

氧化应激在猪肠道冠状病毒感染中的作用及相关治疗的研究进展

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摘要: 猪肠道冠状病毒(porcine enteric coronaviruses, PECs)包括猪流行性腹泻病毒(porcine epidemic diarrhea virus, PEDV)、传染性胃肠炎病毒(transmissible gastroenteritis virus, TGEV)和猪 δ 冠状病毒(porcine deltacoronavirus, PDCoV)。PECs感染会导致猪(尤其是新生仔猪)出现严重腹泻,具有高致死率,给全球养猪业带来重大威胁并造成经济损失。PECs感染会引发氧化应激,进而激活多种转录因子,改变其转录途径,影响细胞代谢和病毒的生命周期,最终导致细胞功能障碍,并进一步促进病毒增殖,形成恶性循环。PECs感染增加的氧化应激被视为潜在的共同病因之一。本文综述了PECs感染引起的相关氧化应激信息,并强调抗氧化是应对PECs感染的有效策略之一。

关键词: 猪肠道冠状病毒(PECs); 猪流行性腹泻病毒(PEDV); 传染性胃肠炎病毒(TGEV); 猪 δ 冠状病毒(PDCoV); 氧化应激; 抗氧化策略

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Research progress in the role of oxidative stress in porcine enteric coronavirus infection and related therapies

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Abstract: Porcine enteric coronaviruses (PECs) include porcine epidemic diarrhea virus (PEDV), transmissible gastroenteritis virus (TGEV), and porcine deltacoronavirus (PDCoV). Infections with PECs can cause severe diarrhea in pigs, particularly newborn piglets, resulting in high mortality rates and posing a serious threat and economic loss to the global swine industry. Such infections induce oxidative stress to activate various transcription factors and alter their transcriptional pathways, thereby affecting cellular metabolism and the viral life cycle. This leads to cellular dysfunction and further promotes viral replication, forming a vicious cycle. The oxidative stress associated with PECs is considered one of the potential common pathogenic mechanisms. This review summarizes the information about the oxidative stress induced by infections with PECs and emphasizes that antioxidant strategies represent one of the effective approaches to counteract such infections.

Keywords: PECs; PEDV; TGEV; PDCoV; oxidative stress; antioxidant strategy

冠状病毒(coronaviruses, CoVs)是最大的单股正链 RNA 病毒, 包含 α 冠状病毒(α -CoV)、 β 冠状病毒(β -CoV)、 γ 冠状病毒(γ -CoV)和 δ 冠状病毒(δ -CoV) 4 个冠状病毒属^[1]。该类病毒主要损害动物和人类的消化、呼吸、内分泌及中枢神经系统, 已被视为重大公共卫生问题^[2-4]。从 2003 年暴发的严重急性呼吸综合征冠状病毒(severe acute respiratory syndrome coronavirus, SARS-CoV)、2012 年发现的中东呼吸综合征冠状病毒(Middle East respiratory syndrome-CoV, MERS-CoV), 再到大规模流行严重急性呼吸综合征冠状病毒 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), 进一步凸显了冠状病毒的威胁^[5-6]。在动物中由冠状病毒引发的急性肠道传染病导致严重的经济损失, 已成为全球养猪业中最为棘手的问题之一。目前, 传染性胃肠炎病毒(transmissible gastroenteritis virus, TGEV)、猪 δ 冠状病毒

(porcine deltacoronavirus, PDCoV)和猪流行性腹泻病毒(porcine epidemic diarrhea virus, PEDV)均属于猪肠道冠状病毒(porcine enteric coronavirus, PECs)。这 3 种猪肠道冠状病毒中 PEDV 和 TGEV 属于 α 冠状病毒属, PDCoV 属于 δ 冠状病毒属。3 种病毒感染仔猪的临床症状和发病机制极为相似, 表现为肠道绒毛萎缩、肠道细胞坏死、脱落, 导致仔猪肠道吸收不良, 引发仔猪呕吐和急性水样腹泻, 甚至死亡^[7-9]。此外, 近几年出现的 PDCoV 跨越物种传播^[10-16]、TGEV 的重组^[17-20]及 PEDV 的不断变异^[21-26]事件, 表明在预防 PECs 感染方面将面临不可预测的情况。目前, 针对 PECs 感染的有效治疗手段仍然不足, 因此迫切需要开发新的抗病毒策略。

氧化应激是由自由基和活性氧(reactive O₂ species, ROS)的生成与机体抗氧化防御之间的不平衡所引起的。在正常的细胞代谢过程中以 ROS 形式产生的分子氧是有氧代谢的自然组成

部分, 在多种生理过程中充当细胞内信号通路的重要调节因子, 例如参与细胞发育、分化和存活等过程^[27-28]。同时, 细胞内特定的抗氧化系统维持着细胞的氧化还原平衡, 以防止 ROS 过度积累^[29-30]。然而, 当细胞暴露在不利和应激条件下时这种氧化还原平衡被打破, 导致生物大分子(蛋白质、DNA 和脂质)受损, 最终引发组织炎症反应、细胞凋亡和/或潜在的疾病发展^[31-35]。众所周知, 病毒是寄生于活细胞内的微生物, 通常通过受体介导的胞吞作用进入细胞, 并在细胞质中完成复制和增殖^[36]。研究证明, PEDV、TGEV 和 PDCoV 的感染至少部分地与过量产生 ROS 有关, 会导致细胞损伤, 触发氧化应激, 从而影响病毒的复制周期^[37-40]。

因此, 建立宿主的特殊环境以抵抗病毒感染非常重要。本文重点讨论 PECs 感染引起的相关氧化应激信息, 并强调抗氧化剂是预防和治疗 PECs 感染的有效策略之一。

