

· 综述 ·

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柚皮素对自身免疫性肝炎的防治作用及分子机制

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摘要: 自身免疫性肝炎(AIH)是一种由T淋巴细胞介导的慢性炎症性肝病,若未及时干预可进展为肝硬化甚至肝衰竭。天然黄酮类化合物柚皮素(NAR)具有重塑免疫稳态、靶向抑制炎症通路、抗氧化、调节肝细胞代谢与凋亡、改善线粒体功能及调节肠道菌群等多重机制,在AIH防治中展现出潜在价值。但柚皮素自身存在生物利用度低、肝靶向递送效率不足等问题,使其临床转化与应用受到制约。本文系统综述NAR防治AIH的作用机制,深入探讨其在AIH防治中可能涉及的信号通路,并分析当前其转化应用存在的挑战及未来的研究方向,以期为NAR在AIH防治领域的进一步研究和临床应用提供理论参考。

关键词: 柚皮素; 肝炎, 自身免疫性; 免疫调节; 信号转导

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Role of naringenin in the prevention and treatment of autoimmune hepatitis and its molecular mechanism

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Abstract: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease mediated by T lymphocytes, and it can progress to liver cirrhosis or even liver failure without timely intervention. As a natural flavonoid compound, naringenin (NAR) shows a potential value in the prevention and treatment of AIH through multiple mechanisms such as remodeling immune homeostasis, targeted inhibition of inflammatory pathways, antioxidation, regulating hepatocyte metabolism and apoptosis, improving mitochondrial function, and regulating intestinal flora. However, the clinical translation and application of NAR is limited by issues such as low bioavailability and insufficient efficiency of liver-targeted delivery. This article systematically reviews the mechanism of action of NAR in the prevention and treatment of AIH, explores the potential signaling pathways involved in this process, and analyzes existing challenges in its translation and application and future research directions, so as to provide a reference for further research on NAR and its application in the prevention and treatment of AIH.

Key words: Naringenin; Hepatitis, Autoimmune; Immunomodulation; Signal Transduction

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自身免疫性肝炎(autoimmune hepatitis, AIH)是一种以血清转氨酶升高、高 γ -球蛋白血症、循环自身抗体阳性及肝组织界面性肝炎为特征的慢性肝脏炎症性疾病,全球患病率为(5~20)/10万,女性发病率显著高于男性(比例约为3:1)^[1-2]。遗传易感性、环境触发与免疫调节失衡的交互作用是其核心发病机制^[3]。在确诊时,约33%的AIH患者已进展至肝硬化,糖皮质激素联合硫唑嘌呤的一线治疗方案虽可使超过80%的患者获得生化缓解,但长期用药易引发骨质疏松、股骨头坏死及继发感染等严重不良反应,且约20%患者存在治疗无应答或药物不耐受^[1-2]。

近年研究显示,源自中药的天然产物,因多靶点免疫调节活性与良好的安全性^[4],成为实现高效低毒治疗目标的理想候选药物。柚皮素(naringenin, NAR)是柑橘类水果和中草药中常见的黄酮类化合物,具有抗炎、抗氧化应激、抗纤维化及免疫调节等活性^[5]。其结构以C6-C3-C6为骨架,A、B两苯环通过含氧C三环连接。A环5、7位和B环4位的酚羟基是其发挥抗氧化等多种生物活性的关键^[6]。在肝脏疾病领域,NAR已被证明可通过调控核因子 κ B(nuclear factor- κ B, NF- κ B)炎症信号通路、抑制氧化应激与细胞凋亡等机制,显著改善酒精性肝损伤、非酒精性脂肪性肝病及药物性肝损伤等多种肝病^[7-9]。近期研究表明,NAR能显著抑制刀豆蛋白A(concanavalin A, ConA)诱导的AIH模型小鼠肝损伤,呈剂量依赖性下调肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6, TRAF6)/c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)通路,抑制肿瘤坏死因子 α (tumor necrosis factor α , TNF- α)、白细胞介素(interleukin, IL)-6等炎症因子释放,并减轻肝细胞凋亡,为NAR防治AIH提供了重要实验依据^[9]。

