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鸡球虫诱导的宿主细胞凋亡研究进展

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摘要 本文系统综述了鸡球虫-宿主互作中凋亡调控机制的最新研究进展。研究表明:1)不同种属鸡球虫诱导宿主细胞凋亡存在差异性,柔嫩艾美耳球虫最强,巨型艾美耳球虫次之,堆型艾美耳球虫最弱,3种鸡球虫主要通过棒状体蛋白、微线蛋白和热休克蛋白等关键效应分子调控细胞凋亡;2)球虫感染过程中存在时序性凋亡调控细胞,早期通过抑制线粒体途径促进虫体定植,晚期则激活死亡受体途径以利于子代虫体释放;3)抗球虫药物中,化学类药物直接诱导虫体线粒体功能障碍,而中草药通过调节 Bcl-2/Bax, caspase-3 等凋亡因子发挥间接抗球虫作用。综上,这些研究发现不仅阐明了球虫致病的关键分子机制,更为基于调控的新型抗球虫药物设计和精准防控策略制定提供重要理论依据。

关键词 鸡球虫病; 细胞凋亡; 抗球虫药物

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Research advances in *Eimeria*-induced host cell apoptosis in avian coccidiosis

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Abstract The latest research on the mechanism regulating apoptosis in the relationship between chicken coccidium and host are systematically reviewed in this article. Researches indicates that: 1) Different species of chicken coccidia induce host cell apoptosis differently; *Eimeria tenella* is the strongest, followed by *Eimeria maxima* and *Eimeria acervulina*. Each of these species primarily control cell apoptosis through important effector molecules including rhoptry proteins, microneme proteins and heat shock proteins. 2) The coccidia infection process involves a number of apoptotic regulatory cells. During the early stages, these cells inhibit the mitochondrial pathway to encourage parasite colonisation, and in the later stages, they activate the death

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receptor pathway to facilitate the release of progeny parasites. 3) Among the anticoccidial drugs, chemical medicines cause the parasites to directly breakdown their mitochondria, while Chinese herbal remedies work indirectly by controlling apoptotic factors such caspase-3 and Bcl-2/Bax. In summary, these studies not only shed light on the primary molecular pathways of coccidiosis pathogenesis, but also they provide a crucial theoretical foundation for the development of specifically designed prevention and control measures as well as new anti-coccidiosis medicines based on regulation.

Keywords avian coccidiosis; cell apoptosis; anticoccidial drug

鸡球虫病是家禽业面临的重大疾病威胁之一,每年造成的经济损失约130亿美元^[1]。目前公认的鸡球虫种类有7种,不同艾美耳球虫的寄生部位、致病性、卵囊形态和最短潜伏期等均有差异。当球虫感染肠上皮细胞后使肠绒毛形态改变、消化吸收功能受损,如消化酶活性和转运体蛋白表达抑制,并且破坏肠道菌群稳态,引发采食量减少、腹泻,还可能继发产气荚膜梭菌等病原菌感染,严重时导致死亡^[2-5]。目前,常用的鸡球虫防控方法主要包括药物和疫苗。在药物防控方面,市场上抗球虫药物种类少且长期使用不规范导致鸡球虫耐药性问题凸显。据2018—2023年调查报道,我国大部分地区多数虫株均呈中度及以上耐药^[6]。疫苗防控虽有一定成效,但其不能对所有鸡球虫种类和不同发育阶段虫体都产生良好保护效果。因此,探寻鸡球虫病防控的新方向显得尤为紧迫,而近年来细胞凋亡在抗球虫领域的研究逐渐为解决这一难题带来了新的思路 and 希望。

细胞凋亡是宿主抵御病原体的关键自我防御机制,在组织稳态维持与免疫调控中发挥核心作用。鸡球虫感染时,宿主激活细胞凋亡通路清除感染细胞,但球虫进化出多重逃逸策略对抗宿主的免疫清除。首先,Th1型细胞因子分泌(如IFN- γ 和IL-12)及Toll样受体表达受到调控,阻断免疫激活与病原体识别^[7];其次,诱导调节性T细胞分泌IL-10和TGF- β 等抑制性细胞因子,抑制Th1型免疫反应的极化并构建免疫抑制微环境^[7-8]。此外,棒状体蛋白、微线蛋白和热休克蛋白等效应分子直接作用宿主细胞凋亡关键通路,降低免疫细胞对感染细胞的识别效率^[9-11]。感染中晚期,鸡球虫免疫逃逸效果减弱,细胞凋亡加快^[12]。针对球虫-宿主互动中的凋亡调控通路,抗球虫药物形成两大干预体系并展现差异化优势。化学合成类药物主要靶向虫体线粒体及离子稳态诱导凋亡,而中草药及其提取物通过作用凋亡核心分子、修复肠道屏障、调节免