1 PECs 概述

1.1 PECs 的基因组与结构

PECs 的基因组为线性非节段正链 RNA, 全长 25–29 kb, 具有 5'帽子和 3'多聚腺苷酸尾巴结构。基因组的 5'端 2/3 区域由 2 个大型开放阅读框(open reading frame, ORF) ORF1a 和 ORF1b 组成, ORF1a 的末端与 ORF1b 的起始端重叠, 这 2 个开放阅读框编码多达 16 种非结构蛋白质(non-structural protein, nsp1–16)以及 4 种结构蛋白: 刺突(spike, S)蛋白、包膜(envelope, E)蛋白、膜(membrane, M)蛋白和核衣壳(nucleocapsid, N)蛋白^[41-44]。本文主要以 PEDV、TGEV 和 PDCoV 作为 PECs 的代表, 总结氧化应激在 PECs 感染相关致病性中的作用。

1.2 PECs 的生物学特性

早在 1946 年, 美国首次报道发现 TGEV^[45]。TGEV 可引起具有高度传染性的猪传染性胃炎, 该病毒可在肠道和呼吸道中复制^[46-47]。

TGEV 感染仔猪可出现呕吐、腹泻和脱水症状, 且以出生 2 周龄以内仔猪死亡率高为特点^[48]。PEDV 于 1971 年在英国首次被发现, 随后于 1978 年在比利时被分离出来^[49]。2010 年左右, 一种具有 100% 死亡率的高度致病性突变株(GII 型)在中国暴发, 导致当年中国养猪业遭受毁灭性打击^[50]。PEDV 可感染所有年龄段的猪, 仔猪是受影响的主要群体, 其临床症状和病理变化与 TGEV 非常相似^[7]。PEDV 主要感染仔猪的空肠和回肠细胞, 引起肠绒毛萎缩, 导致仔猪腹泻或呕吐^[51]。与 TGEV 和 PEDV 的发现时间相比, PDCoV 发现较晚, 于 2012 年在中国香港被发现^[52]。在中国, PDCoV 于 2015 年首次被报道, 并迅速蔓延至全国^[44,53-55]。PDCoV 也可感染不同年龄段的猪, 其感染程度与仔猪日龄呈负相关^[56-58]。然而, 其疾病严重程度低于 TGEV 和 PEDV^[59-60], 感染后哺乳仔猪的死亡率高达 30%–40%^[61]。与 TGEV 和 PEDV 类似, PDCoV 主要在小肠中广泛复制。此外, PDCoV 还可引起胃腺窝上皮病变和轻度间质性肺炎, 在血液、肺脏、肝脏等组织中也可检测到 PDCoV RNA, 表明 PDCoV 具有多系统感染的可能性^[62]。此外, 该病毒还可感染雏鸡^[10,63]、火鸡^[11]、小鼠^[12,64-65]、牛^[13], 人类细胞也可被 PDCoV 感染^[14]。最近的研究表明, 雪貂和水禽(鸭、鹅)对 PDCoV 也具有易感性^[15-16], 说明 PDCoV 具有强大的跨物种感染能力。

从流行病学的角度来看, PECs 在全球猪群中的分布及在不同物种间的传播倾向非常令人担忧。猪是第二大家畜物种^[66], 并且是人畜共患病毒的中间宿主^[67-68], 这凸显了预防或治疗 PECs 感染的重要性。

2 氧化应激概述

氧化应激的概念自 1985 年被引入氧化还原生物学和医学研究领域后迅速发展成为细胞生理学的一个研究分支^[69-70]。氧化应激涉及源自氧和氮的活性物质的化学反应。ROS 是氧化应

激中涉及的主要成分, 其定义为含有氧的活性化学物质, 包括超氧离子(superoxide ion, O_2^-)、过氧化氢(hydrogen peroxide, H_2O_2)、羟基自由基(hydroxyl radical, $^{\cdot}OH$)和单线态氧^[71]。通常, ROS 在细胞代谢中通过线粒体、内质网(endoplasmic reticulum, ER)和过氧化物酶体(peroxisomes)隔室中的各种酶产生^[29-30]。ROS 在细胞生物学中具有双重作用, 既是细胞生理代谢的有害产物, 又是细胞生长和发育的重要调节剂, 这取决于 ROS 的来源以及细胞的反应^[72]。 $^{\cdot}OH$ 具有高度的反应活性, 半衰期短, 它们可以与 DNA 分子反应形成加合物, 从而改变转录过程, 并进而导致蛋白质功能的变化^[73]。细胞在受到生理刺激时产生的 H_2O_2 可以充当第二信使^[74]。在氧化应激状态下, 非生理条件下的 H_2O_2 生成可能会导致氧化还原信号转导出现错误^[75]。因此, 氧化应激可被定义为“信号传导和氧化控制失调”^[76]。氧化应激能够通过蛋白质修饰、炎症、细胞凋亡、自噬失调、线粒体功能障碍等多种机制影响细胞生物过程^[73]。这些后果通常会加重疾病症状及病理进程。

2.1 线粒体与活性氧

在大多数真核细胞中, 线粒体是活性氧生成的主要场所。在有氧呼吸过程中, 电子传递链通过 O_2 的单电子还原生成具有高度氧化性的 O_2^- ^[77], 其中大约 80% 的 O_2^- 被释放到线粒体膜间隙中, 20% 左右被释放到线粒体基质中^[78-79]。 O_2^- 清除是通过超氧化物歧化酶(superoxide dismutase, SOD)利用 Mn (线粒体基质中的 SOD2)或 Zn/Cu (线粒体膜间隙和细胞质中的 SOD1)中心催化下迅速转化为 H_2O_2 来实现^[77]。在人体中, 已经鉴定出 40 多种生成 O_2^-/H_2O_2 的酶^[31]。 H_2O_2 是一种高度可扩散的第二信使, 可以通过水通道蛋白(aquaporins, AQP)家族的特定成员穿过线粒体膜^[80]。因此, 细胞膜上 H_2O_2 转移速率的模式有助于建立稳定的浓度梯度。线粒体基质中的 H_2O_2 相对稳定, 但在亚铁离子(Fe^{2+})存在的作用下, H_2O_2 生成 $^{\cdot}OH$ ^[81]。 $^{\cdot}OH$ 作

