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环形泰勒虫介导宿主细胞转化的多维调控机制研究进展

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摘 要 环形泰勒虫(*Theileria annulata*)是热带泰勒虫病(Tropical theileriosis)的主要病原,其裂殖体通过分泌蛋白扰乱宿主细胞调控网络并诱发转化,但现有研究局限于单一分子或通路,缺乏对整体调控构架的认知。基于此,本文提出环形泰勒虫诱导宿主细胞转化的多维调控机制,涵盖四大层面:1)基因组突变与适应性进化为转化奠定遗传基础;2)劫持NF-κB、ERK/AP-1及PI3K-AKT等核心通路,形成增殖与存活的信号枢纽;3)通过组蛋白修饰与非编码RNA网络,将瞬时的信号固化为持久的转化表型;4)诱导免疫抑制、氧化应激与自噬逃逸重塑,有利于虫体寄生与细胞转化的微环境。四大层面存在紧密协同:基因组不稳定性持续放大信号通路异常,过度激活的信号通路重塑表观遗传调控,表观转录后调控又造成通路紊乱,而免疫失衡、氧化应激、自噬逃逸反向加剧DNA损伤与通路持续激活,形成闭环促转化调控网络。本文解析了环形泰勒虫诱导宿主细胞转化的多维调控网络组成和互作机制,为全面理解其分子机制奠定了新的理论基础,并为靶向该网络关键节点研发抗寄生虫与抗肿瘤策略提供了新思路。

关键词 环形泰勒虫;效应蛋白;细胞转化;基因突变;信号通路劫持
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Advances in the multidimensional regulatory mechanisms of *Theileria annulata*–induced host cell transformation

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Abstract *Theileria annulata* is the main causative agent of tropical theileriosis, and its schizont stage manipulates host cell regulatory networks and induces transformation through secreted proteins. However, existing studies are limited to a single molecule or pathway and lack understanding of the overall regulatory framework. Therefore, This article proposes a multidimensional regulatory mechanism underlying host cell transformation induced by *Theileria annulata*, encompassing four key dimensions: 1) Genomic mutations and adaptive evolution provide the genetic basis for transformation. 2)Hijacking core signaling pathways, including NF-κB, ERK/AP-1, and PI3K-AKT, to form a signaling hub for proliferation and survival. 3) By modifying histones and non-coding RNA networks, transient signals are solidified into a sustained transformed phenotype. 4) The induction of immunosuppression, oxidative stress, and autophagy escape remodels a microenvironment favorable for parasite persistence and cellular transformation. There is close coordination at four levels: genomic instability continuously amplifies aberrant signaling; overactivated signaling pathways reshape epigenetic regulation; epigenetic and post-transcriptional dysregulation further disrupts pathway homeostasis; while immune imbalance, oxidative

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stress, and autophagy escape in turn exacerbate DNA damage and sustain pathway activation, thus forming a closed-loop pro-transformation regulatory network. This review systematically elaborates on the composition and interplay mechanisms of this network, thereby laying a new theoretical foundation for a comprehensive understanding of its molecular mechanism and offering novel insights for developing anti-parasitic and anti-tumor strategies that target key nodes of this network.

Keywords effector proteins; cell transformation; gene mutation; signaling pathway hijacking

环形泰勒虫(*Theileria annulata*)是泰勒属内致病性最强的蜱传性寄生虫,可侵染并转化牛B淋巴细胞、巨噬细胞与树突状细胞,是导致养牛业遭受重大经济损失的主要病原[1-2]。其致病机制的核心在于虫体裂殖体分泌蛋白(如TashAT和SVSP家族等)经由宿主细胞质/细胞核的转运,进而干扰宿主细胞信号网络和表观遗传调控系统,从而驱动细胞异常增殖与转化,引发肿瘤表型变化[3-4]。因此,该转化细胞为研究虫体和宿主细胞互作提供了理想的生物模型。

