Caspase 9使下游效应Caspase 3和Caspase 7激活并切割底物等，最终引发细胞凋亡[8-9]。MOMP受B细胞淋巴瘤-2

(B cell lymphoma 2, BCL-2)家族蛋白的严格调控，根据其在凋亡通路中的作用，BCL-2 家族蛋白可分为促凋亡和抗凋亡蛋白两类，不同成员通过调控 MOMP 发挥作用；例如，在人类中含有多 BCL-2 同源结构域(BCL-2 homology domain, BH)的抗凋亡蛋白[如 BCL-2、BCL-2 类蛋白 1 (BCL-2 like protein 1, BCL-2L1，也称 BCL-XL)、BCL-2 类蛋白 2 (BCL-2 like protein 2, BCL-2L2，也称 BCL-W)、髓样细胞白血病 1 (mast cell leukemia 1, MCL1)、BCL-2 相关蛋白 A1 (BCL2-related protein A1, BCL-2A1)和 BCL-2 类蛋白 10 (BCL2-like protein 10, BCL-2L10，也称 BCL-B]；含多 BH 结构域的促凋亡蛋白[如 BCL-2 同源拮抗剂 K (BCL-2 associated K protein, BAK)、BCL-2 同源拮抗剂 X (BCL-2 associated X protein, BAX)和 BCL-2 相关卵巢杀伤蛋白(BCL-2-related ovarian killer protein, BOK)]和仅含 BH3 结构域的促凋亡蛋白[如 BH3 相互作用域死亡激动剂(BH3-interacting domain death agonist, BID)、BCL-2 相互作用介质(BCL-2 interacting mediator, BIM)、BCL-2 相关的细胞死亡激动因子(BCL-2-associated agonist of cell death, BAD)、BCL-2 相互作用杀伤蛋白(BCL-2 interacting killer, BIK)、佛波酯诱导蛋白 1 (phorbol-12-myristate-13-acetate-induced protein 1, *PMAIP1* 基因产物常写为 NOXA)、p53 上调凋亡调控因子(P53 upregulated modulator of apoptosis, PUMA)、BCL-2 修饰因子(BCL-2 modifying factor, BMF)和 Harakiri BCL2 相互作用蛋白(harakiri, BCL-2 interacting protein, HRK)][10]。BAK 和 BAX 是线粒体外膜上最重要的促凋亡蛋白，寡聚化后直接在线粒体外膜形成膜孔，抗凋亡蛋白 BCL-2 与促凋亡蛋白 BAX/BAK 相互作用后阻止其寡聚化和膜孔形成，进而阻断细胞凋亡；仅含 BH3 结构域的促凋亡蛋白可以直接激活促凋亡蛋白 BAX/BAK 以促进膜孔形成和细胞凋亡，也可与抗凋亡蛋白 BCL-2 互作，破坏 BCL-2 和 BAX/BAK 的平衡，进而促进膜孔形成与细胞凋亡[11]。因此，BCL-2 家族蛋白如同“三元开关”调控线粒体凋亡通路。BH 结构域基序在进化上高度保守，BCL-2 蛋白不仅存在于哺乳动物中，还广泛存在于多细胞动物和一些病毒中[12]。

1.2 外源性凋亡通路

外源性细胞凋亡通路主要由细胞外配体结合细胞表面的死亡受体触发，这些死亡受体在胞内区域都具有一个蛋白互作结构域，称为死亡结构域(death domain, DD)，例如凋亡相关因子(factor-related apoptosis, Fas)、肿瘤坏死因子受体 1 (tumor necrosis factor receptor 1, TNFR1)、肿瘤坏死因子相关凋亡诱导配体受体 1/死亡受体 4 (TNF-related apoptosis-inducing ligand receptor 1/death receptor 4, TRAIL-R1/DR4)和肿瘤坏死因子相关凋亡诱导配体受体 2/死亡受体 5 (TNF-related apoptosis-inducing ligand receptor 2/death receptor 5, TRAIL-R2/DR5)，它们由相应的胞外配体激活[1]。例如，Fas 配体(Fas-ligand, FASL)或肿瘤坏死因子(tumor necrosis factor, TNF)-α 与其细胞表面相对应的死亡受体 Fas 或 TNF 受体(TNF receptor, TNFR)结合，激活其死亡结构域并募集胞内 TNF 受体相关因子 2 (TNF receptor-associated factor 2, TRAF2)、受体相互作用蛋白 1 (receptor-interacting protein kinase 1, RIPK1)、细胞内凋亡抑制蛋白(cellular inhibitor of apoptosis protein, cIAP)、TNFR 相关死亡结构域蛋白(TNFR-associated death domain protein, TRADD)，组装形成初级死亡信号复合体，而后进一步招募 Fas 相关死亡结构域蛋白(Fas-associated death domain protein, FADD)、Caspase 8、TRADD 和 RIPK1 等蛋白，通过与 FADD 相互作用激活 Caspase 8，活化的 Caspase 8 直接激活下游效应 Caspase 3 和 Caspase 7，最终引发细胞凋亡[13]。同时，在某些细胞中 Caspase 8 可以裂解并活化线粒体中仅有 BH3 结构域的蛋白 BID，进而激活 BAX 和 BAK，导致线粒体细胞凋亡[8]。当 Caspase 8 活性被抑制时，活化的 RIPK1 与

RIPK3 结合并使其活化，进而 RIPK3 又磷酸化激活混合谱系激酶结构域样蛋白(mixed lineage kinase domain-like protein, MLKL)，通过破坏质膜的完整性来介导坏死性凋亡[14]。

2 病原感染调控宿主细胞凋亡

病原感染过程中宿主细胞凋亡在抵御病原体方面发挥着重要作用，这一过程受到宿主与病原体的双重调控。宿主细胞通过诱导凋亡来清除被感染的细胞，从而限制病原体的扩散并激活免疫反应[15]。然而，病原体也进化出了多种策略来调控宿主细胞凋亡，其调控机制复杂且动态。某些病毒在感染前期抑制宿主细胞凋亡，而在后期通过诱导宿主细胞凋亡来释放子代病毒，进而快速感染邻近的健康细胞；而一些胞内寄生病原需要在宿主细胞内存活较长时间以完成其生命周期，这些病原体通过抑制宿主细胞凋亡来延长宿主细胞的存活时间，保证其在宿主细胞内的生存微环境[16]。尽管宿主细胞凋亡通常对病原体有害，但部分病原体可利用细胞死亡途径进行播散。其调控机制的复杂性不仅源于细胞凋亡调控网络，还与感染剂量、宿主细胞类型、感染持续时间等变量相关。本文将重点综述胞内病原(病毒、细菌、真菌和寄生虫)对宿主细胞凋亡的调控策略(图 1)。

2.1 病毒调控宿主细胞凋亡

病毒感染后的宿主细胞凋亡研究最为广泛。感染引起的宿主细胞凋亡对病毒复制具有双重作用。一方面，宿主细胞通过凋亡消除被病毒感染的细胞，进而消灭病毒；另一方面，病毒诱导宿主细胞凋亡作为释放和传播后代病毒的方式。在这 2 种情况下病毒都需要编码一些产物来阻止或延迟宿主细胞凋亡以实现病毒复制产生足够多的后代，一些病毒在复制时期会抑制宿主细胞凋亡，而在释放子代病毒时期会诱导细胞凋亡以增强传播[17]。病毒调控宿主细胞凋亡的策略主要有 2 类：一是通过上游信号通

