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铁死亡和焦亡：与三种神经退行性疾病的关联

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摘　要

铁死亡(ferroptosis)和焦亡(pyroptosis)这两种新型细胞死亡模式因其在多种疾病发展中的重要作用而备受关注。铁死亡是一种铁依赖性、非凋亡性细胞死亡形式，其特征为细胞内活性氧(ROS)的积累。焦亡是由炎症驱动的程序性细胞死亡类型，其特征为大量炎症介质的释放。神经退行性疾病(NDDs)表现为神经元功能受损，某些情况下甚至出现神经元死亡。铁死亡和焦亡可加剧神经退行性疾病的起始和进展。本综述旨在探讨铁死亡和焦亡的生物学过程，为三种常见神经退行性疾病的治疗和预防提供新视角。

关键词

铁死亡，焦亡，神经退行性疾病

Ferroptosis and Pyroptosis: Association with Three Types of Neurodegenerative Diseases

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Abstract

Two novel modes of cell death, ferroptosis and pyroptosis, have attracted a lot of interest recently

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since their important roles in the development of different diseases. An iron-dependent, non-apoptotic form of cell death, ferroptosis is typified by the accumulation of intracellular reactive oxygen species (ROS). Pyroptosis is a type of programmed cell death driven by inflammation marked by the release of large amounts of inflammatory mediators. A class of neurological diseases known as neurodegenerative diseases (NDDs) consists of compromised neuronal function and in some cases, neuronal death. Ferroptosis and pyroptosis can aggravate the beginning and spread of NDDs. The objective of this review is to provide novel perspectives on the treatment and prevention of three prevalent NDDs. The review investigates the processes of ferroptosis and pyroptosis and their respective consequences.

Keywords

Ferroptosis, Pyroptosis, Neurodegenerative Disease

1. 引言

神经退行性疾病(NDDs)包括阿尔茨海默病(AD)、帕金森病(PD)、亨廷顿病(HD)等，是一组以神经元变性与功能障碍为特征的慢性进行性神经系统疾病[1]。全球人口老龄化趋势与预期寿命延长加剧了神经退行性疾病的社会经济影响，严重损害了数百万患者的生活质量，从而给家庭和社会带来沉重负担[2]。尽管神经退行性疾病的临床表现各异，但其致病机制尚未完全阐明。现有研究表明，异常蛋白质动态变化、活性氧介导的氧化应激、线粒体功能障碍、DNA 损伤及神经炎症是导致这些疾病的主要病理生理过程[3]。

近年来，随着对细胞死亡机制研究的深入，除了细胞凋亡和坏死外，铁死亡和焦亡作为新型的程序性细胞死亡方式，也引起了人们的广泛关注[4]。铁死亡是一种铁依赖性的非凋亡性细胞死亡方式，其特征是细胞内自由铁的过度积累，导致脂质过氧化物的生成，进而引发神经元损伤[5]。焦亡则是一种由 Gasdermin 家族蛋白介导的细胞死亡方式。在细胞膜上形成孔洞，导致细胞内容物外泄，引发强烈的炎症反应，进一步加剧神经元的损伤[6]。

目前，针对铁死亡和焦亡的研究已经取得了一定的进展，但仍有许多问题亟待解决，如铁死亡和焦亡在神经退行性疾病中的具体调控机制、它们之间的相互作用以及如何针对这些细胞死亡方式开发有效的治疗方法等。因此，探讨铁死亡和焦亡的调控机制，寻找有效的干预策略，可能为 NDDs 的预防和治疗提供新的思路。本综述旨在系统总结铁死亡和焦亡在三种常见神经退行性疾病中的研究进展，探讨它们的分子机制和相互关系，评估其在疾病中的作用机制，为未来的研究和临床应用提供参考。

2. 铁死亡

2.1. 定义与特征

铁死亡(Ferroptosis)是一种铁依赖性的非凋亡性的细胞死亡形式，由 Dixon 等人于 2012 年首次系统阐明[7]。铁死亡主要由 erastin 等小分子化合物通过抑制胱氨酸/谷氨酸逆向转运体(system X_c^-)的活性，导致谷胱甘肽(GSH)合成受阻，谷胱甘肽过氧化物酶 4 (Gpx4)失活，进而引发 ROS 积累和脂质过氧化[8]。不同于其他细胞死亡形式，铁死亡的特征主要体现在多不饱和脂肪酸(PUFAs)的异常代谢和铁诱导的脂质

活性氧(lipid ROS)大量生成[9]。在铁死亡进程中，线粒体发生明显变化，出现线粒体体积缩小，外膜破裂，线粒体嵴密度减少或消失等现象，而细胞核形态在铁死亡过程中则保持正常[10]。