为活性最强的 ROS, 极易氧化生物大分子(DNA、蛋白质和脂质), 导致细胞损伤^[81]。另一方面, 为防止 H_2O_2 积累引发的氧化损伤, 谷胱甘肽过氧化物酶(Glutathione peroxidase, GPx)利用原型谷胱甘肽(glutathione, GSH)将其还原为 H_2O ^[82]。

2.2 内质网与活性氧

除了线粒体之外, 内质网应激(endoplasmic reticulum stress, ERS)也是 ROS 的主要来源之一。内质网是负责蛋白质折叠、生物合成、运输和翻译后修饰的主要细胞器。在蛋白质代谢过程中, 对于进入分泌途径的蛋白质而言, 一个主要环节是形成二硫键, 这一过程会在内质网中通过氧化蛋白质折叠的方式进行。内质网氧化还原酶 1 (endoplasmic reticulum oxidoreductin 1, ERO1)与蛋白质二硫键异构酶(protein disulfide isomerases, PDI)家族蛋白合作, 通过形成二硫键进行氧化折叠^[83]。ERO1 接受 PDI 的电子后, 将电子传递给原子氧而产生 H_2O_2 ^[83]。产生的 H_2O_2 随后可被 GPx 还原为 H_2O ^[82], 进一步促进氧化折叠, 同时减轻内质网的氧化负担。氧化还原平衡通过氧化型 GSH-还原型 GSH 循环和 PDI 反应 2 种系统共同作用, 确保细胞在应对氧化应激时保持稳态^[84]。

内质网氧化还原平衡的失衡也与未折叠蛋白反应(unfolded protein response, UPR)的激活有关, 该反应通常旨在通过应对内质网应激来恢复内质网的稳态。在 UPR 信号通路中, 通过 3 种主要的信号转导机制: 肌醇酶 1 α (inositol requiring enzyme 1 α , IRE1 α)、蛋白激酶 R 样内质网[protein kinase R (PKR)-like ER kinase, PERK]和激活转录因子 6 (the activating transcription factor 6, ATF6)检测内质网腔中的异常情况, 并将信号传递到细胞质, 然后通过转录因子将信号引导至细胞核诱导下游反应^[85]。此外, 内质网应激会通过线粒体相关内质网膜(mitochondria-associated endoplasmic reticulum membranes, MAMs)促使内质网中的钙离子释放到线粒体中, 线粒体负载过量的钙离子, 从而

产生 ROS^[86]。相反, 线粒体产生的 ROS 会作用于内质网, 加剧内质网应激, 并促进更多的钙离子释放, 这进一步导致线粒体功能障碍、细胞凋亡或坏死^[87]。

3 氧化应激与病毒感染

病毒感染会引发氧化应激反应, 这一现象最早于 1979 年在对仙台病毒的研究中被描述^[88]。此后, 很多病毒都被证实会通过产生 ROS 和改变氧化还原平衡的方式导致细胞损伤^[89-91]。ROS 主要由吞噬细胞和中性粒细胞通过呼吸爆发机制, 在细胞膜受到刺激时产生。病毒入侵细胞后会利用宿主细胞机制进行病毒基因组复制、转录和病毒粒子组装, 在这个过程中病毒会增加细胞的炎症反应, 导致 T 细胞的线粒体和内质网的氧化应激增强^[92]。线粒体和内质网功能障碍会导致 ROS 物质过度生成。氧化应激还可能激活抗病毒炎症信号通路^[92-95]、内在线粒体通路、外在死亡受体通路和 ER 的应激通路, 最终触发细胞凋亡^[96], 从而促进病毒的致病过程。以上发现表明, 氧化应激在病毒感染中既是病毒复制导致细胞损伤的后果, 也是促进病毒病理进展的关键驱动因素。

3.1 氧化应激与冠状病毒感染

21 世纪以来, 3 种 β 型冠状病毒(SARS-CoV、MERS-CoV 和 SARS-CoV-2)先后引发人类严重肺炎暴发, 在全球范围内造成巨大经济负担, 严重威胁人类健康。与其他许多病毒类似, 氧化应激在冠状病毒感染过程中扮演着关键角色^[97-98]。SARS-CoV-2 是最新引发肺炎大流行的冠状病毒, 目前大部分实验数据都将 ROS 和活性氮(reactive nitrogen species, RNS)列为该病毒引发肺损伤的主要介质之一^[99]。当该病毒的刺突蛋白与其膜受体血管紧张素转换酶 2(angiotensin converting enzyme 2, ACE2)结合后, 会激活 NADPH 氧化酶 2 型(NOX2)依赖性 ROS

的产生, 导致血管炎症反应。炎症因子白细胞介素(interleukin, IL)-6 还会以依赖 NOX2 的方式诱导 ROS 生成, 加剧内皮氧化应激, 进而持续引发内皮功能障碍和血管炎症^[100]。慢性炎症会进一步导致细胞内皮损伤, 破坏血小板线粒体动力学及其功能, 从而增加 COVID-19 患者出现高凝状态和血栓形成的风险^[101]。研究表明, SARS-CoV-2 还可通过破坏线粒体 DNA (mitochondrial DNA, mtDNA)、改变线粒体膜电位和钙稳态来损害线粒体动态功能, 引起 ROS 生成增加, 导致氧化应激反应, 造成肺组织损伤^[102-104]。此外, 在 SARS-CoV-2 感染过程中, 细胞内的核因子 E2 相关因子 2 (nuclear factor erythroid-2 related factor 2, Nrf2)水平在氧化应激过程中起着核心作用^[105]。