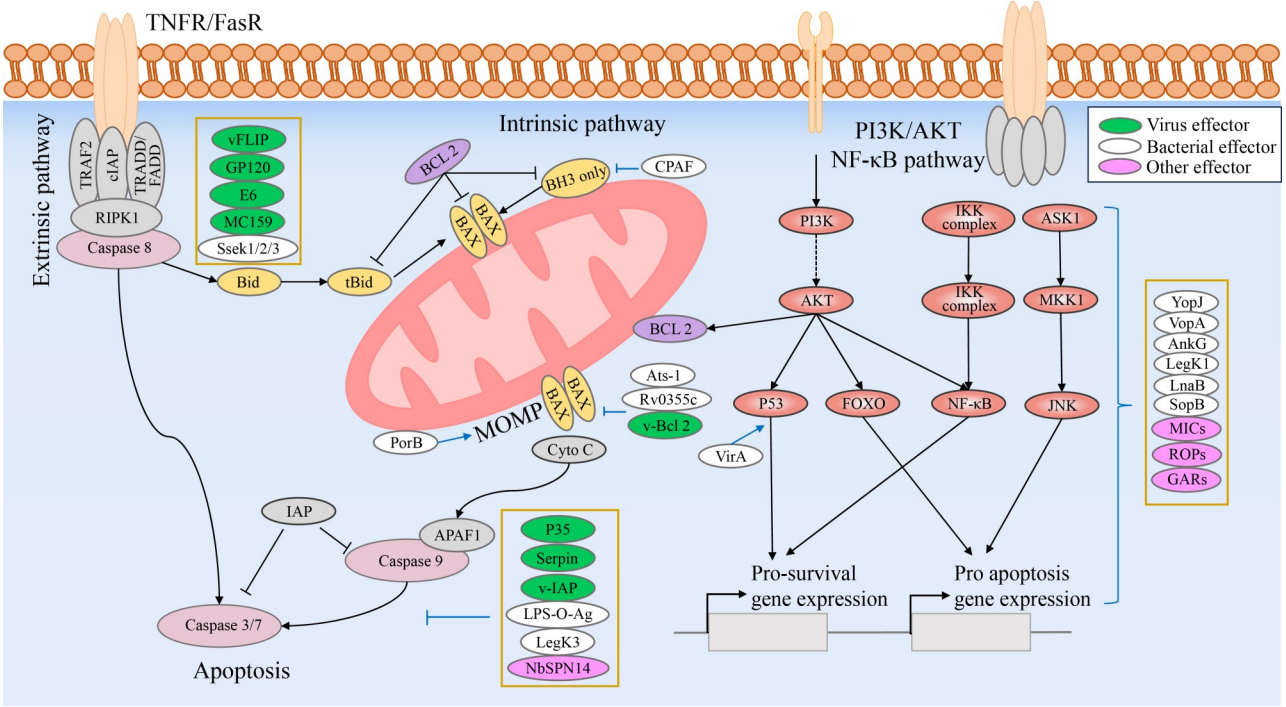

图1 胞内病原效应蛋白调控宿主细胞凋亡策略的模式图

Figure 1 Schematic of the strategies intracellular pathogen effectors regulate host cell apoptosis.

路调控凋亡相关基因的表达；二是直接调控细胞凋亡通路中的关键环节，例如直接调控线粒体外膜通透性、死亡信号传导过程及 Caspase 蛋白酶活性。

病毒感染后可通过调控凋亡相关基因表达进而调控宿主细胞凋亡。日本脑炎病毒(Japanese encephalitis virus, JEV)感染导致 DNA 损伤，从而促进 P53 在细胞核中的磷酸化，并诱导 BAX 等促凋亡基因表达，进而影响宿主细胞凋亡[18]。鸭坦布苏病毒(duck Tembusu virus, DTMUV)感染鸭胚成纤维细胞后，激活 Caspase 8 介导的死亡受体凋亡通路和 Caspase 9 介导的线粒体凋亡通路，诱导鸭胚成纤维细胞凋亡[19-20]。人类免疫缺陷病毒 HIV 会通过调控死亡受体介导的细胞凋亡促进病毒感染，使宿主 $CD4^+$和 $CD8^+$ T 细胞 Fas、DR4 和 DR5 表达增加，导致这些细胞对死亡受体介导的细胞凋亡敏感，进而引起 T 细胞耗竭，同时 HIV 感染还上调巨噬细胞中 FasL 的表达，进一步加剧 T 细胞凋亡，以此来削弱宿主免疫[21-22]。

病毒编码模仿宿主抗凋亡 BCL-2 (vBCL-2)蛋白，抑制线粒体细胞色素 C 的释放，劫持内源性凋亡通路[23]。例如，腺病毒、小鼠 γ-疱疹病毒、EB 病毒和人疱疹病毒等产生哺乳动物 BCL-2 蛋白类似物可抑制 BAX 和 BAK 活性，进而抑制宿主细胞凋亡[17]。相比之下，大多数痘病毒(Poxvirus)缺乏 BCL-2 同系物，但在黏液瘤病毒(Myxoma)中发现了一个凋亡抑制蛋白 M11L，该蛋白结构与 BCL-2 类似，但序列相似性较低，以此为基础从痘病毒中鉴定出 6 个 BCL-2 结构类似蛋白，如羊痘病毒(sheep Poxvirus)编码的 SPPV14 蛋白可直接作用于 BAX 和 BAK，抑制宿主细胞凋亡[24]。

病毒编码蛋白能激活或抑制死亡受体介导的凋亡信号传导。死亡受体诱导的细胞凋亡过程：配体与受体结合后，衔接蛋白 FADD 通过死亡结构域组装成高阶死亡诱导信号复合体(death inducing signaling complex, DISC)，招募并激活 Caspase 8，进而激活下游执行 Caspase，最终引发凋亡[1,13]。HIV 编码的包膜糖蛋白 GP120/GP41 与受感染和未感染的 $CD4^+$ T 细胞的凋亡过程相关，其中 GP120 可与 CD4 受体和趋化因子共受体(C-C motif chemokine receptor type 5, CCR5 和 C-X-C chemokine receptor type 4, CXCR4)结合并交联，GP120 对 $CD4^+$ T 细胞的交联诱导 Fas 介导的细胞凋亡敏感性增强[25-26]。病毒编码的 vFLIP (Fas-associated death domain-like interleukin-1β-converting enzyme inhibitory protein)含有与 Caspase 8 相同的死亡效应结构域，可竞争性结合 FADD，进而阻止 FADD-Caspase 8 复合体组装，导致 Caspase 8 不能被激活，从而抑制细胞凋亡的发生[27]。除此之外，人乳头瘤病毒 16 型(human papillomavirus-16, HPV-16)的 E6 蛋白虽并非 vFLIP 类蛋白，但也可靶向 DISC 的组装，从而抑制死亡受体诱导的凋亡，E6 不仅可结合 TNFR1 的死亡结构域 DD，阻止 TNF 受体相关死亡结构域蛋白 TRADD 招募，从而阻止 DISC 的形成；还可结合 FADD 和 Caspase 8 的死亡效应结构域，发挥与 vFLIP 类似作用阻断细胞凋亡[28-29]。

病毒编码蛋白直接抑制 Caspase 家族蛋白酶活性调控宿主细胞凋亡。病毒编码 3 类抑制蛋白来拮抗半胱天冬酶活性，从而抑制宿主细胞凋亡。这些抑制蛋白包括丝氨酸蛋白酶抑制剂(serine protease inhibitor, Serpin)、p35 家族成员、细胞凋亡抑制蛋白(viral inhibitor of apoptosis proteins, vIAP)[30]。第一个被发现的病毒 Caspase 抑制剂是牛痘病毒(Cowpox virus)编码的细胞因子反应修饰剂 A (cytokine response modifier A, CrmA)，其属于 Serpin 超家族[31]。它最初被确定为白细胞介素(interleukin, IL) -1β 转化酶(IL-1β-ICE)的抑制剂，后发现 CrmA 能抑制多种 Caspase 活性并防止宿主细胞凋亡和炎症[32]。P35 是从苜蓿银纹夜蛾核型多角体病毒(*Autographa californica* Nucleopolyhedrovirus, AcMNPV)中鉴定出的广谱 Caspase 抑制剂，可

抑制病毒感染的昆虫细胞凋亡，也可抑制线虫CED-3、果蝇效应半胱天冬酶DrICE、哺乳动物Caspase 1、Caspase 3、Caspase 6等的活性[33-34]。在杆状病毒中寻找可弥补p35缺失后抑制宿主细胞凋亡的效应因子时鉴定到细胞凋亡抑制蛋白IAP[35]。除了杆状病毒外，IAP同系物还在昆虫痘病毒(Entomopoxvirus)、非洲猪瘟病毒(African swine fever virus)以及从酵母到人类的多种生物中被鉴定，在抑制Caspase活性及细胞凋亡中起重要作用[36]。病毒调控宿主细胞凋亡的效应分子及信号通路见表1。

2.2 胞内病原细菌调控宿主细胞凋亡

细菌病原体通常通过分泌效应蛋白调控宿主信号通路，进而干预凋亡过程。尽管不同病原体在不同宿主细胞中调控凋亡的机制差异显著，但其调控策略仍存在一些共性，包括病原细菌分泌效应蛋白调控细胞凋亡上游信号通路