2.2. 发生机制

2.2.1. 铁代谢异常

在正常的生理条件下，细胞对铁离子的摄取、储存及利用维持动态平衡[11] [12]。三价铁(Fe^{3+})与转铁蛋白(transferrin, TF)结合形成 TF-Fe^{3+}复合物，通过转铁蛋白受体 1 (TfR1)介导的内吞途径进入细胞内[13] [14]。进入细胞后，Fe^{3+}在金属还原酶 STEAP3 的催化作用下被还原为二价铁(Fe^{2+}) [15]，随后通过二价金属转运蛋白 1 (DMT1)进入细胞质中的不稳定铁池(LIP) [16]。一部分 Fe^{2+}被储存于铁蛋白(ferritin)中，以维持细胞内铁离子的稳态，另一部分则参与细胞内的多种代谢活动[17]。多余的 Fe^{2+}则通过膜铁转运蛋白(Fpn)的作用被排出细胞外[18]。

当细胞内 Fe^{2+}含量超出正常范围时，不稳定铁池的稳定性受损，过量的 Fe^{2+}会触发芬顿反应(Fenton reaction) [19]，生成高度活跃的羟基自由基(·OH)，导致细胞内活性氧(ROS)水平显著升高[20]。ROS 具有强大的氧化能力，能够攻击细胞膜上的多不饱和脂肪酸(PUFAs)，引发脂质过氧化链式反应[21] [22]。这一过程中生成的一系列不稳定且具有毒性的脂质过氧化物破坏细胞膜的完整性，引发细胞内容物泄漏，最终触发铁死亡[23]。实验研究显示，外源性铁负荷可显著提升胞内 Fe^{2+}浓度，其剂量依赖性地增强脂质过氧化水平，并呈现典型的铁死亡形态学特征[24]。

2.2.2. 脂质过氧化加剧

脂质过氧化在铁死亡过程中发挥着关键作用[7]。生理状态下，细胞膜磷脂双分子层通过抗氧化防御系统维持氧化还原稳态，确保膜结构完整性和生理功能的正常运作[25] [26]。在铁死亡触发条件下，铁超载介导的 Fenton 反应通过催化活性氧(ROS)生成，驱动多不饱和脂肪酸(PUFAs)发生级联过氧化反应[27]。PUFAs 作为细胞膜磷脂的重要组成部分，其结构富含多个不饱和双键，使其对氧化反应高度敏感[28]。在铁死亡过程中，细胞内累积的 Fe^{2+}通过芬顿反应生成羟基自由基，这些自由基会特异性地攻击 PUFAs，引发脂质过氧化链式反应[29]。具体而言，羟基自由基首先从 PUFAs 的不饱和双键上抽取氢原子，生成脂质自由基(L·)；随后，脂质自由基与氧气结合，形成脂质过氧自由基(LOO·) [30]。脂质过氧自由基进一步从另一个 PUFAs 分子上夺取氢原子，生成脂质过氧化物(LOOH)，并释放出新的脂质自由基[31]。该过程循环进行，最终形成大量具有细胞毒性的脂质过氧化终产物(lipid peroxidation end products)。

2.2.3. 抗氧化系统失活

在铁死亡中，铁离子的累积与脂质过氧化物的产生往往导致抗氧化系统失衡。抗氧化酶在细胞抗氧化防御机制中扮演着核心角色，其中谷胱甘肽过氧化物酶 4 (GPX4)尤为关键[32]。GPX4 通过利用还原型谷胱甘肽(GSH)作为辅助因子，将脂质过氧化物(LOOH)还原为脂质醇(LOH)，从而遏制脂质过氧化的进程[33]。铁死亡期间，胱氨酸/谷氨酸反向转运体(system Xc-)活性受抑制，导致胱氨酸摄取减少，作为 GSH 合成的重要前体，胱氨酸的缺乏进而引发 GSH 合成减少和含量下降[34]。GSH 水平的降低抑制了 GPX4 的活性，削弱了其对脂质过氧化物的清除效能，促使脂质过氧化物在细胞内大量积聚[35]。

除了抗氧化酶，细胞内还存在维生素 E、辅酶 Q10 等抗氧化物质，它们在维持细胞氧化还原平衡中同样发挥着不可或缺的作用。维生素 E 作为一种高效的脂溶性抗氧化剂，能够直接与脂质自由基结合，中断脂质过氧化的链式反应。辅酶 Q10 则通过参与细胞呼吸链的电子传递过程，减少活性氧(ROS)的生成，并具备直接清除 ROS 的能力[36]。然而在铁死亡过程中，这些抗氧化物质的含量可能减少，或其抗氧化活性受到抑制，从而无法有效抵御脂质过氧化和 ROS 造成的损害。研究表明，在铁死亡诱导剂处理