在冠状病毒感染引起犊牛腹泻的病例中, 通过血清生化指标研究发现, 炎症因子和氧化应激相关指标存在很强的相关性, 表明病毒感染过程中存在剧烈的氧化应激反应^[106]。另有大量证据表明, 猪肠道冠状病毒(PEDV、TGEV 和 PDCoV)在感染宿主细胞时能够巧妙地劫持或干扰宿主的正常细胞机制以获取优势, 其中也包括调控宿主细胞内的氧化还原状态^[37-40]。

3.2 TGEV 与氧化应激

众所周知, TGEV 能够诱导肠上皮细胞发生凋亡, 从而有利于自身从感染的细胞中释放和传播。氧化应激是启动细胞内凋亡途径的刺激因素之一^[107-108], 这表明氧化应激可能是 TGEV 导致肠上皮凋亡的原因。如图 1 所示, TGEV 感染引发的 ROS 可通过凋亡诱导因子(apoptosis inducing factor, AIF)途径在 PK-15 细胞中诱导细胞凋亡^[109]。TGEV 还可利用产生的 ROS 诱导潘氏细胞凋亡, 潘氏细胞的缺失驱动肠道 Lgr5+干细胞异常分化为杯状细胞, 导致黏液分泌增加, 从而促进 TGEV 感染^[110]。此外, TGEV 还可通过激活 p53 和 p38 丝裂原活化蛋白激酶(mitogen-

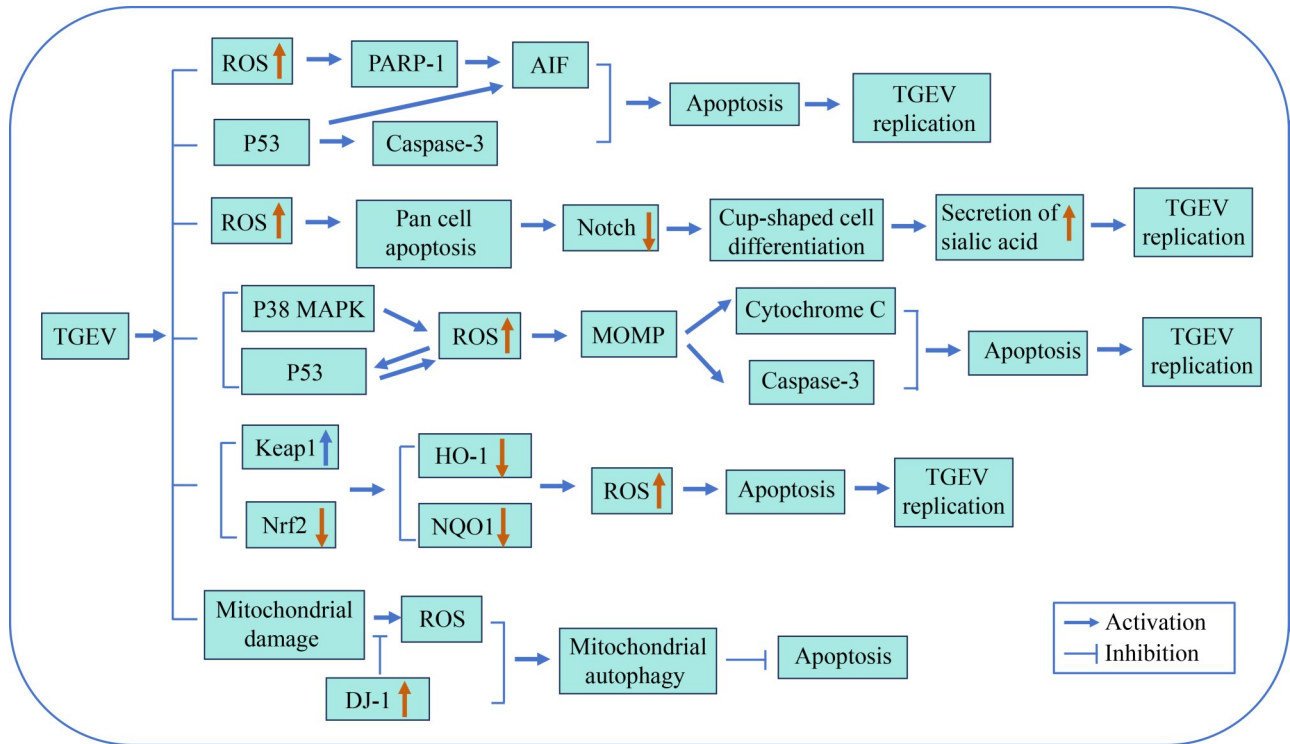


图1 TGEV感染与氧化应激的关系

Figure 1 The relationship between TGEV infection and oxidative stress. During the infection process of TGEV, the p53 and ROS-mediated AIF pathway and caspase-dependent pathway jointly participate in the apoptosis process induced by TGEV; TGEV activates the production of ROS, induces apoptosis of Paneth cells and loss of Notch factors, affecting the normal self-renewal and differentiation of Lgr5⁺ stem cells; Abnormal differentiation of Lgr5⁺ stem cells into goblet cells results in the secretion of sialylated mucus, which provides favorable conditions for TGEV infection and exacerbates intestinal damage and viral replication; The ROS generation induced by TGEV may activate p38 MAPK and phosphorylation of p53, and p53 may partially regulate the generation of ROS; The accumulation of ROS leads to changes in mitochondrial outer membrane permeability (MOMP), release of cytochrome c, and subsequently activates Caspase-3, initiating the intrinsic apoptotic pathway; TGEV infection may upregulate Keap1 expression, inhibit Nrf2 and its downstream antioxidant genes (Ho-1, NQO1), resulting in accumulation of oxidative stress and induction of apoptosis; TGEV also inhibits oxidative stress induced by mitochondrial damage through upregulation of DJ-1 protein. This process can inhibit apoptosis, promote selective autophagy degradation of damaged mitochondria, and enhance viral infection.