疫信号通路等多维干预,成研发新方向^[13-16]。

因此,本综述系统解析了鸡球虫和宿主细胞互作过程中细胞凋亡的调控机制,以及抗球虫药物对宿主细胞凋亡通路的干预作用和抗感染机理。通过深入揭示球虫感染过程中凋亡相关信号网络的调控规律,不仅为阐明球虫的致病机制和耐药性产生提供了新的理论依据,更为研发基于凋亡调控的新型抗球虫药物和疫苗设计奠定了重要基础。

1 不同种属的鸡球虫诱导宿主细胞凋亡的差异性

柔嫩艾美耳球虫(*E. tenella*)作为高致病性虫株,在入侵早期快速释放多种蛋白与酶类激活凋亡相关基因,启动凋亡程序,其早熟株后期诱导细胞凋亡能力显著弱于强毒株^[17]。其致病机制与多种效应分子密切相关:*Ei*ROP1作为首个鉴定的功能激酶,通过与宿主细胞p53蛋白相互作用并磷酸化Thr387位点,阻滞细胞周期发展^[18]; *Ei*ROP2通过激活p38MAPK信号通路加速体内外裂殖子发育及产生,而*Ei*ROP38反向抑制该通路以阻断细胞凋亡^[19-20];此外,EGF-*Ei*MIC4和EGF-*Ei*MIC7与宿主EGFR结合,调控凋亡通路中*Akt*、*ERK*和*Bcl-2*关键基因表达,干预细胞凋亡进程^[21-22]。巨型艾美耳球虫(*E. maxima*)寄生于小肠中段,致病性较强,其凋亡抑制机制依赖虫体抗原(如SAG家族蛋白和热休克蛋白)。这些蛋白通过磷酸化ERK1/2从而抑制ERK-MAPK信号通路,降低IL-12的表达,使球虫寄生环境稳定^[23]。堆型艾美耳球虫(*E. acervulina*)寄生于十二指肠,致病性弱,其与*E. tenella*均能抑制6%乙醇凋亡诱导剂发挥作用,从而抑制细胞凋亡^[24],*Ea*MIC3可模拟宿主表面正常蛋白,靶向E3泛素化连接酶CBL,干扰宿主信号转导通路以逃逸免疫清除^[25](表1)。

表 1 主要鸡球虫种类及其凋亡调控特征

Table 1 Major chicken coccidia species and their apoptotic regulatory features

鸡球虫种类 Chicken coccidia species	寄生部位 Parasitic site	凋亡程度 Degree of apoptosis	关键效应分子 Key effector molecules	免疫逃逸途径 Immune escape pathways	参考文献 References
<i>E. tenella</i>	盲肠	强(++++)	<i>EtROP1</i>	p53/p21 信号通路	[18]
			<i>EtROP2</i>	激活 p38MAPK 信号通路	[19]
			<i>EtROP30</i>	抑制 NF-κB 信号通路	[26-27]
			<i>EtROP38</i>	抑制 p38MAPK 信号通路	[20]
			<i>EtMIC4</i>	EGFR-Akt 信号通路	[22]
			<i>EtMIC7</i>		[21]
			<i>EtAMA1</i>	调控线粒体途径和死亡受体途径	[28]
<i>E. maxima</i>	小肠中段	中等(++)	<i>EmSAG</i>	ERK-MAPK 信号通路	[7,23]
			<i>EmHPSP-1</i>		
			<i>EmHPSP-2</i>		
<i>E. acervuline</i>	十二指肠	弱(+)	<i>EaMIC3</i>	靶向宿主受体-CBL 蛋白	[25]