1 NAR防治AIH的作用机制

1.1 调节免疫细胞功能,恢复免疫稳态

1.1.1 抑制T淋巴细胞过度激活 AIH的核心发病机制源于对肝细胞抗原的免疫耐受缺陷,其特征为CD4⁺T细胞亚群失衡及调节性T细胞(regulatory T cell, Treg)功能受损,导致自身反应性T细胞异常活化。活化的辅助性T细胞(helper T cell, Th)1通过分泌干扰素 γ 激活巨噬细胞与细胞毒性T细胞,直接介导肝细胞损伤^[10]。网络药理学及分子动力学研究表明,NAR与T细胞介导的自身免疫疾病和AIH存在455个共同靶点,同时NAR可通过

调控NF- κ B、促分裂原活化的蛋白质激酶(mitogen-activated protein kinase, MAPK)等特定细胞信号通路减少Th1和Th17免疫反应,从而增强AIH中抗炎性Treg的活性^[11]。在ConA诱导的实验性AIH小鼠模型中,120 mg/kg高剂量NAR干预可使模型小鼠血清中IL-6和TNF- α 分别降低约40.3%和56.6%,并抑制肝组织NF- κ B的活化,使NF- κ B核转位减少,从而拮抗T淋巴细胞的过度激活^[9]。此外,对其他黄酮类化合物的分子机制研究可从侧面进一步揭示NAR防治AIH的潜在机制。例如,在AIH模型中,雷公藤红素通过阻断磷脂酰肌醇3-激酶/蛋白激酶B通路使促炎因子IL-1 β 、IL-6表达明显降低^[12],而其结构类似物槲皮素则可通过抑制巨噬细胞IL-1 β 分泌,减轻CD8⁺T细胞介导的肝细胞凋亡^[13]。因此,基于上述研究结论可以推断,NAR可通过阻断炎症信号通路,抑制自身反应性T细胞的活化与增殖,减少肝组织内效应T细胞浸润,从而缓解AIH的免疫性肝损伤。

1.1.2 调控Treg/Th17平衡 在AIH中,CD4⁺T细胞亚群内Treg与Th17的失衡是驱动肝脏炎症的核心机制。Treg以叉头框蛋白P3为特征性转录因子,通过分泌IL-10、转化生长因子 β (transforming growth factor- β , TGF- β)等抑制性细胞因子维持外周免疫耐受;而Th17依赖转录因子维甲酸相关孤儿受体 γ t的表达,产生促炎因子IL-17A,其异常活化可加剧组织损伤^[14]。AIH患者肝组织及外周血中普遍存在Treg数量减少及其免疫活性降低,如叉头框蛋白P3表达下调、IL-10和TGF- β 分泌能力下降以及对效应T细胞增殖抑制能力减弱,并伴随Th17比例升高的现象,这种失衡与血清转氨酶水平呈正相关,是构成持续性肝损伤的关键病理基础^[10]。NAR可通过靶向IL-6/信号转导与转录激活因子(signal transducer and activator of transcription, STAT)3信号通路双向调节免疫平衡。数据挖掘及网络药理学研究发现,STAT3磷酸化是NAR防治AIH的关键靶点^[15],在AIH、系统性红斑狼疮和实验性自身免疫性脑脊髓炎等自身免疫性疾病模型中,均证实NAR可通过拮抗IL-6/STAT3信号通路,抑制STAT3磷酸化及转录因子维甲酸相关孤儿核受体- γ t的表达,显著降低IL-17A、TNF- α 等促炎因子水平,同时促进抗炎因子IL-10分泌,进而减少Th17细胞生成,增强TGF- β /Smad通路活性,上调叉头框蛋白P3表达以促进Treg细胞扩增及功能,改善肝脏免疫微环境^[16-17]。然而,现有针对ConA或S100诱导的标准化AIH动物模型的直接体内实验数据仍显不足,有待在规范化体内模型中进一步补充和验证。

1.1.3 抑制巨噬细胞炎症极化 巨噬细胞作为固有免疫系统的核心组分,其表型可塑性受微环境信号动态调节,M1(经典活化)与M2(替代活化)极化代表连续谱系的两极,而非绝对二分状态^[18]。在AIH病理进程中,肝内巨噬细胞呈现动态极化失衡:早期M1表型通过Toll样受体(Toll-like receptor, TLR)/NF- κ B通路加剧肝细胞损伤;后期若向M2表型转换出现障碍,则可能导致AIH慢性化,因此巨噬细胞极化失衡也参与了AIH的发病过程^[19-20]。NAR通过多通路协同调控巨噬细胞极化,以重塑肝脏免疫微环境。研究证实,通过靶向调控TLR/TRIF-NF- κ B或mTOR信号通路调控巨噬细胞极化,可有效改善AIH炎症应答及肝再生过程^[20]。而NAR则可通过抑制ERK/JNK/p38 MAPK信号通路磷酸化及 κ B抑制蛋白 α (inhibitor of κ B, I κ B α)的降解,阻断NF- κ B核转位,同时通过调节lncRNA-mRNA轴减少氧化应激,显著降低TNF- α 和IL-6等促炎因子分泌^[21-22];并通过PI3K/AKT信号通路增强自噬流,进一步平衡极化表型,增强抗炎与组织修复功能^[23]。