近年来,环形泰勒虫介导宿主细胞转化机制,已成为寄生虫学与肿瘤生物学交叉领域的研究热点[5],早期研究多聚焦于核转录因子等单一信号通路的激活,如今拓展至涵盖基因突变、信号转导网络重构、表观遗传与宿主病理响应等多维度[6-12]。尽管已有大量虫体蛋白与信号通路已被证实,但该领域仍存在明显研究短板:现有研究未能系统梳理虫体分泌蛋白与宿主靶标互作逻辑、宿主基因突变与信号通路之间是否存在互作尚不清楚。多数研究仅关注转化细胞内分子变化,缺乏细胞表型与宿主免疫应答、氧化应激及自噬等病理响应相互关联的探讨,导致对虫体介导宿主细胞转化完整机制仍未得到阐述。因此,本综述突破传统单一分子或通路研究局限,以多维协同调控网络为框架,依次梳理基因组突变与适应性进化、信号通路劫持(NF-κB与ERK/AP-1、PI3K/AKT通路)、表观遗传(组蛋白修饰、DNA甲基化)与转录后(miRNA网络)调控及宿主系统性病理响应(免疫调控、氧化应激、自噬逃逸)等方面的最新进展。在厘清各层面核心机制的基础上,进一步指出各层面间已揭示或潜在的关键交互关系,旨在系统阐释环形泰勒虫介导宿主细胞转化的复杂调控网络,为该转化机制的解析提供理论基础。

1 基因组突变与适应性进化

1.1 宿主基因组的突变特征与驱动机制

在宿主-寄生虫共进化的过程中,大多数寄生性原虫的诱变机制被归为随机DNA损伤的传统范畴[13]。顶复门寄生虫的基因组在蛋白质组规模缩小的同时,常伴随DNA修复基因显著丢失,这可能是其突变率升高的重要内在原因[14]。环形泰勒虫也印证了这一特征,印度虫株在微卫星序列、全基因组位点及抗原基因等多个层面均存在广泛的基因突变,仅染色体1积累的SNP最多(3 210)[15]。该虫诱导宿主基因组发生广泛体细胞突变,共鉴定出35 341个SNVs和InDels,其中7 867个外显子区域突变为所有细胞系共有,说明寄生虫并非随机诱变宿主基因组,而是通过特定机制系统性诱导基因组变异[6]。*ROS1*基因中发现错义突变(如c.6884A>G等)致激酶构象异常,激活MAPK/PI3K-Akt通路,且其抑制剂克唑替尼处理细胞,导致转化细胞凋亡,证实ROS1依赖信号作为虫体感染白细胞增殖的介导因子[6]。此外,宿主TP53/p21通路信号传导受阻、BARD1/KMT2C突变加剧基因组不稳定性,并且虫体上调APOBEC3H,诱导C→T/C→G突变(占SNVs总数42%),提示虫体可能借助宿主DNA编辑酶加速基因组突变,从而实现免疫逃逸[6]。

1.2 耐药基因突变与群体遗传进化

虫体Cyt b基因突变是虫体对布帕伐醌产生耐药性的分子基础,已报道耐药突变位点包括M128I、G129S、S253R、S262R,另有V203I、V219I两类新型突变位点被陆续发现[16-17]。除Cyt b外,TaPIN1也是介导布帕伐醌耐药的关键基因,该基因P26A、K121E、G124E位点突变,与国外报道的耐药虫株高度一致[18-19];另有A53P和A53T两突变位点对虫体产生耐药表型[20]。其中TaPIN1-A53P突变也帮助虫体逃避布帕伐醌对PKM2/HIF1α通路的抑制作用,从而产生特异性耐药表型[21]。由于TaPIN1和Cyt b基因联合突变普遍存在,可作为追踪非洲、中东和亚洲耐药性传播的重要生物标志物[22]。全球环形泰勒虫分离株存在显著遗传异质性,其中印度北部与伊朗分离株亲缘关系较近,而中国新疆分离

株则形成独立遗传进化支，表明该虫在地理扩散过程中发生显著的适应性进化[23]。对南亚、中东、北非和欧亚四大区域的虫株比较发现，各地虫株均具备较高的遗传多样性，且结合蜱的生物学习性、宿主因素（年龄、性别和品种）以及地理屏障共同限制了种群间基因交流，使耐药突变具有地域独立性；媒介传播与宿主免疫选择促进虫株进化，进而造成不同地区宿主细胞转化的表型存在差异[24]。