2 鸡球虫感染对宿主关键凋亡通路的影响

2.1 鸡球虫感染中宿主凋亡的双相调控：从抑制到激活的转变

在子孢子入侵阶段(0~24 h),虫体主要通过线粒体途径介导凋亡。主要表现为:阻断线粒体通透性转换孔(MPTP)开放,延缓膜电位($\Delta\Psi_m$)下降 ≥ 6 h,并抑制细胞色素 c 释放和 caspase-9/3/7 级联反应^[29-30]。研究表明,环孢菌素 A(CsA)、Z-LEHD-FMK 等抑制剂的使用和 ATP 敏感性钾通道(mitoKATP)开放可显著减轻鸡胚盲肠上皮细胞损伤^[29,31-32]。此外,虫体分泌 *EtSerp*in、*EtHSP90* 等效应蛋白,直接靶向 caspase-8/3 的激活,从多层面阻断细胞凋亡^[9,11]。在裂殖体增殖阶段(24~72 h),球虫与宿主互动模式发生改变。大量裂殖子导致 ATP 水平骤降,引发 MPTP 不可逆开放和细胞色素 c 释放量显著增加 80%^[30]。同时,内质网应激加剧,钙离子超载和活性氧爆发共同促进凋亡信号级联反应^[33]。钙蛋白酶促进 Bax/Bid 表达,加速 caspase 依赖性凋亡^[34]。此阶段还伴随自噬活动增强,通过清除病原体和调控程序性死亡参与宿主防御^[35]。研究表明,柔嫩艾美耳球虫分泌的 *HP* 基因等效应分子可直接诱导宿主细胞凋亡^[36]。

2.2 鸡球虫感染中信号通路的动态调控机制

在鸡球虫感染中,PI3K/Akt、MAPK 和 TNF 信号通路通过动态调控宿主细胞的存活与凋亡。PI3K/Akt 通路能使凋亡级联相关蛋白磷酸化或通

过 NF-κB 上调抗凋亡基因的表达,抑制细胞凋亡^[21,37]。宿主细胞 P13K/Akt 通路活性提升 2~3 倍,促进 p-Akt 表达从而限制 MPTP 开放,为虫体存活提供环境^[37]。与此同时,感染早期,NF-κB 通路被激活,抑制凋亡;中晚期,其活性受抑制,促进凋亡以清除感染细胞^[38]。p38MAPK 信号通路调节 Bax 活性和 cFos/AP-1 复合体形成,显著抑制球虫入侵^[20,39]。ASK1 作为 MAPK 中的一个关键磷酸酶,由于 *EtPP5* 过表达阻止其激活,从而抑制细胞凋亡^[40]。此外,肿瘤坏死因子受体相关死亡结构域(TRADD)蛋白的调控功能发生转换:早期与 RIP1 结合维持细胞存活,后期与 FADD 结合激活 caspase-8,启动外源性凋亡通路,同时 FasL 激增 4.5 倍,死亡受体信号传导强化^[41-42]。

2.3 影响细胞凋亡的关键因子

Bcl-2 蛋白家族通过调控线粒体途径在细胞凋亡中发挥核心作用。Bcl-2/Bax 和 Bcl-xl/Bid 的平衡状态决定细胞命运,其中 Bcl-xl 通过抑制细胞色素 c 释放发挥抗凋亡作用,而 Bid 则促进凋亡因子的释放^[30,43]。当凋亡信号激活时,细胞色素 c 从线粒体释放并与 Apaf-1 结合形成凋亡小体,进而激活 caspase 级联反应^[29]。caspase 家族可分为起始酶(caspase-8/10)和效应酶(caspase-3/7),起始酶通过激活效应酶引发下游凋亡执行过程^[44]。尽管凋亡激活途径存在差异,但 caspase 级联反应始终是凋亡信号转导的共同终末通路,最终导致细胞结构和功能的不可逆损伤。

3 抗球虫药物调控宿主细胞凋亡

3.1 化学合成类抗球虫药物

这类药物主要靶向虫体线粒体与离子稳态的凋亡干预。莫能菌素能与线粒体膜上的阳离子(Na^+/K^+)特异性结合导致线粒体膜电位、形态改变,使 Na^+/K^+ ATP酶的活性增加,通过氧化应激导致乳酸积累和ATP耗竭,发生自噬^[13]; *E. tenella*莫能菌素耐药株肌动蛋白表达上调和微线蛋白4(MIC4)表达下调^[45]。地克珠利作为化学合成类药物中的三嗪类药物之一,通过干扰钙稳态导致第二代裂殖子(Mz2)早期细胞凋亡和晚期细胞凋亡/坏死率显著增加,并伴有线粒体膜电位(MMP)的突然和快速下降,导致线粒体呼吸链酶表达量改

变^[14]; *E. tenella*地克珠利耐药株对DIC诱导的与蛋白磷酸酶5相关的细胞凋亡表现出耐受性^[46]。

3.2 中草药类抗球虫药物

这类药物基于宿主内源性通路的多维干预。其中,血根碱、川楝素、青蒿素、胡椒和蛇床子等通过作用于凋亡核心分子(如Bcl-2/Bax、caspase-3、线粒体膜电位),直接调控感染细胞或正常细胞的凋亡程序发挥作用^[15-16, 47-49];鬼针草、乌尼酸和单宁酸等通过肠道屏障功能修复及病原协同感染抑制,改善球虫感染导致的局部组织损伤微环境^[50-51];血根碱、青蒿素和柴胡皂苷等通过NF- κ B等免疫信号通路,平衡抗球虫免疫应答与炎症损伤,避免过度免疫引发的细胞凋亡级联反应^[15, 47, 52](表2)。