表1 部分病毒编码的效应蛋白调控宿主细胞凋亡

Table 1 Partial viral-encoded effector proteins regulate apoptosis of host cells

Virus	Classification	Viral effector	Mediated signaling	References
African swine fever virus (ASFV)	Viral pro survival BCL-2 proteins	A179L	MOMP	[37]
Pseudorabies virus		gM	MOMP	[38]
γ-herpesviruses 68		M11	MOMP	[39-40]
Adenovirus		E1B19K	MOMP	[41]
Epstein-Barr virus		BHRF1	MOMP	[42-43]
Kaposi’s sarcoma-associated herpesvirus		Ks-Bcl-2	MOMP	[44]
Türkiye herpesvirus		vNr-13	MOMP	[45]
Orfvirus		ORFV125	MOMP	[46]
Hepatitis B virus		HBx	MOMP	[47]
Grouper iridovirus		GIV66	MOMP	[48]
Myxoma virus		M11L	MOMP	[49]
Vaccinia virus		F1L	MOMP	[50]
Ectromelia virus		EMV025	MOMP	[51]
Sheeppox virus		SPPV14	MOMP	[52]
Deerpox virus		DPV022	MOMP	[53]
Fowlpox virus		FPV029	MOMP	[54]
Canarypox		CNP058	MOMP	[55]
Tanapoxvirus		TANV16L	MOMP	[56]
HIV-1	Death receptor activator	Tat/Env/Vpu/gp120	Fas, TNF-R	[21,57]
HCV		Core protein	Fas, TNF-R	[58]
Epstein-Barr virus		LMP2A/LMP1	Fas	[59-60]
Lyssavirus		Matrix protein	TRAIL-R	[61]
γ-herpesviruses	Death receptor inhibitor	vFLIP	DISC	[62]
Molluscum contagiosum virus		MC159	DISC	[63]
HPV		E6	DISC	[28]
Poxvirus	Caspase inhibitor	Serpin	Caspase	[64]
Baculovirus		P35	Caspase	[34]
Virus		IAP	Caspase	[36]

(如 PI3K/Akt 等)、内源和外源凋亡通路关键蛋白以及凋亡通路下游关键蛋白酶等。

宿主细胞感知病原入侵后能通过 P53、PI3K/Akt、核因子 κB (nuclear factor kappa-B, NF-κB)等信号通路调控细胞凋亡或凋亡相关基因的转录，胞内病原细菌分泌系统通过分泌效应蛋白干扰这些细胞信号通路，从而调控宿主细胞凋亡[65]。例如，弗氏志贺氏菌(*Shigella flexneri*)感染上皮细胞后 P53 细胞凋亡通路被激活，试图清除病原体，弗氏志贺氏菌通过III型分泌系统(type III secretion system, T3SS)分泌效应蛋白 VirA，靶向降解钙蛋白酶抑制剂，解除其对 P53 的保护作用，进而促进 P53 降解，抑制宿主细胞凋亡[66-67]。弗氏志贺氏菌还分泌一种磷脂酰肌醇磷酸酶 IpgD，将磷脂酰肌醇-4,5-二磷酸(phosphatidylinositol 4,5-bisphosphate, PIP2)转换成磷脂酰肌醇-5-磷酸(phosphatidylinositol 5-phosphate, PI5P)，进而促进表皮生长因子受体(epidermal growth factor receptor, EGFR)信号通路以维持 PI3K/Akt 激活，从而防止细胞凋亡[68]。假结核耶尔森氏菌(*Yersinia pseudotuberculosis*)通过六型分泌系统(type VI secretion system, T6SS)分泌脱氧核糖核酸酶效应蛋白 TkeA，并转运至宿主细胞内诱导 DNA 损伤，进而激活 cGAS-STING-TNF 轴诱导宿主细胞凋亡[69]。肠沙门氏菌(*Salmonella enterica*)感染肠道上皮细胞时，通过 T3SS 分泌效应蛋白 SopB 介导 PI3K/Akt 通路激活，导致 Akt 磷酸化并影响细胞色素 C 的释放，抑制宿主细胞凋亡[70-71]；沙门氏菌还可以在巨噬细胞中复制，并分泌效应蛋白 SipB 和 SipD 诱导巨噬细胞凋亡，从而减少炎症细胞因子的释放[72]。同种病原对不同宿主细胞的凋亡调控策略不同：在用于增殖的宿主细胞中抑制凋亡，而在免疫防御细胞中诱导凋亡以规避宿主免疫应答。除此之外，嗜肺军团菌(*Legionella pneumophila*)分泌蛋白 LegK1 和 LnaB[73-74]，假结核耶尔森氏菌分泌蛋白 YopJ[75]，副溶血弧菌(*Vibrio parahaemolyticus*)分泌蛋白 VopA[76]，伯氏考克斯氏体(*Coxiella burnetii*)分泌蛋白 AnkG 等效应因子[77]，这些效应蛋白均可靶向宿主细胞 NF-κB 等信号通路，调控凋亡相关基因表达，从而干预宿主细胞凋亡。

一些胞内病原细菌通过分泌效应蛋白调控宿主 BCL-2 家族蛋白的表达、激活、降解及功能等多个方面进而调控宿主细胞凋亡。结核分枝杆菌(*Mycobacterium tuberculosis*)能够侵染巨噬细胞并在其胞内复制，其分泌的 MPT64 蛋白下调宿主 miR-21 的表达后增加抗凋亡蛋白 BCL-2 的表达，进而抑制宿主细胞凋亡[78]。此外，结核分枝杆菌分泌蛋白 Rv0355c 模拟真核生物的 BCL-2 蛋白，靶向宿主细胞线粒体，进而抑制宿主细胞凋亡[79]。沙眼衣原体(*Chlamydia trachomatis*)感染具有很强的抗宿主细胞凋亡能力，感染后宿主细胞线粒体中细胞色素 C 释放受阻、Bax 和 Bak 激活受抑制，研究发现其分泌的蛋白酶 CPAF 能够降解仅含 BH3 结构域的促凋亡 BCL-2 家族成员，增强了衣原体的抗凋亡活性[80]，并且沙眼衣原体外膜蛋白 OmpA 通过外膜囊泡运输到宿主线粒体膜上，可以干扰促凋亡蛋白 Bax 的激活[81]。同样地，脑膜炎奈瑟氏球菌(*Neisseria meningitidis*)分泌蛋白 PorB 也通过外膜囊泡运输到宿主细胞的线粒体外膜上，导致线粒体膜电位丧失、细胞色素 C 释放等促进宿主巨噬细胞凋亡，抑制宿主先天免疫反应[82]。新兴病原体嗜包涵体无形体(*Anaplasma phagocytophilum*)分泌的 Ats-1 蛋白，其蛋白 N 端能够靶向并插入线粒体后被宿主线粒体肽酶切割，切割产物在线粒体外膜堆积，阻断 Bax 插入和膜孔形成，进而抑制线粒体膜通透性改变、细胞色素 C 释放和细胞凋亡[83]。综上所述，一些胞内病原细菌调控宿主细胞凋亡的具体机制虽有差异，但都可以靶向细胞凋亡通路中关键的 BCL-2 蛋白家族策略来调控宿主细胞凋亡。

Caspase 蛋白酶是细胞凋亡通路中下游的信号传导与执行分子，在细胞凋亡中起关键作用，

一旦效应 Caspase 被激活细胞凋亡进程不能逆转，仅能被延迟。在长期的进化过程中，一些胞内细菌病原体为了适应宿主环境也演变出了一些策略调控 Caspase 活性[84]。例如，包括弗氏志贺氏菌在内的革兰氏阴性菌，其脂多糖的 O 抗原部分能够直接与效应 Caspase 结合，通过抑制其活性有效延长宿主细胞的存活时间，为细菌自身的生存和繁殖争取更多时间和空间[85]。嗜肺军团菌分泌类似真核生物的 Ser/Thr 激酶 LegK3，可使效应 Caspase 3、Caspase 7 和 Caspase 9 的关键 Ser/Thr 位点发生磷酸化，这些修饰干扰执行 Caspase 作为上游起始 Caspase 底物的功能，进而影响细胞凋亡的进程，但不影响执行 Caspase 的水解活性[86]。为了在宿主细胞内更好地存活，细菌通过分泌效应蛋白采取多种策略调控宿主细胞凋亡，包括干预信号通路、调控凋亡相关基因表达，以及影响凋亡通路中关键蛋白及蛋白酶活性等。不同病原的策略并不完全相同，随着对细胞凋亡、病原与宿主互作机制的研究越来越深入，越来越多病原调控宿主细胞凋亡的未解之谜将慢慢揭开。部分胞内寄生菌调控宿主细胞凋亡的效应分子及介导的通路见表 2。

2.3 其他胞内寄生病原调控宿主细胞凋亡

除了病毒和细菌外，一些真菌及原生动物等胞内寄生病原也会调控宿主细胞凋亡。例如，微孢子虫(*Microsporidia*)是一类专性胞内寄生的真菌病原，广泛分布于自然界中，目前鉴定的

表2 部分胞内病原细菌分泌效应蛋白调控宿主细胞凋亡

Table 2 Some intracellular pathogenic bacteria secreted effector proteins regulate host cell apoptosis