1.3　基因突变与信号通路的关系

宿主基因突变与信号通路存在密切双向调控关系，ROS1基因发生错义突变可改变激酶空间构象，持续激活PI3K-AKT、ERK/MAPK等关键通路[6]；TP53、BARD1等基因突变加剧基因组不稳定性，增强通路的异常活化。虫体通过上调APOBEC 3H加速宿主基因突变，而信号通路异常活化又会提升突变概率，二者共同推动细胞转化[6]。与此同时，虫体通过Cyt b、TaPIN1等耐药性突变与种群进化，保障其在宿主体内持续定植，而这种持续寄生诱导宿主表型存在差异，伴随着信号通路异常，推动细胞转化进程[16-24]。

2　核心信号转导网络的重构与协同调控

2.1　NF-κB与ERK的双重输入调控AP-1活性

环形泰勒虫感染可诱导宿主基因组发生突变，而信号通路是将基因组变异变为宿主细胞转化表型的核心环节。NF-κB与AP-1两大信号通路的协同激活既是细胞永生化的基础，又受虫体分泌蛋白直接调控，形成上游信号启动至下游转录的完整致病轴[25]。感染初期，虫体活化IκB激酶（IKK）复合体，促进IκBα磷酸化降解，释放NF-κB（p50/p65异源二聚体）入核，启动靶基因转录[26]。其次，虫体诱导TNFα自分泌激活JNK通路，异常激活ATF-2等转录因子，进而稳定AP-1复合物[27]。NF-κB激活可上调MAP4K4及ERM等细胞骨架调节蛋白，MAP4K4是NF-κB下游的关键激酶，通过磷酸化修饰进一步激活JNK信号，影响细胞增殖；而ERM蛋白连接肌动蛋白细胞骨架与细胞膜，维持宿主细胞迁移能力[28]。当机体或细胞受到外界因素（炎症因子、DNA损伤及特定的药物）时，NF-κB与AP-1的协同作用可减弱AP-1对MMP9等侵袭基因的特异性激活，降低细胞传播力，体现该调控的情境依赖性[29]。此外，虫体分泌蛋白参与信号通路劫持，如TaSDP与小泰勒虫（*Theileria parva*）TpSCOP为同源蛋白，后者可激活NF-κB通路，提示TaSDP或具类似功能，但具体机制尚待阐明[30]。TaPIN1蛋白可分泌至宿主胞质，结合泛素连接酶FBW7并抑制其对c-JUN的降解，从而稳定c-JUN，促进AP-1持续激活与细胞转化[31]。Ta9蛋白可靶向识别感染牛体内的$CD8^+$T细胞，凭借较强的细胞毒性间接提升AP-1的转录活性，从免疫层面参与通路调控[32]。

ERK1/2介导的MAPK通路是AP-1活化的另一关键通路。环形泰勒虫能特异地重塑宿主细胞磷酸化修饰图谱，ERK1/2是该过程的关键调控节点；阻断ERK1/2会显著下调FOSL2、JUNB的表达与磷酸化水平，证实其正向调控AP-1活性，而该通路与NF-κB、PI3K/AKT的交互作用仍未阐明[26]。该ERK-AP-1轴在感染过程中具有多重生物学效应：ERK1/2被抑制可减弱M1型促炎表型（TNF-α↓、IL-12↓），JNK持续激活促进M2型极化（IL-10↑、TGF-β↑），二者协同实现虫体免疫逃逸[33]。其次，虫体膜表面的热休克蛋白70（HSP70）同源物可通过TLR4-MyD88通路激活ERK-AP-1轴，进而上调cyclin D1和CDK4表达，推动细胞周期G1/S期转换[7]，并通过上调端粒酶逆转录酶维持细胞永生化[34]。此外，多种虫体蛋白参与MAPK通路的稳态调控：TaPIN1稳定c-Jun以激活AP-1，TashAT家族可能参与该调控网络[7]。靶向Ta9截短体的重组疫苗可阻断虫体与宿主Hck蛋白结合，恢复MAPK-AP-1通路正常功能[35-36]。综上，虫体通过激活NF-κB上调MAP4K4并激活JNK，从而调控MAPK/AP-1通路；而ERK激活的AP-1与NF-κB协同调控下游靶基因转录，诱导宿主细胞增殖。然而，ERK1/2与NF-κB或PI3K/AKT之间是否存在直接调控，以及PI3K/AKT在转化中的具体作用机制仍不明确，需进一步研究。