1.2 抑制炎症信号通路,阻断炎症级联反应

1.2.1 抑制TRAF6/JNK通路 TRAF6作为一种E3泛素连接酶,可通过其RING结构域与二聚体E2酶Ubc13/Uev1A协同催化自身K63泛素化,激活TLR及IL-1受体信号传导^[24]。K63泛素化驱动TGF- β 活化激酶1的磷酸化,进而激活MKK4/7-JNK-p38MAPK级联反应及下游NF- κ B通路^[24-25]。JNK的持续活化促进c-Jun磷酸化及激活蛋白-1转录因子复合物形成,诱导TNF- α 、IL-6等促炎因子表达,在肝脏病理微环境中,JNK信号异常活化与炎症性肝损伤密切相关^[26];同时,TRAF6也介导TGF- β 非经典信号通路,通过TGF- β 活化激酶1依赖机制激活JNK/p38MAPK,参与肝纤维化重塑过程^[27]。因此,靶向TRAF6可调节肝脏免疫细胞与实质细胞的动态平衡。近年研究表明,NAR通过多靶点干预TRAF6信号网络,发挥AIH肝脏保护效应。在12 mg/kg ConA诱导的AIH小鼠模型中,NAR干预可通过抑制TRAF6的表达,从而抑制JNK的磷酸化,有效降低TNF- α 、IL-6等促炎因子水平,减轻ConA诱导的肝脏炎症损伤和肝细胞凋亡坏死^[9]。在肝实质细胞-肝巨噬细胞共培养模型中,使用20 μ mol/L的NAR处理24 h可使TRAF6蛋白表达量降低58%,同时促进抗炎因子IL-10的分泌^[22]。此外,NAR还可抑制TRAF6自身K63泛素化,可能通过阻断Ubc13/Uev1A二聚体与RING结构域结合,降低TGF- β 活化激酶1激酶活化效率^[28],为该通路作为治疗靶点提供了实验依据。

1.2.2 激活腺苷一磷酸活化的蛋白质激酶(adenosine monophosphate-activated protein kinase, AMPK)/核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)通路 氧化应激作为细胞内活性氧产生与清除失衡的病理状态,是肝脏炎症反应的核心驱动力,尤其在AIH中可引发脂质过氧化、蛋白质变性和细胞死亡,成为肝损伤的关键病理基础^[29]。AMPK/Nrf2信号轴作为调控肝脏氧化还原稳态的核心通路,通过AMPK介导的Nrf2磷酸化促进其核转位,激活抗氧化响应元件(antioxidant response element, ARE)介导的基因转录,维持内源性防御体系^[30]。研究证实,NAR通过多机制调节Nrf2通路以有效减轻肝损伤。在AIH模型和对乙酰氨基酚诱导的急性肝损伤模型中,NAR干预可显著促进Nrf2核转位,上调血红素加氧酶-1和醌氧化还原酶1的表达,从而抑制胱天蛋白酶3及Bcl-2相关X蛋白(Bcl-2 associated X protein, Bax)等凋亡蛋白的活性,降低血清转氨酶水平及肝组织丙二醛含量,同时提升谷胱甘肽(glutathione, GSH)水平和超氧化物歧化酶活性,发挥抗炎与抗氧化的协同作用,缓解氧化应激损伤^[9,30-31]。