Bacterium	Effector	Targeted pathway	Mediated signaling	References
Shigella flexneri	VirA	P53	P53	[66-67]
	IpgD	PI3K/Akt	PI3K/Akt	[87-88]
	OspZ	TAB2/3, IkB	NF-κB, transcription	[89]
Salmonella enterica	SopB/SigD	PDK1/Rictor	PI3K/Akt	[70,90]
	SseK1, SseK 2, SseK 3	TRADD	NF-κB	[91-92]
Legionella pneumophila	LegK1, LnaB	IκBα	NF-κB	[74,93]
	SidF	BCL-2	MOMP	[94]
	LegK3	Caspase 3, Caspase 7, Caspase 9	Caspase	[86]
	LPS O-antigen	Caspase	Caspase	[85]
Chlamydia trachomatis	CPAF	BH-3 only	MOMP	[75]
	OmpA	Bax/Bak	MOMP	[81]
	CT622	Unknow	MAPK	[95]
Yersinia pseudotuberculosis	YopJ	ERK/p38/JNK	NF-κB, MAPK	[75]
	YopK	Unknow	Extrinsic	[96]
Vibrio parahaemolyticus	VopA	MAPKKs	MAPK	[76]
Coxiella burnetii	AnkG	P32	Intrinsic	[77,97]
	CaeA	Unknown	Intrinsic/extrinsic	[98]
Mycobacterium tuberculosis	MPT64	BCL-2	MOMP	[73]
	Rv0355c	BAK	MOMP	[79]
	Rv2387	Caspase 3, Caspase 8	Caspase	[99]
	ESAT-6	Caspase 3, Caspase 8	ROS/MAPK-Caspase	[99]
Neisseria meningitidis	PorB	BCL-2	MOMP	[82]

微孢子虫超过 1 800 种[100]。微孢子虫早期被认为是原虫，后被归类为与真菌亲缘关系密切的姊妹群[101]。微孢子虫营细胞内专性寄生，高度依赖宿主细胞存活。研究发现兔脑炎微孢子虫、蜜蜂微孢子虫和家蚕微粒子虫等感染相应宿主细胞后均出现抑制宿主细胞凋亡的现象，涉及阻止凋亡因子 P53 入核、抑制宿主细胞内活性氧生成及调控凋亡相关基因转录等[102-105]。最新研究发现，家蚕微粒子虫中存在 serpin 蛋白家族成员 NbSPN14，该蛋白被分泌到宿主细胞中，与宿主家蚕细胞凋亡通路关键效应 Caspase 酶 BmICE 相互作用并抑制其活性，进而抑制宿主细胞凋亡，首次鉴定了微孢子虫中抑制宿主细胞凋亡的效应分子[106-108]。

顶复门原虫是一类专性细胞内寄生原虫，包含弓形虫、疟原虫、隐孢子虫、球虫等多种病原体，感染后抑制宿主细胞凋亡，为自身生长、繁殖创造有利条件[109]。顶复门原虫通过 3 种方式抑制细胞凋亡。(1) 分泌微线体蛋白(microneme proteins, MICs)，这些蛋白在寄生虫侵入宿主细胞和抑制凋亡中起重要作用。例如，鸡球虫的 MIC4 蛋白通过与表皮生长因子受体(EGFR)相互作用激活 EGFR/Akt 信号通路，从而抑制宿主细胞凋亡[110]。同样地，弓形虫的 MIC3、MIC6 和 MIC8 蛋白借助其含有的 EGF 结构域激活 EGFR/Akt 信号通路，抑制宿主细胞凋亡[111-112]。(2) 分泌棒状体蛋白(rhoptry proteins, ROPs)，弓形虫分泌 ROP16 蛋白激活 STAT3 和 STAT6 信号通路，抑制宿主细胞凋亡[113-114]。ROP18 蛋白通过磷酸化 P65 促进其降解，抑制 NF-κB 激活，从而抑制宿主细胞凋亡[115]。(3) 分泌致密颗粒蛋白(dense granule proteins, GRAs)来抑制宿主细胞凋亡，例如弓形虫分泌 GRA24 蛋白通过激活 p38 MAPK，诱导 GPCR/PI3K/Akt 信号通路抑制宿主细胞凋亡[116]。此外，热激蛋白(heat shock proteins, HSPs)在顶复门原虫中也发挥重要作用，弓形虫的 HSP70 蛋白通过抑制细胞色素 C 的释放、促进抗凋亡蛋白表达和抑制 Caspase 活性从而抑制宿主细胞凋亡[117]。这些寄生虫通过劫持 NF-κB、PI3K-Akt 和线粒体凋亡通路等机制共同作用，使得顶复门原虫能够在感染后抑制宿主细胞凋亡，为其自身的生长、发育和繁殖创造有利条件。

3 总结与展望

宿主与病原体的相互作用作为生物进化的主要驱动力，引发了二者在防御与逃避策略上的“军备竞赛”。多细胞生物中调节性细胞死亡作为古老的免疫防御机制，其激活和执行机制十分复杂且受到严格调控，在限制病原体传播和保护自身存活中发挥重要作用；而病原体也发展出多种策略逃避或干扰调节性细胞死亡的信号传导[118]。本文综述了胞内寄生病原调控宿主细胞凋亡的机制与策略，总结了胞内寄生病原通过调控细胞凋亡上游信号通路来调控凋亡相关基因表达，产生效应分子直接调控细胞凋亡通路信号传导和执行过程，如调节 BCL-2 家族蛋白影响线粒体外膜通透性、调控死亡信号受体与配体结合及 Caspase 8 活性、直接调控凋亡执行分子效应 Caspase 活性等策略调控宿主细胞凋亡。细胞凋亡是第一个被确定的调节性细胞死亡形式，其调控机制研究已十分深入和清晰[5]，但细胞凋亡在对抗病原感染方面的具体效果如何，诸多胞内寄生病原抑制或诱导细胞凋亡的分子机制尚不完全清楚，胞内寄生病原感染与细胞凋亡及其他调节性细胞死亡交叉调控关系等问题有待深入探究。胞内寄生病原侵入宿主细胞后依赖并利用宿主细胞资源进行复制和传播，因此需要保证宿主细胞存活以完成其增殖，但最终都会导致宿主细胞死亡。未来的研究应聚焦于深入解析病原体产生的效应分子操纵宿主细胞死亡的分子机制，这将有助于揭示病原与宿主相互作用的奥秘，为开发新的抗感染策略和治疗手段提供理论依据。

作者贡献声明

冉茂双：数据收集和处理及文章撰写；包佳玲：修订审阅；潘国庆：论文构思和审阅，项目管理。

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] NEWTON K, STRASSER A, KAYAGAKI N, DIXIT VM. Cell death[J]. Cell, 2024, 187(2): 235-256.

[2] TANG DL, KANG R, VANDEN BERGHE T, VANDENABEELE P, KROEMER G. The molecular machinery of regulated cell death[J]. Cell Research, 2019, 29(5): 347-364.

[3] GALLUZZI L, BRAVO-SAN PEDRO JM, VITALE I, AARONSON SA, ABRAMS JM, ADAM D, ALNEMRI ES, ALTUCCI L, ANDREWS D, ANNICCHIARICO-PETRUZZELLI M, BAEHRECKE EH, BAZAN NG, BERTRAND MJ, BIANCHI K, BLAGOSKLONNY MV, BLOMGREN K, BORNER C, BREDESEN DE, BRENNER C, CAMPANELLA M, et al. Essential versus accessory aspects of cell death: recommendations of the NCCD 2015[J]. Cell Death & Differentiation, 2014, 22(1): 58-73.

[4] FUCHS Y, STELLER H. Programmed cell death in animal development and disease[J]. Cell, 2011, 147(4): 742-758.

[5] AI YW, MENG YT, YAN B, ZHOU QY, WANG XD. The biochemical pathways of apoptotic, necroptotic, pyroptotic, and ferroptotic cell death[J]. Molecular Cell, 2024, 84(1): 170-179.

[6] VITALE I, PIETROCOLA F, GUILBAUD E, AARONSON SA, ABRAMS JM, ADAM D, AGOSTINI M, AGOSTINIS P, ALNEMRI ES, ALTUCCI L, AMELIO I, ANDREWS DW, AQEILAN RI, ARAMA E, BAEHRECKE EH, BALACHANDRAN S, BANO D, BARLEV NA, BARTEK J, BAZAN NG, et al. Apoptotic cell death in disease: current understanding of the NCCD 2023[J]. Cell Death & Differentiation, 2023, 30(5): 1097-1154.