2.2　PI3-K-AKT通路介导的转化机制

PI3K-AKT/mTOR通路相关基因在感染细胞中显著富集，尤以PI3KR3的特异性高表达为特征，经PI3K抑制剂LY294002处理或布帕伐醌（Bw720c）杀虫后，PI3KR3表达显著降低，感染细胞表现出明显的增殖抑制与凋亡启动[37]。虫体通过分泌效应蛋白催化PIP2向PIP3转化，诱导AKT在Ser473位点持续性磷酸化，进而激活NF-κB，保护

其免受转化过程中自发凋亡[38]。而活化的AKT进一步与bHSP90、bTERT构成三元复合物，通过促进bTERT的磷酸化、激活及核转位，重激活端粒酶以延长端粒，阻断宿主复制性衰老，实现永生化转化[9]。因此，靶向干预策略（如HSP90抑制剂新生霉素）可通过破坏AKT-bHSP90-bTERT复合物形成，下调p-Akt水平并抑制端粒酶活性，实现对感染细胞的选择性清除[39]。此外，裂殖体表面蛋白TaSP和p104通过介导寄生虫-宿主细胞骨架互作，并在特定细胞周期发生磷酸化，形成稳定信号平台，持续招募和激活PI3K-AKT复合物[40]。这种持续激活不仅间接抑制p53通路，降低DNA损伤修复能力，还导致转化细胞中富集大量涉及ROS1、FLT4及PI3K-Akt通路的体细胞突变[6]。

2.3 通路与其他调控层面的关联

虫体依赖TaPIN1、Ta9、TaSP等分泌蛋白持续激活NF-κB、ERK/AP-1、PI3K-AKT通路[30-32,40]。活化的AKT可反向激活NF-κB，并通过JNK、ERK协同调控转录因子AP-1，形成紧密的信号网络，连接上游基因组信号与下游病理应答：PI3K-AKT通路抑制p53通路活性，降低DNA损伤修复能力，引发ROS1、FLT4等基因突变累积；通路异常诱发代谢紊乱与氧化应激，加剧基因组不稳定性[6,37-38]。其次，ERK-AP-1与AKT协同调控细胞周期和端粒酶活性，诱导细胞转化；MAPK通路参与巨噬细胞极化，ERK1/2抑制M1型促炎反应，JNK则促进M2型极化，免疫微环境的改变又支撑通路的活化[5,7,33]。因此，以信号通路为纽带，连接基因突变、氧化应激、免疫紊乱等多因素，共同介导宿主细胞转化与全身病理损伤。

3 表观遗传与转录后调控核心

3.1 组蛋白与RNA表观遗传修饰

信号通路对基因表达进行初始调控，表观遗传与转录后机制通过重塑染色质状态与mRNA稳定性，将瞬时信号刺激转化为稳定的转化表型。虫体感染会重塑H3K27me3全基因组分布模式，修饰区域由局部窄峰变为大片染色质结构域、整体丰度显著上升，使细胞对PRC2抑制剂产生脱敏效应[8]。组蛋白修饰还存在空间区室化特点，即核质富集H3K27me3、H3K9me1/2等抑制性标记，而虫体-宿主核互作界面周围则富集H3K4me3、H3K18me1及H3K27ac等激活性标记[41]。虫体TaSETup1介导的H3K18甲基化可抑制基因表达，KDMi抑制剂可干预此过程并影响分化[42]。而虫体编码的TaHDAC1可维持染色质乙酰化平衡，是调控虫体发育的潜在靶点[43]。此外，除组蛋白修饰外，RNA表观遗传修饰亦在转化中发挥重要作用。感染细胞m^6A甲基化水平与增殖速率正相关，通过稳定E2F4等mRNA促进细胞周期转运，并揭示HIF-1α可招募p300乙酰转移酶，上调H3K27ac等激活性标记，从而建立细胞代谢与表观遗传调控间的核心联系[11,44]。

3.2 miRNA介导的转录后调控网络

宿主微小RNA（miRNA）是转录后调控的核心分子，差异表达的miRNA主要靶向JNK、PI3K-Akt、MAPK等通路，影响宿主表型。在转化细胞中bta-miR-2285t、bta-miR-34a和bta-miR-150等miRNA表达显著上调，且差异表达主要富集在MAPK等信号通路[9]。研究表明，bta-miR-155抑制DET1蛋白，导致JNK/c-Jun通路持续活化，引起被感染的细胞无限增殖[45]；bta-miR-34c-3p通过抑制prkar2b导致PKA通路失活，加剧细胞侵袭迁移[46]；miR-126-5p显著下调DLK1蛋白表达，进而激活JNK通路，促使下游靶基因转录[47]。此外，细胞外囊泡（EVs）可在细胞间传递miRNA与蛋白分子，环形泰勒虫耐药株感染牛的血清EVs中筛选出239种共有miRNA组分，其中65种为未感染牛特有（如bta-let-7d），58种为感染特异性（如bta-miR-206上调6.35倍）[48]。这些EVs可转运虫源蛋白与miRNA实现细胞间信号，在全身范围内重塑利于虫体存活的抑制性免疫微环境，参与调控宿主细胞转化进程[49]。