1.2.3 调控NF- κ B通路 NF- κ B作为炎症调控的核心转录因子,静息时与I κ B结合滞留于细胞质;TNF- α 、脂多糖等外界刺激可激活I κ B激酶(I κ B kinase, IKK)复合体,触发I κ B磷酸化及泛素化降解,促使p65/p50二聚体转位入核,诱导TNF- α 、IL-6等促炎因子表达,驱动肝病炎症进展^[32]。在AIH等肝脏炎症性疾病中,NF- κ B信号异常活化与组织损伤显著相关,抑制该通路可减轻肝细胞炎症性浸润与纤维化^[33]。NAR主要通过靶向IKK-I κ B α 轴抑制该通路:其可与IKK- β 的腺苷三磷酸结合域直接相互作用,竞争性抑制IKK磷酸化活性^[34];实验证实,其可降低I κ B α 磷酸化水平,阻断p65核转位,并下调TNF- α 、IL-1 β 的基因转录,对ConA诱导的AIH具有良好的治疗效果^[11,35]。新近研究发现,NAR可通过抑制环鸟苷酸-腺苷酸合酶/干扰素基因刺激因子通路,交叉调控NF- κ B活性,减轻AIH及肝纤维化中IL-6、TNF- α 的过度分泌,同时增强抗氧化酶活性,进而综合改善AIH炎症微环境^[11,36]。这种多靶点作用为NAR防治AIH提供了分子基础。

1.3 调节肝细胞代谢与凋亡,防止肝纤维化 肝细胞损伤是AIH进展的核心环节,其诱发的细胞凋亡与坏死通过损伤相关分子模式释放及肝星状细胞活化,驱动炎症与纤维化级联反应^[37]。NAR通过多靶点机制协同调控细胞死亡与纤维化进程:在抗凋亡方面,其通过上调Bcl-2/Bax比值稳定线粒体膜电位,抑制细胞色素c释放,使胱天蛋

白酶3活性下降约40%^[38-39];同时,通过抑制内质网应激关键因子C/EBP同源蛋白的表达,使TUNEL阳性凋亡细胞减少63.4%^[8,40]。在抗纤维化方面,NAR不仅通过降低TGF- β 1 mRNA表达和Smad2/3蛋白磷酸化水平以抑制经典TGF- β /Smad通路,同时可激活自噬依赖性铁死亡机制,经微管相关蛋白轻链3-II/Beclin-1通路诱导活化的肝星状细胞死亡,使平滑肌肌动蛋白 α 阳性细胞减少64.8%^[41-42]。这种“抗凋亡-抗纤维化”的双重作用为AIH提供了多靶点干预策略。

1.4 抗氧化应激与线粒体保护 线粒体作为细胞能量中枢,其功能障碍在AIH等相关肝损伤中可引发活性氧过量累积,诱导线粒体膜通透性转换孔开放及胱天蛋白酶依赖性凋亡,加剧肝细胞死亡^[43]。因此,靶向线粒体抗氧化防御系统是发挥AIH肝保护作用的核心策略。NAR通过酚羟基直接清除羟自由基 $\cdot\text{OH}$ 与超氧阴离子自由基 $\text{O}_2^{\cdot-}$,显著降低脂质过氧化物水平^[39]。其核心机制在于激活Kelch样ECH关联蛋白1(Kelch-like ECH-associated protein 1,Keap1)/Nrf2/ARE通路:通过变构调节Keap1的Kelch结构域促进Nrf2核转位,上调血红素加氧酶-1、醌氧化还原酶1等抗氧化酶表达^[44],并增强线粒体超氧化物歧化酶2和GSH过氧化物酶活性^[45]。最新研究表明,NAR可通过Nrf2/GSH轴增强线粒体GSH还原酶活性,减少活性氧积累^[30]。在能量代谢调控方面,NAR可激活AMPK/SIRT1/过氧化物酶体增殖物激活受体 γ 辅激活因子1 α (peroxisome proliferator-activated receptor coactivator 1 α , PGC-1 α)通路:通过去乙酰化增强PGC-1 α 的转录活性,上调核呼吸因子1和线粒体转录因子A表达,促进腺苷三磷酸的生成^[46]。2023年的一项研究进一步揭示,该通路可协调线粒体生物合成与自噬循环,通过清除损伤线粒体以维持稳态^[47]。动物实验证实,50 mg $\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ 的NAR干预可使AIH模型Bcl-2/Bax比值升高2.4倍,显著抑制细胞色素c释放及凋亡级联,并使血清丙氨酸氨基转移酶/天冬氨酸氨基转移酶水平降低52%~58%^[9,39]。上述多靶点机制为NAR防治AIH肝损伤提供了新的分子依据。