[7] NAGATA S. Apoptosis and clearance of apoptotic cells[J]. Annual Review of Immunology, 2018, 36: 489-517.

[8] BOCK FJ, TAIT SWG. Mitochondria as multifaceted regulators of cell death[J]. Nature Reviews Molecular Cell Biology, 2019, 21(2): 85-100.

[9] NADENDLA EK, TWEEDELL RE, KASOF G, KANNEGANTI TD. Caspases: structural and molecular mechanisms and functions in cell death, innate immunity, and disease[J]. Cell Discovery, 2025, 11(1): 42.

[10] SORA V, PAPALEO E. Structural details of BH3 motifs and BH3-mediated interactions: an updated perspective[J]. Frontiers in Molecular Biosciences, 2022, 9: 864874.

[11] ZHANG Y, TIAN L, HUANG G, GE XF, KONG F, WANG PQ, XU YG, SHI YG. Structural basis of BAX pore formation[J]. Science, 2025, 388(6754): eadv4314.

[12] BANJARA S, SURAWEERA CD, HINDS MG, KVANSAKUL M. The BCL-2 family: ancient origins, conserved structures, and divergent mechanisms[J]. Biomolecules, 2020, 10(1): 128.

[13] GREEN DR. The death receptor pathway of apoptosis[J]. Cold Spring Harbor Perspectives in Biology, 2022, 14(2): a041053.

[14] YUAN JY, OFENGEIM D. A guide to cell death pathways[J]. Nature Reviews Molecular Cell Biology, 2023, 25(5): 379-395.

[15] ZITVOGEL L, KEPP O, KROEMER G. Decoding cell death signals in inflammation and immunity[J]. Cell, 2010, 140(6): 798-804.

[16] HÄCKER G. Apoptosis in infection[J]. Microbes and Infection, 2018, 20(9/10): 552-559.

[17] ZHOU XC, JIANG WB, LIU ZS, LIU S, LIANG XZ. Virus infection and death receptor-mediated apoptosis[J]. Viruses, 2017, 9(11): 316.

[18] YANG K, LI XR, YANG SQ, ZHENG Y, CAO SJ, YAN QG, HUANG XB, WEN YP, ZHAO Q, DU SY, LANG YF, ZHAO S, WU R. Japanese encephalitis virus infection induces mitochondrial-mediated apoptosis through the proapoptotic protein BAX[J]. Frontiers in Microbiology, 2024, 15: 1485667.

[19] PAN YH, CAI WJ, CHENG AC, WANG MS, CHEN S, HUANG J, YANG Q, WU Y, SUN D, MAO S, ZHU DK, LIU MF, ZHAO XX, ZHANG SQ, GAO Q, OU XM, TIAN B, YIN ZQ, JIA RY. Duck Tembusu virus infection induces mitochondrial-mediated and death receptor-mediated apoptosis in duck embryo fibroblasts[J]. Veterinary Research, 2022, 53(1): 53.

[20] HUANG YF, ZHANG YF, YANG S, SHI YH, CHU XY, AHMED N, WU JX, CHEN QS. Tembusu virus induced apoptosis in vacuolate spermatogenic cells is mediated by Cytc-mediated mitochondrial apoptotic signaling pathway[J]. Theriogenology, 2024, 215: 312-320.

[21] MEHRBOD P, ANDE SR, ALIZADEH J, RAHIMIZADEH S, SHARIATI A, MALEK H, HASHEMI M, GLOVER KKM, SHER AA, COOMBS KM, GHAVAMI S. The roles of apoptosis, autophagy and unfolded protein response in arbovirus, influenza virus, and HIV infections[J]. Virulence, 2019, 10(1): 376-413.

[22] GARG H, JOSHI A. Host and viral factors in HIV-mediated bystander apoptosis[J]. Viruses, 2017, 9(8): 237.

[23] KVANSAKUL M, CARIA S, HINDS MG. The BCL-2 family in host-virus interactions[J]. Viruses, 2017, 9(10): 290.

[24] SURAWEERA CD, BURTON DR, HINDS MG, KVANSAKUL M. Crystal structures of the sheeppox virus encoded inhibitor of apoptosis SPPV14 bound to the proapoptotic BH3 peptides Hrk and Bax[J]. FEBS Letters, 2020, 594(12): 2016-2026.

[25] ETHELL DW, BUHLER LA. Fas ligand-mediated

apoptosis in degenerative disorders of the brain[J]. Journal of Clinical Immunology, 2003, 23(6): 439-446.
[26] LI WW, QIN Z, NAND E, GRUNST MW, GROVER JR, BESS JW Jr, LIFSON JD, ZWICK MB, TAGARE HD, UCHIL PD, MOTHES W. HIV-1 Env trimers asymmetrically engage CD4 receptors in membranes[J]. Nature, 2023, 623(7989): 1026-1033.
[27] LAGUNAS KM, SAVCIGIL DP, ZRILIC M, FRAILE CC, CRAXTON A, SELF E, URANGA-MURILLO I, de MIGUEL D, ARIAS M, WILLENBORG S, PIEKAREK M, ALBERT MC, NUGRAHA K, LISEWSKI I, JANAKOVA E, IGUAL N, TONNUS W, HILDEBRANDT X, IBRAHIM M, BALLEGEER M, et al. Cleavage of cFLIP restrains cell death during viral infection and tissue injury and favors tissue repair[J]. Science Advances, 2023, 9(30): eadg2829.
[28] FILIPPOVA M, PARKHURST L, DUERKSEN-HUGHES PJ. The human papillomavirus 16 E6 protein binds to Fas-associated death domain and protects cells from Fas-triggered apoptosis[J]. The Journal of Biological Chemistry, 2004, 279(24): 25729-25744.
[29] LIAO YQ, CHEN RZ, TANG EQ, TANG SY. HPV16 E6 and *Chlamydia trachomatis* Pgp3 proteins inhibit TNF-α-induced apoptosis through Daxx-mediated MDM2-p53 pathway[J]. Microbial Pathogenesis, 2025, 206: 107849.
[30] BEST SM. Viral subversion of apoptotic enzymes: escape from death row[J]. Annual Review of Microbiology, 2008, 62: 171-192.
[31] RAY CA, BLACK RA, KRONHEIM SR, GREENSTREET TA, SLEATH PR, SALVESEN GS, PICKUP DJ. Viral inhibition of inflammation: cowpox virus encodes an inhibitor of the interleukin-1 beta converting enzyme[J]. Cell, 1992, 69(4): 597-604.
[32] BLOOMER DT, KITEVSKA-ILIOSKI T, PANTAKI-EIMANY D, JI YH, MILES MA, HERAS B, HAWKINS CJ. CrmA orthologs from diverse poxviruses potently inhibit caspases-1 and -8, yet cleavage site mutagenesis frequently produces caspase-1-specific variants[J]. Biochemical Journal, 2019, 476(9): 1335-1357.
[33] YU QL, WANG MH, DING XM, HAN JC, MA HC, LI J, ZHENG GL, ZHANG B, LI CY. The expression of P35 plays a key role in the difference in apoptosis induced by AcMNPV infection in different *Spodoptera exigua* cell lines[J]. International Journal of Molecular Sciences, 2023, 24(17): 13228.
[34] BRAND IL, CIVCIRISTOV S, TAYLOR NL, TALBO GH, PANTAKI-EIMANY D, LEVINA V, CLEM RJ, PERUGINI MA, KVANSAKUL M, HAWKINS CJ. Caspase inhibitors of the P35 family are more active when purified from yeast than bacteria[J]. PLoS One, 2012, 7(6): e39248.
[35] CROOK NE, CLEM RJ, MILLER LK. An apoptosis-inhibiting baculovirus gene with a zinc finger-like motif[J]. Journal of Virology, 1993, 67(4): 2168-2174.
[36] CHEN Y, WU M, YUAN ZH, WANG QY, XU H, SUN L. Cnidaria XIAP activates caspase-mediated cell death[J]. International Journal of Biological Macromolecules, 2025, 310(Pt 4): 143427.
[37] REIS AL, RATHAKRISHNAN A, GOULDING LV, BARBER C, GOATLEY LC, DIXON LK. Deletion of the gene for the African swine fever virus BCL-2 family member A179L increases virus uptake and apoptosis but decreases virus spread in macrophages and reduces virulence in pigs[J]. Journal of Virology, 2023, 97(10): e0110623.
[38] ZHOU QQ, SHI DS, TANG YD, ZHANG LF, HU BL, ZHENG CF, HUANG L, WENG CJ. Pseudorabies virus gM and its homologous proteins in herpesviruses induce mitochondria-related apoptosis involved in viral pathogenicity[J]. PLoS Pathogens, 2024, 20(4): e1012146.
[39] WANG GH, GARVEY TL, COHEN JI. The murine gammaherpesvirus-68 M11 protein inhibits Fas- and TNF-induced apoptosis[J]. Journal of General Virology, 1999, 80(Pt 10): 2737-2740.
[40] LOH J, HUANG QL, PETROS AM, NETTESHEIM D, van DYK LF, LABRADA L, SPECK SH, LEVINE B, OLEJNICZAK ET, VIRGIN HW 4th. A surface groove essential for viral BCL-2 function during chronic infection *in vivo*[J]. PLoS Pathogens, 2005, 1(1): e10.
[41] AGUIRRE-HERNÁNDEZ C, MAYA-PINEDA H, MILLÁN JS, STELLA MAN YK, LU YJ, HALLDÉN G. Sensitisation to mitoxantrone-induced apoptosis by the oncolytic adenovirus AdΔΔ through BCL-2-dependent attenuation of autophagy[J]. Oncogenesis, 2018, 7: 6.
[42] SURAWEERA CD, HINDS MG, KVANSAKUL M. Crystal structures of Epstein-Barr virus BCL-2 homolog BHRF1 bound to bid and *Puma* BH3 motif peptides[J]. Viruses, 2022, 14(10): 2222.
[43] KVANSAKUL M, WEI AH, FLETCHER JI, WILLIS SN, CHEN L, ROBERTS AW, HUANG DCS, COLMAN PM. Structural basis for apoptosis inhibition by Epstein-Barr virus BHRF1[J]. PLoS Pathogens, 2010, 6(12): e1001236.
[44] SARID R, SATO T, BOHENZKY RA, RUSSO JJ, CHANG Y. Kaposi's sarcoma-associated herpesvirus encodes a functional BCL-2 homologue[J]. Nature Medicine, 1997, 3(3): 293-298.
[45] REDDY VRAP, SADIGH Y, TANG N, YAO YX, NAIR V. Novel insights into the roles of BCL-2 homolog nr-13 (vNr-13) encoded by herpesvirus of turkeys in the virus replication cycle, mitochondrial networks, and apoptosis inhibition[J]. Journal of Virology, 2020, 94(10): e02049-19.
[46] SURAWEERA CD, HINDS MG, KVANSAKUL M. Structural investigation of orf virus BCL-2 homolog ORFV125 interactions with BH3-motifs from BH3-only proteins Puma and Hrk[J]. Viruses, 2021, 13(7): 1374.
[47] KUSUNOKI H, SAKAMOTO T, KOBAYASHI N, KOHNO T, WAKAMATSU K, NAGATA T. Structural insights into the interaction between the C-terminal-deleted BH3-like motif peptide of hepatitis B virus X protein and BCL-x_L[J]. Biochemistry, 2024, 63(5): 632-643.