的细胞中，维生素 E 和辅酶 Q10 的含量显著下降，细胞的抗氧化防御能力明显减弱[37]。

3. 焦亡

3.1. 定义与特征

焦亡(Pyroptosis)是一种由 Gasdermin (GSDM)家族蛋白介导的程序性细胞死亡形式[38]，其主要特征包括 GSDM 蛋白经 caspase 酶切割后，其 N 端结构域在细胞膜上形成 1~2 nm 孔道，导致渗透压失衡、细胞肿胀及膜完整性丧失[39]。伴随胞质内容物(如 IL-1β、IL-18)的释放，通过模式识别受体(如 TLR4)激活强烈的炎症级联反应[40] [41]。与细胞凋亡和坏死性凋亡不同，焦亡过程中细胞核通常保持完整，无凋亡样染色质凝聚与核碎裂，也不发生坏死时细胞器的广泛损伤和细胞膜的破裂[42]。

3.2. 发生机制

3.2.1. 经典途径

焦亡(Pyroptosis)的分子调控机制可以分为经典和非经典两种途径。经典通路中，炎症小体是位于细胞质内的多蛋白复合物，主要由模式识别受体(PRRs)、接头蛋白 ASC 以及无活性的前体胱天蛋白酶-1 (pro-caspase-1)组成[43]。当细胞受到病原体相关分子模式(PAMPs)或损伤相关分子模式(DAMPs)等外界刺激时，PRRs 识别这些信号，促使炎症小体组装并激活 caspase-1 [44] [45]。以 NLRP3 炎症小体为例，细胞受刺激后，NLRP3 蛋白发生构象变化，与 ASC 和 pro-caspase-1 相互作用，形成 NLRP3 炎症小体复合物，进一步促进 pro-caspase-1 的切割，生成活性 caspase-1 [46]。在焦亡过程中，活化的 caspase-1 发挥核心作用[47]。作为一种半胱氨酸蛋白酶，caspase-1 特异性切割 Gasdermin D (GSDMD)，释放出具有活性的 N-末端结构域(GSDMD-N) [48]。GSDMD-N 具有膜结合特性，能够嵌入细胞膜，形成孔道，导致细胞内容物外泄，引发强烈的炎症反应[49]。这一过程与细胞肿胀和膜破裂相关，最终导致细胞死亡。

在焦亡过程中，活化的胱天蛋白酶-1 (caspase-1)不仅切割 Gasdermin D (GSDMD)，形成具有细胞毒性的 N-末端片段(GSDMD-N)，导致细胞膜孔道形成和细胞溶解[50]，还切割炎性细胞因子前体，如白细胞介素-1β 前体(pro-IL-1β)和白细胞介素-18 前体(pro-IL-18)，将其转化为具有生物活性的成熟形式(IL-1β 和 IL-18) [51] [52]。成熟的 IL-1β 和 IL-18 通过细胞膜上的 GSDMD 形成的孔道释放到细胞外，发挥强烈的促炎作用[53]。IL-1β 能够刺激其他细胞产生更多的炎症介质，如肿瘤坏死因子-α (TNF-α)，从而放大炎症信号[54]。IL-18 则促进 T 细胞和自然杀伤细胞的活化，增强机体的免疫反应[55]。这些细胞因子共同引发并加剧了炎症反应，导致组织损伤和病理过程的进一步发展[56]。

3.2.2. 非经典途径

非经典途径主要由人类的胱天蛋白酶-4 (caspase-4)和 caspase-5，以及小鼠的 caspase-11 介导[57]。在这一途径中，这些胱天蛋白酶能够直接识别细胞质中的脂多糖(LPS)等病原相关分子[58] [59]。一旦激活，它们会直接切割 Gasdermin D (GSDMD)，从而引发焦亡[60]。与经典途径不同，非经典途径的激活无需炎症小体的参与。然而，在某些情况下，非经典途径激活产生的 GSDMD-N 端片段可能与炎症小体相互作用，进一步加剧炎症反应[57]。研究表明，在细菌感染的情况下，非经典途径能够迅速启动焦亡，以清除病原体，保护机体免受感染[61]。

4. 铁死亡与焦亡的相互作用

铁死亡和焦亡作为两种不同的程序性细胞死亡方式，并非孤立存在，它们在多种病理生理过程中相互影响、协同作用。近年来的研究表明，两者之间存在复杂的分子交互网络，共同参与神经退行性疾病的发生发展。