1.5 调节肠道屏障功能及脂质代谢 基于肠-肝轴理论的最新研究,肠道屏障功能障碍与菌群失调已被证实是AIH发病的促进因素^[48]。肠道通透性增加导致脂多糖等微生物产物经门静脉入肝,通过激活肝巨噬细胞和肝星状细胞的TLR4信号通路,触发持续性肝脏炎症反应,构成AIH自身免疫应答的重要机制^[49]。同时,AIH常与脂质代谢紊乱交织,肝脏脂质过载通过增强氧化应激和内质网应激,加剧免疫介导的肝损伤,其中约40%的AIH患者并发非酒精性脂肪性肝病,凸显了两者在病理上的重叠特

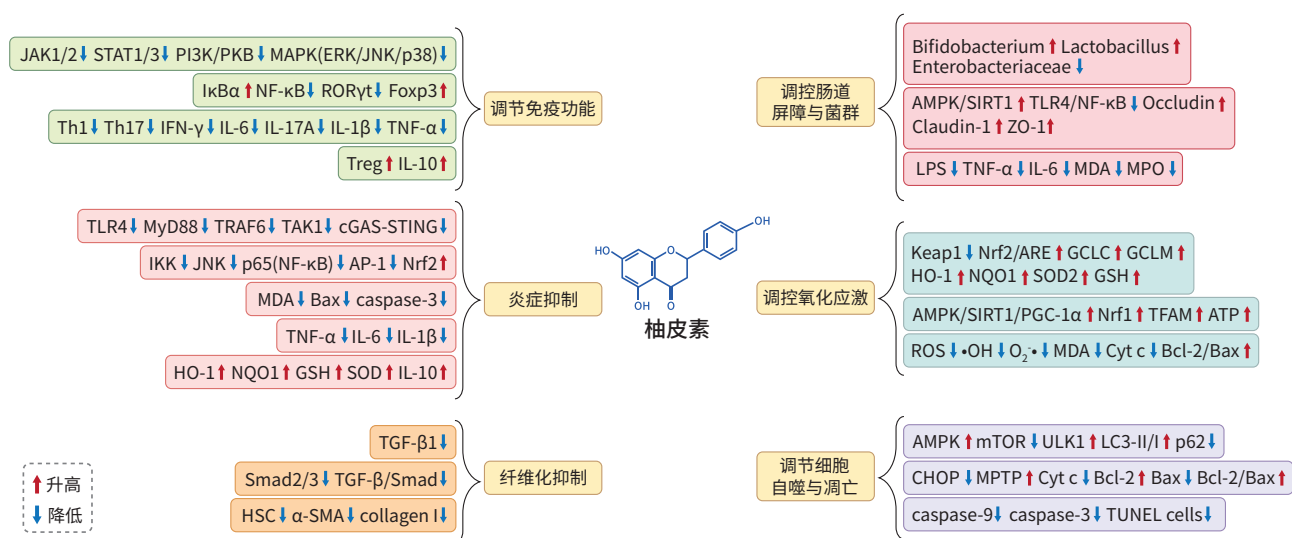
征^[50]。NAR通过多重分子通路协同调控肠-肝轴。实验证实,NAR能增加双歧杆菌等有益菌属的丰度,优化肠道微生态^[51];通过抑制NF- κ B通路及减轻氧化应激,上调紧密连接蛋白(闭合蛋白、紧密连接蛋白-1、闭合小环蛋白1)的表达,从而增强肠道屏障功能^[52-53]。在醋酸诱导的结肠炎模型中,NAR可显著降低丙二醛、髓过氧化物酶及TNF- α 、IL-6等促炎因子的水平,缓解肝脏持续性炎症刺激,发挥其肠道屏障修复作用^[54]。另一方面,分子对接及点突变实验证实,NAR可通过增加能量消耗,直接结合AMPK γ 1亚基,激活AMPK/SIRT1信号轴并调节自噬,显著改善脂肪肝变性评分,降低血清总胆固醇及低密度脂蛋白水平,从而发挥改善非酒精性脂肪性肝病的作用^[55]。尽管针对AIH的直接研究仍需深化,但基于其在肠道屏障修复、菌群调控及脂质-炎症通路干预的多效性,NAR有望通过“上游”阻断肠源性炎症触发,为AIH提供系统性治疗策略。