[48] BANJARA S, MAO JH, RYAN TM, CARIA S, KVANSAKUL M. Grouper iridovirus GIV66 is a BCL-2 protein that inhibits apoptosis by exclusively sequestering Bim[J]. Journal of Biological Chemistry, 2018, 293(15): 5464-5477.

[49] SU J, WANG G, BARRETT JW, IRVINE TS, GAO XJ, McFADDEN G. Myxoma virus M11L blocks apoptosis through inhibition of conformational activation of Bax at the mitochondria[J]. Journal of Virology, 2006, 80(3): 1140-1151.

[50] WASILENKO ST, BANADYGA L, BOND D, BARRY M. The vaccinia virus F1L protein interacts with the proapoptotic protein Bak and inhibits Bak activation[J]. Journal of Virology, 2005, 79(22): 14031-14043.

[51] MEHTA N, TAYLOR J, QUILTY D, BARRY M. Ectromelia virus encodes an anti-apoptotic protein that regulates cell death[J]. Virology, 2015, 475: 74-87.

[52] OKAMOTO T, CAMPBELL S, MEHTA N, THIBAULT J, COLMAN PM, BARRY M, HUANG DCS, KVANSAKUL M. Sheeppox virus SPPV14 encodes a BCL-2-like cell death inhibitor that counters a distinct set of mammalian proapoptotic proteins[J]. Journal of Virology, 2012, 86(21): 11501-11511.

[53] BANADYGA L, LAM SC, OKAMOTO T, KVANSAKUL M, HUANG DC, BARRY M. Deerpox virus encodes an inhibitor of apoptosis that regulates Bak and Bax[J]. Journal of Virology, 2011, 85(5): 1922-1934.

[54] ANASIR MI, CARIA S, SKINNER MA, KVANSAKUL M. Structural basis of apoptosis inhibition by the fowlpox virus protein FPV039[J]. Journal of Biological Chemistry, 2017, 292(22): 9010-9021.

[55] ANASIR MI, BAXTER AA, POON IKH, HULETT MD, KVANSAKUL M. Structural and functional insight into canarypox virus CNP058 mediated regulation of apoptosis[J]. Viruses, 2017, 9(10): 305.

[56] SURAWEERA CD, ANASIR MI, CHUGH S, JAVORSKY A, IMPEY RE, HASAN ZADEH M, SOARES Da COSTA TP, HINDS MG, KVANSAKUL M. Structural insight into tanapoxvirus-mediated inhibition of apoptosis[J]. The FEBS Journal, 2020, 287(17): 3733-3750.

[57] PERFETTINI JL, CASTEDO M, ROUMIER T, ANDREAU K, NARDACCI R, PIACENTINI M, KROEMER G. Mechanisms of apoptosis induction by the HIV-1 envelope[J]. Cell Death and Differentiation, 2005, 12(Suppl 1): 916-923.

[58] ZHU N, KHOSHNAN A, SCHNEIDER R, MATSUMOTO M, DENNERT G, WARE C, LAI MM. Hepatitis C virus core protein binds to the cytoplasmic domain of tumor necrosis factor (TNF) receptor 1 and enhances TNF-induced apoptosis[J]. Journal of Virology, 1998, 72(5): 3691-3697.

[59] INCROCCI R, HUSSAIN S, STONE A, BIEGING K, ALT LAC, FAY MJ, SWANSON-MUNGERSON M. Epstein-Barr virus latent membrane protein 2A (LMP2A)-mediated changes in Fas expression and Fas-dependent apoptosis: role of Lyn/Syk activation[J]. Cellular Immunology, 2015, 297(2): 108-119.

[60] Le CLORENNEC C, YOULYOUZ-MARFAK I, ADRIAENSSENS E, COLL J, BORNKAMM GW, FEUILLARD J. EBV latency III immortalization program sensitizes B cells to induction of CD95-mediated apoptosis *via* LMP1: role of NF-kappaB, STAT1, and p53[J]. Blood, 2006, 107(5): 2070-2078.

[61] KASSIS R, LARROUS F, ESTAQUIER J, BOURHY H. Lyssavirus matrix protein induces apoptosis by a TRAIL-dependent mechanism involving caspase-8 activation[J]. Journal of Virology, 2004, 78(12): 6543-6555.

[62] BERTIN J, ARMSTRONG RC, OTTILIE S, MARTIN DA, WANG Y, BANKS S, WANG GH, SENKEVICH TG, ALNEMRI ES, MOSS B, LENARDO MJ, TOMASELLI KJ, COHEN JI. Death effector domain-containing herpesvirus and poxvirus proteins inhibit both Fas- and TNFR1-induced apoptosis[J]. Proceedings of the National Academy of Sciences of the United States of America, 1997, 94(4): 1172-1176.

[63] HU S, VINCENZ C, BULLER M, DIXIT VM. A novel family of viral death effector domain-containing molecules that inhibit both CD-95- and tumor necrosis factor receptor-1-induced apoptosis[J]. The Journal of Biological Chemistry, 1997, 272(15): 9621-9624.

[64] YARON JR, CHEN H, AMBADAPADI S, ZHANG LQ, TAFOYA AM, MUNK BH, WAKEFIELD DN, FUENTES J, MARQUES BJ, HARRIPERSAUD K, BARTEE MY, DAVIDS JA, ZHENG DH, RAND K, DIXON L, MOYER RW, CLAPP WL, LUCAS AR. Serp-2, a virus-derived apoptosis and inflammasome inhibitor, attenuates liver ischemia-reperfusion injury in mice[J]. Journal of Inflammation, 2019, 16: 12.

[65] ROBINSON KS, AW R. The commonalities in bacterial effector inhibition of apoptosis[J]. Trends in Microbiology, 2016, 24(8): 665-680.

[66] BERGOUNIOUX J, ELISEE R, PRUNIER AL, DONNADIEU F, SPERANDIO B, SANSONETTI P, ARBIBE L. Calpain activation by the *Shigella flexneri* effector VirA regulates key steps in the formation and life of the bacterium's epithelial niche[J]. Cell Host & Microbe, 2012, 11(3): 240-252.