activated protein kinase, MAPK)通路来诱导氧化应激, 进而导致细胞凋亡^[108]。Nrf2 是一种关键的转录因子, 它通过诱导和调节多种抗氧化蛋白的表达来激活氧化应激防御系统以保护细胞免受各种氧化损伤^[111]。最近的一项研究报道称, TGEV 感染诱导的氧化应激与破坏 Keap1-Nrf2-

ARE 抗氧化防御系统有关^[40]。

此外, TGEV 为了能够持续感染, 诱发的氧化应激会诱导细胞自噬(pexophagy)^[112-113]。DJ-1 是一种多功能蛋白, 在细胞氧化应激反应、线粒体功能调节及神经保护中起关键作用。研究揭示, 在 TGEV 感染过程中通过上调 DJ-1 蛋白

及部分抗氧化基因表达可抑制病毒感染诱导的氧化应激, 促进受损线粒体的选择性自噬降解, 减少细胞凋亡, 从而有利于病毒感染和持续存在^[114]。

3.3 PEDV 与氧化应激

小肠上皮细胞是 PEDV 感染的主要靶细胞, 该病毒感染可引起线粒体结构异常, 包括线粒体形态变化、线粒体膜电位降低以及 ROS 积累, 从而损害正常细胞功能^[115]。如图 2 所示, 这种机制可能是由于 PEDV 通过转录因子 CREB3L1 激活 miR-34c/COX1 轴, 从而导致肠上皮细胞中的线粒体损伤^[115]。ROS 生成量增加已被广泛认为是胃肠道黏膜疾病发病过程中的一个重要因

素^[116-117]。另有报道, PEDV 可以在断奶仔猪的肠上皮细胞^[118]以及 Vero E6 细胞^[119-120]中诱导 ER 应激和 UPR。UPR 的 3 个分支(即 PERK、IRE1 和 ATF6)的激活可调节丝裂原活化蛋白激酶激活、自噬和凋亡等多种信号通路。PERK 在细胞的氧化应激反应中起上游调节作用, 在 PEDV 感染过程中通过 PERK-CHOP-ERO1 α -ROS 轴操纵内质网以扰乱其氧化还原稳态^[120]。肝脏中的脂质过氧化物是细胞增殖和死亡的关键介质, PEDV 可以通过抑制 ROR γ /Nrf2 介导的转录来诱导肝脏中抗氧化酶活性和基因表达的异常调节, 从而导致感染 PEDV 仔猪体内 ROS 产生增加, 导致脂质过氧化^[121]。PEDV 引起的 ROS 生

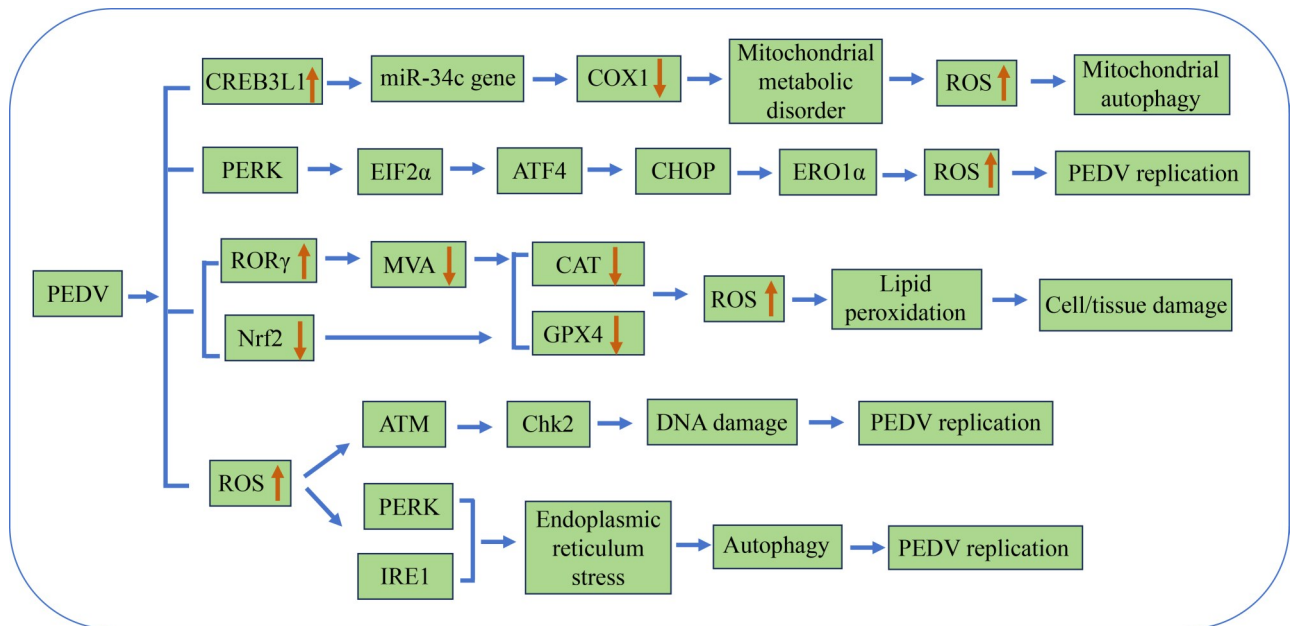


图2 PEDV感染与氧化应激的关系

Figure 2 The relationship between PEDV infection and oxidative stress. PEDV infection induces mitochondrial metabolic disorder through the CREB3L1/miR-34c/COX1 axis, increases mitochondrial ROS accumulation, and stimulates mitochondrial autophagy; PEDV controls endoplasmic reticulum to perturb its redox homeostasis through the PERK-CHOP-ERO1 α -ROS axis in favor of its replication. In PEDV-infected piglets, ROR γ /NRF2 regulates the transcriptional levels of key genes of mevalonate (MVA) through epigenetic mechanisms, blocking the biosynthesis of GPx4 and reducing catalase (CAT), resulting in lipid peroxidation in the piglet's liver. PEDV induces DNA damage response through the ROS-ATM signaling pathway, thereby promoting its early replication, or through oxidative stress, induced by the PERK and IRE1 pathways, promoting endoplasmic reticulum stress and cell autophagy.