3.3 表观调控与其他层面的关联

宿主信号通路持续活化会诱发表观遗传现象，而表观修饰与miRNA表达变化又反向维持通路活性。虫体分泌的TaHDAC1、TaSETup1等表观修饰酶能够改变组蛋白修饰特征与重塑染色质构象[42-43]，并诱导bta-miR-155、miR-126-5p等miRNA异常上调[45,47]，从而持续激活NF-κB、MAPK/JNK、PI3K-AKT通路，将短暂刺激转变为稳定的细胞转化表型[25,31,37-38]。此外，细胞外囊泡可携带miRNA完成细胞间传递信号[48-49]，重塑全身免疫抑制微环境，免疫失衡又进一步增强通路

活化[25,31,37-38,42-43,45,47-49]。

4　宿主系统性病理响应

4.1　免疫调控

环形泰勒虫感染可引起细胞免疫应答、细胞应激与自噬过程，保障其胞内寄生与增殖[50]。虫体激活宿主下丘脑-垂体-肾上腺轴（HPA轴），导致糖皮质激素释放，长期作用下引发免疫紊乱，为虫体寄生提供有利生存条件[51]。在慢性感染阶段，宿主炎症稳态被显著破坏，患病牛血清中Hp和PCT含量显著升高，提示机体存在持续性全身性炎症[52]；且显著下调NOD1、NLRP3、CASP1表达，而上调IL-1β表达，引起炎症小体功能失调，进而加剧组织损伤[53]。在急性感染期，虫体还显著抑制IL-2介导的免疫应答，下调$CD8^+$T细胞表面受体CD2的表达，阻碍T细胞接收增殖与分化信号而功能受损[54]。被感染的抗原呈递细胞（APCs）异常高表达MHC II类分子，引发T细胞过度活化与免疫稳态失衡，进而抑制B细胞成熟及抗体生成，导致宿主体液免疫与细胞免疫应答均受到严重抑制[55]。针对环形泰勒虫复杂的胞内感染周期，多表位重组蛋白疫苗通过结合子孢子和裂殖体阶段的特定抗原表位，可同时激活体液免疫与细胞免疫应答，进而恢复T、B细胞的正常免疫功能[35,56]。综上，这种复杂的免疫调控机制，其病理意义核心在于驱动宿主细胞转化：不仅确保虫体在宿主体中长期定植，更导致宿主细胞器（如线粒体）功能失调而引起氧化应激，驱动细胞的异常增殖与转化。

4.2　氧化应激

环形泰勒虫感染可显著扰乱宿主氧化应激稳态，二者存在紧密的调控关联。细胞内活性氧（ROS）异常累积，可直接损伤线粒体结构与功能，诱发DNA氧化损伤；并且持续激活缺氧诱导因子1α（HIF1α）加重慢性炎症，炎症反应又促进ROS生成，进而导致机体多组织广泛性氧化损伤[57]。感染环形泰勒虫的动物体内CAT、PON1等抗氧化酶活性显著降低，MDA水平升高，提示氧化应激持续加剧[58]。研究发现，H_2O_2介导的氧化应激强度与虫体的毒力显著相关，与强毒株相比，感染减毒虫株的巨噬细胞产生H_2O_2的能力显著增强[59]。氧化应激还会诱发严重的靶器官损伤，其中神经损伤表现尤为突出。患病牛血清中神经元特异性标志物S100B、GFAP和Tau蛋白浓度显著上调，证实氧化应激可诱发神经炎症、破坏血脑屏障，进而造成脑组织炎性浸润与神经细胞凋亡[60]，该过程可协助免疫紊乱，促进细胞转化，为虫体寄生创造条件。氧化应激失衡是该病重要病理特征，天然活性物质成为靶向调控氧化应激的理想候选药物，青蒿素衍生物、熊果酸和姜黄素等天然药物通过显著上调ROS水平，诱导线粒体途径的细胞凋亡，实现对虫体细胞的清除[61-63]。