[67] WU HX, JONES RM, NEISH AS. The *Salmonella* effector AvrA mediates bacterial intracellular survival during infection *in vivo*[J]. Cellular Microbiology, 2012, 14(1): 28-39.

[68] RAMEL D, LAGARRIGUE F, PONS V, MOUNIER J, DUPUIS-CORONAS S, CHICANNE G, SANSONETTI PJ, GAITS-IACOVONI F, TRONCHÈRE H, PAYRASTRE B. *Shigella flexneri* infection generates the lipid PI5P to alter endocytosis and prevent termination of EGFR signaling[J]. Science Signaling, 2011, 4(191): ra61.

[69] SONG L, XU L, ZHANG PF, LI SY, QU YC, ZHAO YX, SHI ZK, MA RQ, LI YD, CHEN Y, WANG Y, JIANG ZF, WEI GH, SHEN XH. A dual-targeting T6SS DNase drives bacterial antagonism and eukaryotic apoptosis *via*

the cGAS-STING-TNF axis[J]. Advanced Science, 2025: e2504086.
[70] CHU BX, LI YN, LIU N, YUAN LX, CHEN SY, ZHU YH, WANG JF. *Salmonella* infantis delays the death of infected epithelial cells to aggravate bacterial load by intermittent phosphorylation of Akt with *SopB*[J]. Frontiers in Immunology, 2021, 12: 757909.
[71] ZHANG Y, XU MD, GUO YJ, CHEN L, VONGSANGNAK W, XU Q, LU LZ. Programmed cell death and *Salmonella* pathogenesis: an interactive overview[J]. Frontiers in Microbiology, 2024, 14: 1333500.
[72] LIN HH, CHEN HL, WENG CC, JANAPATLA RP, CHEN CL, CHIU CH. Activation of apoptosis by *Salmonella* pathogenicity island-1 effectors through both intrinsic and extrinsic pathways in *Salmonella*-infected macrophages[J]. Journal of Microbiology, Immunology and Infection, 2021, 54(4): 616-626.
[73] LOSICK VP, HAENSSLER E, MOY MY, ISBERG RR. LnaB: a *Legionella pneumophila* activator of NF-kappaB[J]. Cellular Microbiology, 2010, 12(8): 1083-1097.
[74] GE JN, XU H, LI T, ZHOU Y, ZHANG ZB, LI S, LIU LP, SHAO F. A *Legionella* type IV effector activates the NF-kappaB pathway by phosphorylating the IkappaB family of inhibitors[J]. Proceedings of the National Academy of Sciences of the United States of America, 2009, 106(33): 13725-13730.
[75] ZHANG Y, TING AT, MARCU KB, BLISKA JB. Inhibition of MAPK and NF-kappa B pathways is necessary for rapid apoptosis in macrophages infected with *Yersinia*[J]. Journal of Immunology, 2005, 174(12): 7939-7949.
[76] LUO LP, MATTHEWS JD, ROBINSON BS, JONES RM. *Vibrio parahaemolyticus* VopA is a potent inhibitor of cell migration and apoptosis in the intestinal epithelium of *Drosophila melanogaster*[J]. Infection and Immunity, 2019, 87(3): e00669-18.
[77] ECKART RA, BISLE S, SCHULZE-LUEHRMANN J, WITTMANN I, JANTSCH J, SCHMID B, BERENS C, LÜHRMANN A. Antiapoptotic activity of *Coxiella burnetii* effector protein AnkG is controlled by p32-dependent trafficking[J]. Infection and Immunity, 2014, 82(7): 2763-2771.
[78] WANG QM, LIU SP, TANG Y, LIU QH, YAO YJ. MPT64 protein from *Mycobacterium tuberculosis* inhibits apoptosis of macrophages through NF-κB-miRNA21-BCL-2 pathway[J]. PLoS One, 2014, 9(7): e100949.
[79] MEDHA, PRIYANKA, BHATT P, SHARMA S, SHARMA M. Role of C-terminal domain of *Mycobacterium tuberculosis* PE6 (Rv0335c) protein in host mitochondrial stress and macrophage apoptosis[J]. Apoptosis, 2023, 28(1/2): 136-165.
[80] PIRBHAI M, DONG F, ZHONG YM, PAN KZ, ZHONG GM. The secreted protease factor CPAF is responsible for degrading pro-apoptotic BH3-only proteins in *Chlamydia trachomatis*-infected cells[J]. The Journal of Biological Chemistry, 2006, 281(42): 31495-31501.
[81] WAGUIA KONTCHOU C, GENTLE IE, WEBER A, SCHOENIGER A, EDLICH F, HÄCKER G. *Chlamydia trachomatis* inhibits apoptosis in infected cells by targeting the pro-apoptotic proteins Bax and Bak[J]. Cell Death & Differentiation, 2022, 29(10): 2046-2059.
[82] DEO P, CHOW SH, HAY ID, KLEIFELD O, COSTIN A, ELGASS KD, JIANG JH, RAMM G, GABRIEL K, DOUGAN G, LITHGOW T, HEINZ E, NADERER T. Outer membrane vesicles from *Neisseria gonorrhoeae* target PorB to mitochondria and induce apoptosis[J]. PLoS Pathogens, 2018, 14(3): e1006945.
[83] NIU H, KOZJAK-PAVLOVIC V, RUDEL T, RIKIHISA Y. *Anaplasma phagocytophilum* Ats-1 is imported into host cell mitochondria and interferes with apoptosis induction[J]. PLoS Pathogens, 2010, 6(2): e1000774.
[84] WALL DM, McCORMICK BA. Bacterial secreted effectors and caspase-3 interactions[J]. Cellular Microbiology, 2014, 16(12): 1746-1756.
[85] GÜNTHER SD, FRITSCH M, SEEGER JM, SCHIFFMANN LM, SNIPAS SJ, COUTELLE M, KUFER TA, HIGGINS PG, HORNUNG V, BERNARDINI ML, HÖNING S, KRÖNKE M, SALVESEN GS, KASHKAR H. Cytosolic Gram-negative bacteria prevent apoptosis by inhibition of effector caspases through lipopolysaccharide[J]. Nature Microbiology, 2019, 5(2): 354-367.
[86] GE JL, WANG Y, LI XY, LU Q, YU HQ, LIU HT, MA KL, DENG XM, LUO ZQ, LIU XY, QIU JZ. Phosphorylation of caspases by a bacterial kinase inhibits host programmed cell death[J]. Nature Communications, 2024, 15: 8464.
[87] TRAN van NHIEU G, LATOUR-LAMBERT P, ENNINGA J. Modification of phosphoinositides by the *Shigella* effector IpgD during host cell infection[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 1012533.
[88] ARIZMENDI O, PICKING WD, PICKING WL. Macrophage apoptosis triggered by IpaD from *Shigella flexneri*[J]. Infection and Immunity, 2016, 84(6): 1857-1865.
[89] NEWTON HJ, PEARSON JS, BADEA L, KELLY M, LUCAS M, HOLLOWAY G, WAGSTAFF KM, DUNSTONE MA, SLOAN J, WHISSTOCK JC, KAPER JB, ROBINS-BROWNE RM, JANS DA, FRANKEL G, PHILLIPS AD, COULSON BS, HARTLAND EL. The type III effectors NleE and NleB from enteropathogenic *E. coli* and OspZ from *Shigella* block nuclear translocation of NF-kappaB p65[J]. PLoS Pathogens, 2010, 6(5): e1000898.
[90] KNODLER LA, FINLAY BB, STEELE-MORTIMER O. The *Salmonella* effector protein SopB protects epithelial cells from apoptosis by sustained activation of Akt[J]. Journal of Biological Chemistry, 2005, 280(10): 9058-9064.

[91] LI S, ZHANG L, YAO Q, LI L, DONG N, RONG J, GAO WQ, DING XJ, SUN LM, CHEN X, CHEN S, SHAO F. Pathogen blocks host death receptor signalling by arginine GlcNAcylation of death domains[J]. Nature, 2013, 501(7466): 242-246.

[92] BROWN NF, COOMBES BK, BISHOP JL, WICKHAM ME, LOWDEN MJ, GAL-MOR O, GOODE DL, BOYLE EC, SANDERSON KL, FINLAY BB. *Salmonella phage* ST64B encodes a member of the SseK/NleB effector family[J]. PLoS One, 2011, 6(3): e17824.