成会触发一种与共济失调毛细血管扩张症突变 (ataxia-telangiectasia mutated, ATM)及其下游底物 Chk2 激酶相关的信号通路, 促进 DNA 的损伤反应^[122], 或者通过激活 p53 通路导致细胞凋亡^[39]。为确保自身的生存和传播, PEDV 感染会通过 ROS 依赖的内质网应激调节的自噬作用以限制细胞凋亡^[119]。

PEDV 感染仔猪可增加仔猪血浆和空肠中的 H₂O₂ 浓度^[123], 并显著削弱腓肠肌、淋巴结、肝脏和脾脏的抗氧化能力, 使免疫器官功能受损^[121,124]。这表明氧化应激推动了 PEDV 病理进程。

3.4 PDCoV 与氧化应激

目前, 关于 ROS 对 PDCoV 生命周期影响的报道非常少, 这可能归因于 PDCoV 是一种相对较新的病原体。与其他冠状病毒类似, PDCoV 在细胞质中复制, 会引发细胞凋亡^[125-126]。细胞凋亡与线粒体的功能与结构关系密切。PDCoV 感染细胞后, 线粒体分裂增加诱导了细胞色素 C 的释放, 进而启动凋亡程序^[127]。位于线粒体外膜的线粒体抗病毒信号蛋白 (mitochondrial antiviral signal protein, MAVS), 在视黄酸诱导基因 I 样受体 (retinoic acid-inducible gene I-like receptors, RIG-I) 和黑色素瘤分化相关蛋白 5 (melanoma differentiation-associated protein 5, MDA5) 介导的 I 型干扰素 (interferon-I, IFN-I) 产生过程中发挥核心作用。如图 3 所示, PDCoV 诱发的线粒体损伤, 同时上调 ROS 水平, 进一步触发线粒体自噬, 并导致 MAVS 降解, 从而抑制 IFN-I 的产生, 促进病毒复制^[128]。这可能是由于机体的氧化应激状态失衡, 破坏了机体的免疫系统^[37]。过氧化物酶体作为重要的细胞器, 参与脂质代谢、ROS 解毒、先天免疫和细胞信号传导, 其生物合成由过氧化物酶体生物发生蛋白 (peroxisomal biogenesis proteins, PEXs) 介导并调控其丰度, 在

细胞代谢和稳态维持中扮演着重要作用^[129]。最近的研究表明, 在 PDCoV 感染期间去乙酰化酶 Sirtuin 5 (SIRT5) 能够与 PDCoV 的 M 蛋白相互作用, 并对其去琥珀酰化修饰, 从而激活 ATM-PEX5-p62 通路并诱导自噬, 进一步抑制 I/III 型干扰素的产生, 并提高了 ROS 水平, 最终促进病毒复制^[130]。Nrf2 是调控细胞内抗氧化防御系统的关键转录因子。在 ST 细胞 (猪睾丸细胞系) 中, PDCoV 感染通过抑制 Nrf2 通路, 干扰细胞抗氧化能力, 导致氧化应激, 促进病毒复制, 诱导细胞凋亡^[38]。在仔猪感染模型中, PDCoV 主要靶向小肠上皮细胞, 导致 ROS 积累和氧化应激, 从而促进肠细胞脱落和坏死, 表现为腹泻、脱水等症状^[38]。类似地, 在小鼠试验中, PDCoV 感染抑制了 Nrf2 信号通路, 氧化应激标志物升高, 导致组织炎症和损伤^[65]。此外, 在 PDCoV 感染过程中, 由于病毒蛋白在内质网的过度生成而引发内质网应激^[131]。造成的内质网应激是否与产生的 ROS 有关, 还需要进一步研究。

目前认为, TGEV、PEDV 和 PDCoV 作为 PECs 的代表, 在诱导宿主细胞氧化应激方面展现出既有共性又有特异性的机制。一方面, 这 3 种病毒都可通过病毒复制过程损害线粒体的氧化还原系统或抑制 Nrf2 信号通路引发 ROS 的过度生成, 这些效应破坏细胞稳态, 增强了细胞病变作用。另一方面, 它们也可通过其他不同的途径产生 ROS。比如, TGEV 依赖 p53 和 p38 MAPK 通路来诱导氧化应激, 从而导致细胞凋亡; PEDV 可能通过内质网应激机制来触发 ROS, 为病毒提供有利的复制环境; 而 PDCoV 则凭借 ATM-PEX5-p62 通路破坏细胞氧化还原平衡, 并利用 ROS 来抑制免疫反应, 促进感染发展。这些差异不仅反映了病毒在进化过程中的适应策略, 也为针对不同冠状病毒的抗病毒治疗提供了潜在的靶点。