表2 已知中草药及其提取剂调控细胞凋亡
Table 2 Chinese herbs and their extracts are known to regulate apoptosis

中草药及其提取剂 Chinese herbs and their extracts	凋亡调控相关机制 Apoptosis regulation mechanism	参考文献 Reference
血根碱 Sanguinarine	增加活性氧(ROS)水平,诱导氧化应激相关凋亡;升高钙离子浓度,激活caspase-3凋亡执行酶;降低线粒体膜电位	[15]
川楝素 Toosendanin	激活caspase-3,启动凋亡级联反应;降低抗凋亡蛋白Bcl-2与促凋亡蛋白Bax的比率;浓度为5 mg/kg的川楝素ACI值为164.35	[16]
青蒿素 Artemisinin	上调抗凋亡蛋白Bcl-2,抑制过度凋亡以保护宿主细胞;下调促凋亡蛋白Bax和caspase-3活性,平衡凋亡进程;激活NF- κ B信号通路,通过免疫调节间接调控凋亡相关因子	[47]
胡椒 <i>P. sarmentosum</i>	下调抗凋亡基因Bcl-2表达,上调促凋亡基因Bax表达	[48]
蛇床子 <i>Cnidium monnieri</i>	抑制NF- κ B通路中p65的磷酸化以及Bcl-2蛋白的表达,减少相关炎症因子的释放	[49]
鬼针草 <i>Bidens pilosa</i>	下调Bcl-2、上调Bax,直接调控凋亡蛋白平衡;增强抗氧化酶活性(间接减少氧化应激诱导的异常凋亡)	[50]
乌尼酸和单宁酸 Usnic acid and tannic acid	降低线粒体膜电位,破坏线粒体依赖性凋亡通路;抑制球虫及产气荚膜梭菌生长,减少病原感染引发的宿主细胞凋亡	[51]
柴胡皂苷 Saikosaponin	抑制NF- κ B炎症通路,减少TNF- α 和IL-6等促炎因子诱导的细胞凋亡;ACI为173.13	[52]

4 结论与展望

在鸡球虫感染中,鸡球虫与宿主细胞相互作用通过多种途径调节宿主细胞凋亡。感染早期,延缓宿主细胞损伤从而确保自身在细胞内的生长、发育和繁殖。在感染中后期,细胞结构破坏程度加剧,

营养物质损失,正常生理机能无法维持。通过分子机制的研究,揭示了宿主细胞中调控细胞凋亡的一些关键因素和信号通路,这些因素和信号通路调节细胞凋亡信号转导,以及干扰细胞凋亡的分子机制。这些发现为进一步了解鸡球虫的感染机制和发病机制提供了重要线索,为疫苗设计和药物开发

提供了新思路。

在疫苗设计方面,基于宿主细胞凋亡机制的研究为开发新型疫苗提供了重要思路。通过将靶向鸡球虫调控宿主细胞凋亡的关键分子标志物作为候选抗原,利用基因重组等技术制备成基因工程疫苗,阻断球虫对细胞凋亡通路的调控,恢复宿主细胞凋亡的正常免疫清除功能,为新型疫苗设计提供了新的靶点^[26, 28];此外,结合宿主凋亡信号通路(如线粒体途径、死亡受体途径)的激活机制,设计能够增强肠上皮细胞凋亡清除效率的新型免疫佐剂,可协同提升疫苗对不同发育阶段球虫的保护效果,弥补传统疫苗的保护缺口^[42, 53]。

在药物开发方面,靶向细胞凋亡通路的新型抗球虫药物具有广阔的应用前景。中草药及其提取物展现出了靶向细胞凋亡通路的潜力;纳米材料如纳米乳、无机纳米药物和纳米囊泡,可以有效解决常用抗球虫药物及植物添加剂的不溶性或难溶性、颗粒大小和毒性等问题,降低药物残留,从而增强药物对球虫的治疗效果^[54-58]。此外,球虫耐药性的产生与凋亡通路也相关,结合单细胞测序、分子对接和药物动力学等方法,筛选出具有潜在抗球虫活性且不易突变的靶向位点,通过基因编辑技术验证其作用靶点,为新型抗球虫药物的研发提供了技术支撑^[13, 59-61]。

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