4.3　自噬逃逸机制

异源自噬（Xenophagy）是宿主清除胞内病原体的重要先天免疫防线[64]，环形泰勒虫通过多重机制抑制自噬进程，并利用宿主自噬相关蛋白完成自身寄生，实现自噬逃逸。虫体将真核翻译起始因子5A（eIF5A）锚定于其表面，阻碍底物泛素化与p62募集，抑制自噬体成核；激活AMPK可恢复eIF5A正常功能，重启自噬并清除虫体[12]。其次，虫体持续激活ERK1/2-RSK-TSC2轴，解除TSC2对mTORC1的抑制作用，从上游阻断自噬启动过程；抑制ERK1/2活性诱导感染细胞凋亡，证实该通路对免疫逃逸至关重要[7]。虫体表面蛋白p104将宿主JNK2滞留于细胞质，阻断线粒体ARF介导的保护性自噬，从而促进感染巨噬细胞的增殖；虫体被药物杀死后，裂解物会被LC3阳性结构吞噬，且LC3蛋白在宿主细胞质与虫体内部共定位现象[65]。此外，虫体编码的周期蛋白依赖性激酶7（TaCDK7）的抑制剂升麻素，可诱导宿主细胞自噬发生，有效抑制宿主细胞转化[66]。相比之下，姜黄素处理可通过依赖ROS通路上调酸性液泡数量、促进LC3B脂化并抑制mTOR磷酸化，而NAC预处理可完全逆转上述效应，证明自噬是调控感染细胞存活与凋亡的关键枢纽[63]。

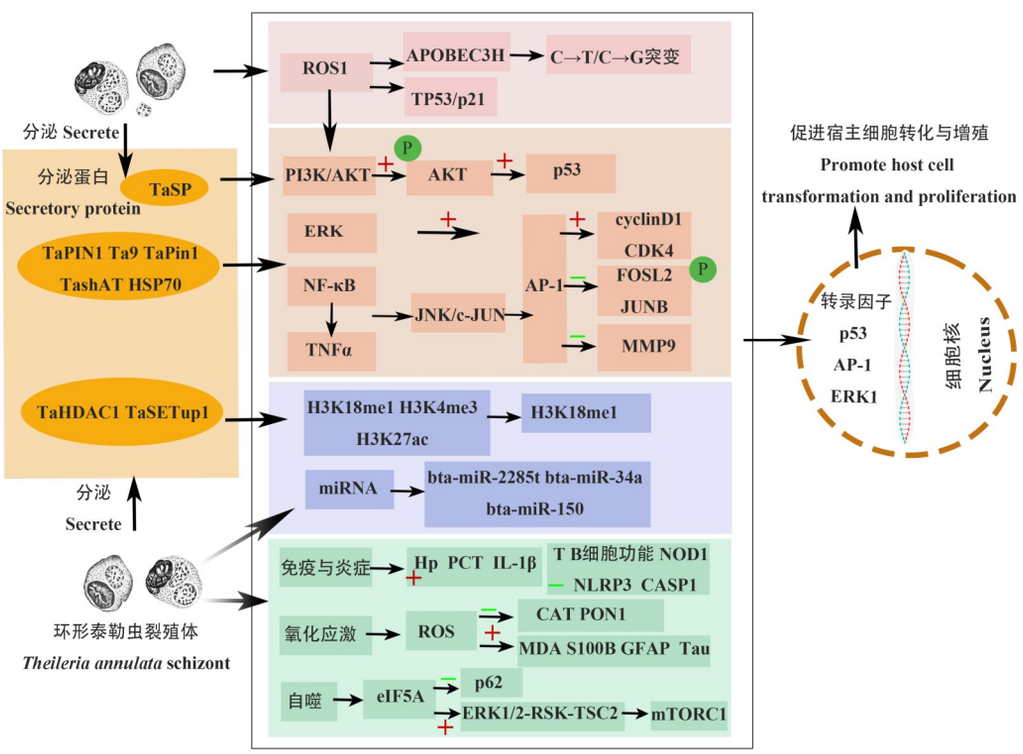
4.4　病理响应与其他三层面的关联

虫体激活NF-κB通路引发慢性炎症，同时激活宿主HPA轴抑制免疫细胞功能[25,51]。机体中NOD1、NLRP3等炎症小体功能失调，同时感染细胞异常高表达MHCII分子，造成T、B淋巴细胞双重免疫功能缺陷[53,55]。免疫紊乱导致胞内ROS蓄积、抗氧化酶活性降低，引起DNA与线粒体损伤，进而加重宿主基因组不稳定性，而HIF1α被激活后，又加剧炎症反应，形成炎症与氧化应激恶性循环[11,57-59]。为实现胞内寄生，虫体利用eIF5A及