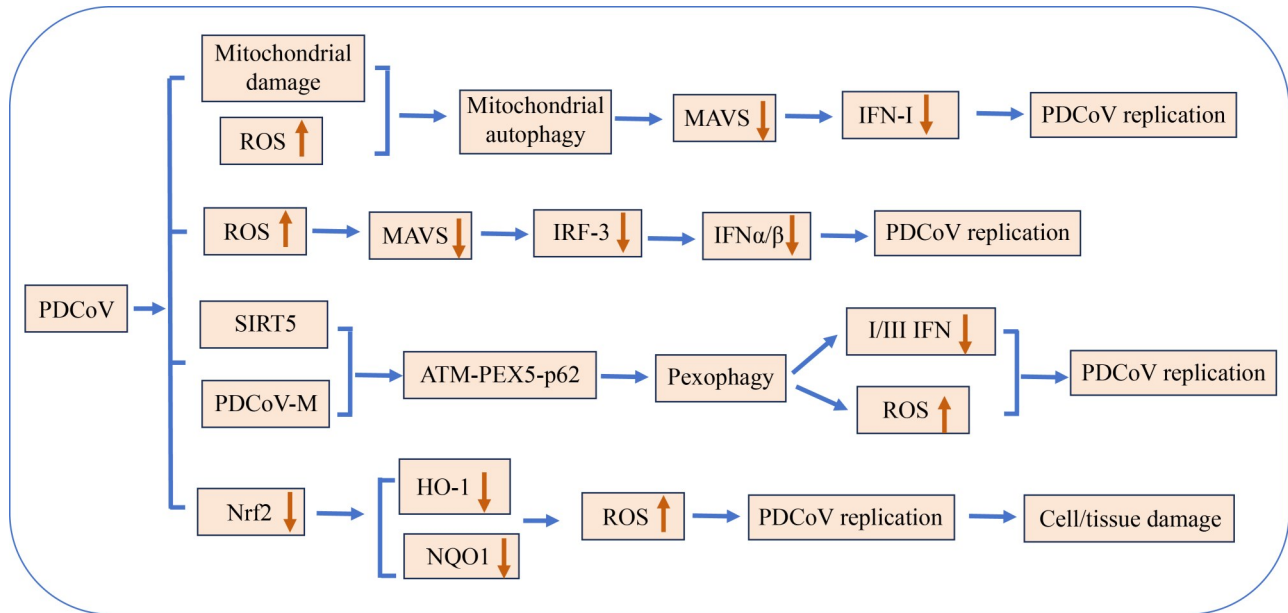


图3 PDCoV感染与氧化应激的关系

Figure 3 The relationship between PDCoV infection and oxidative stress. PDCoV infection can trigger autophagy in cells. Oxidative stress further promotes autophagy activation by generating ROS, interfering with the host immune signaling pathways, thereby facilitating viral replication. PDCoV infection can induce oxidative stress in host cells and affect the expression of mitochondrial antiviral signaling protein (MAVS) and the phosphorylation level of interferon regulatory factor-3 (IRF-3), thereby interfering with the innate immune response. SIRT5 interacts with and desuccinylates the PDCoV membrane (M) protein. This modification activates the ATM pathway to induce the ubiquitination of PEX5 and recruits p62 to initiate selective pexophagy, which disrupts the function of peroxisomes and increases ROS levels, inhibits the production of type I and type III interferons, and thereby promotes viral replication; PDCoV infection inhibits the Nrf2 pathway, reduces the levels of HO-1 and NQO1, leading to oxidative stress, promoting viral replication, and inducing tissue or cell damage.

4 抑制 PECs 感染中的抗氧化活性物质

根据目前的报道, 在具有抗病毒活性且对 PECs 有作用的化合物中, 有些对 TGEV、PEDV 和 PDCoV 同时显示出抑制作用, 例如二十二碳六烯酸(docosahexaenoic acid, DHA)和二十碳五烯酸(eicosapentaenoic acid, EPA), 这 2 种多不饱和脂肪酸可减轻 PECs 感染引起的 ER 应激, 降低炎症反应, 抑制病毒复制, 还能增强细胞的抗氧化能力, 降低 PEDV 引起的 ROS 水平^[132]。本文总结了具有抗 PECs 感染的抗氧化

活性物质及其作用机制(表 1)。

4.1 抗 TGEV 感染的抗氧化活性物质

(+)-儿茶素是一类从茶叶中提取的酚类活性物质, 具有抗 TGEV 的特性, 这与其抗氧化作用有关^[133]。蓼蓝胶原多糖能够减少 ROS 的生成, 抑制 TGEV 的复制, 进而抑制细胞损伤^[134]。丁香酚通过调节 ROS 减轻 TGEV 诱导的肠上皮细胞氧化应激, 影响 Keap1-Nrf2-ARE 信号通路, 减少 TGEV 引起的细胞凋亡^[40]。此外, 丁香酚还可通过阻止 ROS/NLRP3/GSDMD 依赖性细胞焦亡, 减轻 TGEV 引起的肠道损伤^[135]。维生素 A 的主要活性代谢产物——全反

表1 对PECs具有潜在治疗效果的抗氧化药物及其可能的作用机制

Table 1 Antioxidant drugs with potential therapeutic effects on PECs and their possible mechanisms of action