[93] WANG T, SONG XN, TAN JX, XIAN W, ZHOU XT, YU MR, WANG XF, XU Y, WU T, YUAN KK, RAN Y, YANG B, FAN GF, LIU XY, ZHOU Y, ZHU YQ. *Legionella* effector LnaB is a phosphoryl-AMPylase that impairs phosphosignalling[J]. Nature, 2024, 631(8020): 393-401.

[94] BANGA S, GAO P, SHEN XH, FISCUS V, ZONG WX, CHEN LL, LUO ZQ. *Legionella pneumophila* inhibits macrophage apoptosis by targeting pro-death members of the BCL2 protein family[J]. Proceedings of the National Academy of Sciences of the United States of America, 2007, 104(12): 5121-5126.

[95] 胡艺宝, 彭彬峰, 曹倩, 雷文波, 刘双全. 沙眼衣原体T3SS效应蛋白CT622通过激活ERK/p38 MAPK信号通路抑制Hela299细胞凋亡[J]. 中南医学科学杂志, 2024, 52(3): 324-328.
HU YB, PENG BF, CAO Q, LEI WB, LIU SQ. *Chlamydia trachomatis* T3SS effector protein CT622 inhibits Hela299 cell apoptosis by activating ERK/p38 MAPK signaling pathway[J]. Medical Science Journal of Central South China, 2024, 52(3): 324-328 (in Chinese).

[96] PETERS KN, DHARIWALA MO, HUGHES HANKS JM, BROWN CR, ANDERSON DM. Early apoptosis of macrophages modulated by injection of *Yersinia pestis* YopK promotes progression of primary pneumonic plague[J]. PLoS Pathogens, 2013, 9(4): e1003324.

[97] LÜHRMANN A, NOGUEIRA CV, CAREY KL, ROY CR. Inhibition of pathogen-induced apoptosis by a *Coxiella burnetii* type IV effector protein[J]. Proceedings of the National Academy of Sciences of the United States of America, 2010, 107(44): 18997-19001.

[98] BISLE S, KLINGENBECK L, BORGES V, SOBOTTA K, SCHULZE-LUEHRMANN J, MENGE C, HEYDEL C, GOMES JP, LÜHRMANN A. The inhibition of the apoptosis pathway by the *Coxiella burnetii* effector protein CaeA requires the EK repetition motif, but is independent of survivin[J]. Virulence, 2016, 7(4): 400-412.

[99] 王丽萍, 张少言, 冯雅, 陈佳骏, 彭若青, 鹿振辉. 结核分枝杆菌诱导宿主细胞程序性死亡机制及其治疗策略的研究进展[C]//第35届中国防痨协会全国学术大会暨第四届中国防痨科技颁奖大会论文集, 2024: 341-345.

[100] HAN B, PAN G, WEISS LM. Microsporidiosis in humans[J]. Clinical Microbiology Reviews, 2021, 34(4): e0001020.

[101] LEE SC, CORRADI N, BYRNES EJ, TORRES-MARTINEZ S, DIETRICH FS, KEELING PJ, HEITMAN J. Microsporidia evolved from ancestral sexual fungi[J]. Current Biology, 2008, 18(21): 1675-1679.

[102] SOKOLOVA YY, BOWERS LC, ALVAREZ X, DIDIER ES. *Encephalitozoon cuniculi* and *Vittaforma corneae* (phylum *Microsporidia*) inhibit staurosporine-induced apoptosis in human THP-1 macrophages *in vitro*[J]. Parasitology, 2019, 146(5): 569-579.

[103] MARTÍN-HERNÁNDEZ R, HIGES M, SAGASTUME S, JUARRANZ Á, DIAS-ALMEIDA J, BUDGE GE, MEANA A, BOONHAM N. Microsporidia infection impacts the host cell's cycle and reduces host cell apoptosis[J]. PLoS One, 2017, 12(2): e0170183.

[104] HE XY, FU Z, LI MQ, LIU H, CAI SF, MAN NN, LU XM. *Nosema bombycis* (*Microsporidia*) suppresses apoptosis in BmN cells (*Bombyx mori*)[J]. Acta Biochimica et Biophysica Sinica, 2015, 47(9): 696-702.

[105] del AGUILA C, IZQUIERDO F, GRANJA AG, HURTADO C, FENOY S, FRESNO M, REVILLA Y. *Encephalitozoon* microsporidia modulates p53-mediated apoptosis in infected cells[J]. International Journal for Parasitology, 2006, 36(8): 869-876.

[106] RAN MS, YANG WX, FARYAD KHAN MU, LI T, PAN GQ. Microsporidia secretory effectors and their roles in pathogenesis[J]. The Journal of Eukaryotic Microbiology, 2024, 71(5): e13046.

[107] RAN MS, BAO JL, LI BN, SHI YL, YANG WX, MENG XZ, CHEN J, WEI JH, LONG MX, LI T, LI CF, PAN GQ, ZHOU ZY. Microsporidian *Nosema bombycis* secretes serine protease inhibitor to suppress host cell apoptosis *via* Caspase BmICE[J]. PLoS Pathogens, 2025, 21(1): e1012373.

[108] RAN MS, SHI YL, LI BN, XIANG H, TAO ML, MENG XZ, LI T, LI CF, BAO JL, PAN GQ, ZHOU ZY. Genome-wide characterization and comparative genomic analysis of the serpin gene family in microsporidian *Nosema bombycis*[J]. International Journal of Molecular Sciences, 2022, 24(1): 550.

[109] SPARVOLI D, LEBRUN M. Unraveling the elusive rhoptry exocytic mechanism of Apicomplexa[J]. Trends in Parasitology, 2021, 37(7): 622-637.

[110] TOMLEY FM, BILLINGTON KJ, BUMSTEAD JM, CLARK JD, MONAGHAN P. EtMIC4: a microneme protein from *Eimeria tenella* that contains tandem arrays of epidermal growth factor-like repeats and thrombospondin type-I repeats[J]. International Journal for Parasitology, 2001, 31(12): 1303-1310.

[111] LU XQ, AN LW, FAN GJ, ZANG LJ, HUANG WY, LI JJ, LIU J, GE WY, HUANG YW, XU JX, DU SQ, CAO Y, ZHOU TH, YIN HJ, YU L, JIAO S, WANG HX. EGFR signaling promotes nuclear translocation of plasma membrane protein TSPAN8 to enhance tumor

progression *via* STAT3-mediated transcription[J]. Cell Research, 2022, 32(4): 359-374.
[112] MUNIZ-FELICIANO L, van GROL J, PORTILLO JC, LIEW L, LIU B, CARLIN CR, CARRUTHERS VB, MATTHEWS S, SUBAUSTE CS. *Toxoplasma gondii*-induced activation of EGFR prevents autophagy protein-mediated killing of the parasite[J]. PLoS Pathogens, 2013, 9(12): e1003809.
[113] WU L, WU LP, XI C, LIU Y, JIANG XG, CHEN SX, CAO JP. *Toxoplasma gondii* rhoptry protein 16 (ROP16) modifies apoptosis in human 293T cells[J]. Journal of Nanoscience and Nanotechnology, 2020, 20(1): 24-30.
[114] YAMAMOTO M, STANDLEY DM, TAKASHIMA S, SAIGA H, OKUYAMA M, KAYAMA H, KUBO EM, ITO H, TAKAURA M, MATSUDA T, SOLDATI-FAVRE D, TAKEDA K. A single polymorphic amino acid on *Toxoplasma gondii* kinase ROP16 determines the direct and strain-specific activation of Stat3[J]. The Journal of Experimental Medicine, 2009, 206(12): 2747-2760.
[115] DU J, AN R, CHEN LJ, SHEN YX, CHEN Y, CHENG L, JIANG ZR, ZHANG AM, YU L, CHU DY, SHEN YJ, LUO QL, CHEN H, WAN LJ, LI M, XU XC, SHEN JL. Withdrawal: *Toxoplasma gondii* virulence factor ROP18 inhibits the host NF-κB pathway by promoting p65 degradation[J]. Journal of Biological Chemistry, 2022, 298(12): 102719.
[116] KRISHNAMURTHY S, SAEIJ JPJ. *Toxoplasma* does not secrete the GRA16 and GRA24 effectors beyond the parasitophorous vacuole membrane of tissue cysts[J]. Frontiers in Cellular and Infection Microbiology, 2018, 8: 366.
[117] MOSSER DD, CARON AW, BOURGET L, MERIIN AB, SHERMAN MY, MORIMOTO RI, MASSIE B. The chaperone function of hsp70 is required for protection against stress-induced apoptosis[J]. Molecular and Cellular Biology, 2000, 20(19): 7146-7159.
[118] TUMMERS B, GREEN DR. The evolution of regulated cell death pathways in animals and their evasion by pathogens[J]. Physiological Reviews, 2022, 102(1): 411-454.