ERK1/2-RSK-TSC2-mTORC1通路阻断自噬来实现逃逸[12,65]；而AMPK通路激活可逆转该过程。此外，炎症与氧化应激又进一步强化ERK、PI3K/AKT等通路的活性[26,37-38]，加速宿主细胞转化进程；而异常的信号通路还会重塑组蛋白修饰[8,42-43]、改变miRNA表达谱[45,47-49]，通过表观遗传调控将瞬时病理刺激转化为稳定的转化表型。

5 小结与展望

环形泰勒虫诱导宿主细胞转化并非单一信号通路激活的结果，而是对宿主细胞多维度网络的协同操控。虫体裂殖体通过分泌效应蛋白（如TaSP、TaPIN1、组蛋白修饰因子等），以基因组突变奠定细胞转化的遗传基础，调控宿主PI3K/AKT、NF-κB等信号通路、表观遗传修饰及miRNA网络；同时通过干扰免疫应答与炎症、诱导氧化应激及劫持自噬通路，激活AP-1、ERK1等关键转录因子，从而促进转化细胞增殖与存活（图1）。该过程由四大模块协同完成，基因组突变与信号通路正反馈，信号通路介导病理应答与表观重编程，表观遗传调控与病理应答又反向增强通路异常及基因组不稳定性，构成完整调控网络。



黑色箭头：直接关系；黑色渐变箭头：间接关系；红色（＋）：上调/增加，绿色（－）：下调/减少；橙黄色椭圆：环形泰勒虫分泌蛋白；粉色方块：基因不稳定；杏色方块：宿主通路转导；蓝色方块：表观遗传与转录后调控；绿色方块：宿主系统性病理响应；橙色圆形虚线：细胞核，p53/AP-1/ERK1/2启动转录，是转化与增殖的核心调控中心。

Black arrow: direct relationship; Black gradient arrow: indirect relationship; Red (＋): upregulation/increase; Green (－): downregulation/decrease; Orange-yellow ellipse: *Theileria annulata* secretory protein; Pink square: genomic instability; Apricot square: host pathway transduction; Blue square: epigenetic and post-transcriptional regulation; Green square: host systemic pathological response; Orange dashed circle: Nucleus, p53/AP-1/ERK1/2 initiate transcription, central hub for transformation and proliferation.

图1 环形泰勒虫介导宿主细胞转化的多维调控机制图

Fig. 1 Illustration of the multidimensional regulatory mechanisms mediated by *Theileria annulata*in host cell transformation

尽管宿主细胞内NF-κB、AP-1及PI3K/AKT等经典信号已被反复验证，但虫体效应蛋白靶标机制、亚细胞定位及宿主互作机制仍在探索阶段，且存在自噬、氧化应激与免疫调控的体内协同机制，以及表观修饰、基因突变与信号转导间的深层交叉，均缺乏确凿的体内实证数据。此外，Cyt b等靶点的耐药突变在全球范围内频发，多重耐药基因型的风险升高，进而增加了药物与疫苗研发的难度；

且靶向 TaPIN1 及 Ta9 等分泌蛋白，开发特异性小分子抑制剂与多表位疫苗，是突破当前化疗耐药瓶颈的关键。因此，在未来研究中，应建立体内外模型系统以阐明 ERK、NF-κB、PI3K/AKT 等通路间的交互作用及其在感染中的生物学意义，并填补效应蛋白机制与体内协同调控的研究空白；其次，着力于验证 TaPIN1、Ta9 等候选靶点的必需性，为后续设计多靶点联合干预策略，以克服单药耐药；同时，未来需积极利用空间转录组、单细胞测序与活细胞成像等前沿技术，在亚细胞分辨率下，实时解析效应蛋白的转运、定位及其与宿主的动态互作关系。

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