| Antioxidant drugs | Virus type | Antiviral mechanism | References |
|--|--|--|------------|
| Selenomethionine | Porcine deltacoronavirus (PDCoV) | Enhance cellular antioxidant capacity; activate the Nrf2 signaling pathway, reduce ROS levels, and alleviate intestinal damage | [37-38,65] |
| <i>N</i> -acetylcysteine | Porcine epidemic diarrhea virus (PEDV) | Reduced H ₂ O ₂ levels and alleviate intestinal damage. Enhance the spleen's antioxidant, anti-inflammatory, immune, and tissue repair capabilities | [123-124] |
| Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) | Porcine epidemic diarrhea virus (PEDV) | Reduce ER stress, enhance antioxidant capacity, and lower inflammation levels | [132] |
| (+)-catechin | Transmissible gastroenteritis virus (TGEV) | Reduce ROS production | [133] |
| <i>Polygonum cillinerve</i> polysaccharide | Transmissible gastroenteritis virus (TGEV) | Reduce ROS production and alleviate apoptosis | [134] |
| Eugenol | Transmissible gastroenteritis virus (TGEV) | Activate the Keap1-Nrf2-ARE signaling pathway to reduce ROS production and apoptosis; inhibit ROS/NLRP3/GSDMD-dependent pyroptosis to alleviate intestinal injury | [40,135] |
| All- <i>trans</i> retinoic acid | Transmissible gastroenteritis virus (TGEV) | Inhibition of ROS-mediated p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway reduces apoptosis | [136] |
| Aqueous leaf extract | Porcine epidemic diarrhea virus (PEDV) | Interfere with the replication phase of the viral life cycle, suppress oxidative stress, and mitigate apoptosis | [137] |
| Ergosterol peroxide | Porcine epidemic diarrhea virus (PEDV) | By suppressing ROS production and activating the p53 pathway, PEDV replication is inhibited | [138] |
| Luteolin | Porcine epidemic diarrhea virus (PEDV) | By targeting the substrate-binding site of the PEDV Mpro protein, it inhibits the enzyme's activity, thereby disrupting PEDV replication, suppressing inflammatory responses, and activating the Nrf2/HO-1 antioxidant pathway | [139] |
| Chrysin | Porcine epidemic diarrhea virus (PEDV) | Poplar extract inhibits PEDV replication through the ROS/JNK/p53 axis | [140] |
| L-deoxyojirimycin Extracts of mulberry leaves | Porcine epidemic diarrhea virus (PEDV) | L-deoxyojirimycin can reduce ROS production associated with PEDV infection, thereby decreasing MDA levels, enhancing GSH-Px activity, and alleviating the inflammatory response in host cells triggered by PEDV invasion | [141] |

式维甲酸(all-*trans*-retinoic acid, ATRA)已被证明在体外和体内均可抑制 TGEV 引起的氧化应激, 减轻细胞凋亡和肠道炎症^[136]。

4.2 抗 PEDV 感染的抗氧化活性物质

辣木的水叶提取物能够抑制 PEDV 诱导的氧化应激, 通过减少 ROS 和 MDA 的产生恢复 GSH-Px 的活性, 抑制细胞凋亡, 从而抑制 PEDV 病毒在 Vero 细胞中的复制^[137]。过氧化麦角固醇能够通过抑制 ROS 的生成并激活 p53 通路抑制 PEDV 在 Vero 细胞中的感染^[138]。*N*-乙酰半胱氨酸(*N*-acetyl-L-cysteine, NAC)是一种小分子, 易被肠道吸收, 可促进 GSH 的合成, 增强体内抗氧化能力^[123]。在 PEDV 感染的仔猪模型中, NAC 可降低仔猪血浆和空肠黏膜中的 H₂O₂ 水平, 缓解仔猪肠道损伤^[123]。此外, NAC 的使用改善了感染 PEDV 仔猪的脾脏、肠系膜淋巴结和腓肠肌中的氧化还原状态及功能基因表达水平^[124]。研究表明, 在 PEDV 感染的细胞中使用黄酮类化合物, 包括木犀草素和白杨素, 均能显示出抗病毒效果。木犀草素的抗病毒活性主要通过靶向病毒主要蛋白酶(main protease, Mpro)的活性实现, 显著降低 PEDV 的内化、复制和释放, 抑制 PEDV 感染诱导的多种炎症因子[如 IL-6、IL-1 β 和 α 肿瘤坏死因子(tumor necrosis factor- α , TNF- α)]及激活 Nrf2 的表达水平, 发挥抗炎作用^[139]。白杨素可下调 PEDV 感染诱导的 ROS 水平和细胞凋亡, 抑制 JNK 和 p53 信号通路的激活, 显著降低 Caspase 3/8/9 的表达水平及 Bax/Bcl-2 比值, 从而影响 PEDV N 蛋白的表达^[140]。桑叶 L-脱氧野尻霉素提取物对猪流行性腹泻病毒有明显的抗病毒活性, 可减轻 PEDV 感染引起的 ROS 和炎症反应^[141]。另外, DHA 和 EPA 对 PECs 的抗 PEDV 效果也与增强细胞的抗氧化能力有关^[132]。

4.3 抗 PDCoV 感染的抗氧化活性物质

硒是生物体必需的微量元素, 在抗氧化、抗病毒、提高免疫功能等方面起着重要作用。

在 PDCoV 的体外感染模型中, 硒代蛋氨酸(selenomethionine, Se-Met)被证明能够提高细胞的抗氧化能力并抑制 PDCoV 感染^[37]。前期使用仔猪、小鼠及 ST 细胞感染 PDCoV 的体内外感染模型的试验结果表明, Se-Met 可通过激活 Nrf2 信号通路减轻 PDCoV 感染引起的肠道组织或细胞损伤^[38,65]。目前, 关于抑制 PDCoV 感染的抗氧化活性物质的报道相对有限。未来研究应重点关注 ROS 在 PDCoV 感染过程中的具体作用, 进一步揭示 ROS 作为潜在治疗靶点的可行性, 并为抗 PDCoV 策略的开发提供新思路。

5 总结与展望

抗氧化药物在预防或治疗 PECs 感染方面具有重要价值。本文揭示了 PECs 感染与氧化应激的互作关系, 并系统梳理了目前抗氧化药物在 PECs 感染治疗中的具体作用与机制。PECs 感染可通过多种途径触发氧化应激, 破坏细胞稳态, 削弱抗病毒免疫反应, 促进自身复制。抗氧化剂是潜在治疗 PECs 感染的方案, 但这些抗氧化剂的作用效果与其受影响条件之间是否存在相关性尚不明确。部分抗氧化药物的使用仅局限于体外抑制 PECs 感染的潜力, 针对动物模型的防治(包括药物效能、剂量及作用时长)仍需进一步研究验证。

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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。

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