2 NAR防治AIH面临的挑战

尽管NAR在AIH防治中展现出良好潜力,但其临床转化仍面临多重挑战。首要限制是其药代动力学缺陷:口服绝对生物利用度仅为5.8%~15%,主要归因于其水溶性低和显著的首过代谢效应^[56]。目前,新型递送策略和共晶技术虽可显著提升生物利用度^[57-58],但其长期安全性仍需通过优良实验室规范的毒理学研究和Ⅲ期临床试验验证,规模化生产工艺仍待优化。其次,现有证据主要基于化学药物诱导的肝损伤模型,缺乏对AIH核心病理特征——自身反应性T细胞介导的肝细胞攻击的直接模拟。尽管体外研究已证实NAR可抑制NF- κ B通路并降低TNF- α 水平^[9],提示其可通过激活AMPK依赖的自噬通路等机制调控免疫反应^[47],但其在AIH特异性免疫微环境中的调节效能尚未明确,仍需AIH模型进一步验证。

3 小结与展望

AIH是一种慢性、进行性的自身免疫性疾病,其治疗目标聚焦于控制炎症与预防疾病进展。NAR作为一种天然活性成分,凭借其多靶点药理活性,在AIH新疗法中展现出巨大潜力。本文系统综述了NAR通过调控免疫稳态、炎症通路、氧化应激及肝细胞代谢与凋亡等多途径机制防治AIH(图1),但其临床转化仍面临生物利用度低、机制尚不明确及循证证据缺失等挑战。因此,未来研究需构建精准AIH模型、优化给药方案,并基于随机对照试验和欧洲肝病学会复合终点评价疗效,以期AIH药物治疗提供确切的科学依据。



注: JAK1/JAK2, Janus 激酶 1/2; STAT1/STAT3, 信号转导与转录激活因子 1 和 3; PI3K/PKB, 磷脂酰肌醇-3-激酶-蛋白激酶 B; MAPK, 促分裂原活化的蛋白激酶; ERK, 胞外信号调节激酶; JNK, c-Jun 氨基末端激酶; IkB α , κ B 抑制蛋白 α ; NF- κ B, 核因子- κ B; ROR γ t, ROR γ t 转录因子; Foxp3, 叉头框蛋白 P3; Th, 辅助性 T 细胞; IFN- γ , 干扰素 γ ; IL, 白细胞介素; TNF- α , 肿瘤坏死因子 α ; Treg, 调节性 T 细胞; TLR4, Toll 样受体 4; MyD88, 髓系分化初级反应蛋白 88; TRAF6, 肿瘤坏死因子受体相关因子 6; TAK1, 转化生长因子 β 活化激酶 1; cGAS-STING, 环鸟苷酸-腺苷酸酶/干扰素基因刺激因子通路; IKK, IkB 激酶; AP-1, 激活蛋白-1; Nrf2, 核转录因子红系 2 相关因子 2; MDA, 丙二醛; Bax, Bcl-2 相关 X 蛋白; caspase, 胱天蛋白酶; HO-1, 血红素加氧酶-1; NQO1, 醌氧化还原酶 1; GSH, 谷胱甘肽; SOD, 超氧化物歧化酶; TGF- β , 转化生长因子 β ; HSC, 肝星状细胞; α -SMA, 平滑肌肌动蛋白 α ; collagen I, I 型胶原; Bifidobacterium, 双歧杆菌; Lactobacillus, 乳杆菌; Enterobacteriaceae, 肠杆菌; AMPK, 腺苷一磷酸活化的蛋白质激酶; SIRT1, 沉默信息调节因子 1; Occludin, Claudin-1, ZO-1, 均为紧密连接蛋白; LPS, 脂多糖; MPO, 髓过氧化物酶; Keap1, Kelch 样 ECH 关联蛋白 1; ARE, 抗氧化响应元件; GCLC, 谷氨酸-半胱氨酸连接酶催化亚基; GCLM, 谷氨酸-半胱氨酸连接酶调节亚基; PGC-1 α , 过氧化物酶体增殖物激活受体 γ 共激活因子 1 α ; TFAM, 线粒体转录因子 A; ATP, 三磷酸腺苷; ROS, 活性氧; •OH, 羟自由基; O $_2$ •-, 超氧阴离子自由基; Cyt c, 细胞色素 c; ULK1, UNC-51 样激酶 1; LC3-II, 微管相关蛋白 1 轻链 3-II; CHOP, C/EBP 同源蛋白; MPTP, 线粒体膜通透性转换孔。

图 1 柚皮素防治 AIH 的作用机制

Figure 1 Mechanism of Naringenin in preventing and treating AIH

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