铁死亡的特征是脂质过氧化物的积累。脂质过氧化产物如 4-羟基壬烯醛(4-HNE)和丙二醛(MDA)可作为内源性损伤相关分子模式(DAMPs)，被模式识别受体(如 Toll 样受体 4，TLR4)识别[62]。4-HNE 可通过直接与 NLRP3 相互作用以及调节 NF-κB 信号通路来影响 NLRP3 炎症小体活性[63]。同时，铁死亡过程中产生的 ROS 也可直接激活 NLRP3 炎症小体，促进 caspase-1 的活化和 GSDMD 的切割，从而诱发焦亡[64]。此外，铁死亡导致的线粒体功能障碍可释放线粒体 DNA 等 DAMPs，进一步激活炎症小体[65]。铁死亡能够通过产生氧化损伤信号，触发炎症反应和焦亡。焦亡过程中释放的促炎因子如 IL-1β 可通过激活 NF-κB 信号通路上调转铁蛋白受体 1 (TfR1)的表达，促进铁摄取；同时下调膜铁转运蛋白(Fpn)的表达，抑制铁外排，导致细胞内铁超载。铁超载进一步通过芬顿反应产生 ROS，驱动脂质过氧化[66]。同时，ROS 作为焦亡与铁死亡的共享介质：ROS 既可促进炎症小体组装和 caspase-1 激活，驱动焦亡；又可引发芬顿反应介导的脂质过氧化，触发铁死亡[67]。因此，焦亡通过诱导铁稳态失衡和氧化应激，能够为铁死亡创造有利条件。线粒体功能障碍在铁死亡和焦亡中均扮演关键角色。受损的线粒体通过电子漏增加 ROS 生成，促进铁死亡[68]。释放的线粒体 DNA 激活 caspase-1 和炎症小体，诱发焦亡[69]。此外，自噬失调也同时参与两种死亡方式的调控。自噬可降解铁蛋白释放游离铁，促进铁死亡[70]。自噬相关蛋白(如 ATG5)也参与调节炎症小体的活化[71]。

铁死亡与焦亡之间存在双向调节关系，它们通过共享的信号分子和通路相互促进，形成恶性循环，加剧神经元的损伤和死亡。在神经退行性疾病的背景下，理解这一交互作用对于开发联合干预策略具有重要意义。

5. 铁死亡与神经退行性疾病

5.1. 铁死亡与 AD

阿尔茨海默病(AD)是最常见的与年龄相关的神经退行性疾病，临床表现为进行性记忆障碍和认知障碍[72]。AD 的特征性病变包括由 β-淀粉样蛋白(Aβ)沉积形成的老年斑(SPs)、高度磷酸化的 tau 蛋白在细胞内聚集构成的神经纤维缠结(NFTs)、神经元的显著丢失、突触传递功能异常以及神经炎症等[73]。值得注意的是，AD 大脑中存在多种因素使其对铁死亡高度易感。Aβ 肽段具有金属离子结合能力，可促进铁离子在斑块周围聚集。研究表明，Aβ (1-42)与铁蛋白共聚集可导致铁蛋白惰性三价铁核心转化为更具反应性的低价态铁，强烈提示 Aβ 参与 AD 中铁代谢异常[74]。铁在 AD 大脑中积累，通过多因素机制导致神经元功能障碍[75]。tau 蛋白的过度磷酸化可导致线粒体功能障碍，增加 ROS 生成[76]。tau 蛋白过度磷酸化与氧化应激形成恶性循环，诱导认知减退、树突棘丢失和线粒体异常。此外，AD 患者的抗氧化防御系统功能减退，进一步削弱了神经元抵抗脂质过氧化的能力[77]。研究显示，NOX4 通过氧化应激诱导的脂质过氧化促进星形胶质细胞铁死亡，与线粒体代谢受损相关[78]。

越来越多的研究揭示，铁死亡在阿尔茨海默病(AD)的进展过程中扮演着至关重要的角色。AD 患者的大脑内，铁离子积聚现象尤为显著，特别是在与 β-淀粉样蛋白(Aβ)沉积相关的脑区，铁离子浓度明显上升[79] [80]。研究指出，AD 患者脑内的铁离子沉积程度与认知功能损害呈正相关，铁离子的累积或许通过损害线粒体机能，进一步加重神经元损伤[81]。另有研究发现铁离子含量与 Aβ 沉积的严重程度紧密相关，铁离子可能催化 Aβ 的聚合及氧化过程，从而加速 AD 的病理发展[82]。AD 患者脑内多不饱和脂肪酸(PUFA)的代谢出现紊乱，致使脂质过氧化物积累，进而触发铁死亡，加剧神经元突触可塑性的损害[83] [84]。同时，AD 患者大脑中的抗氧化酶活性下降，如谷胱甘肽过氧化物酶 4 (GPX4)的活性减低，以及抗氧化物质如谷胱甘肽(GSH)的含量减少，削弱了神经元对抗氧化应激的能力，使其更易走向铁死亡[85]。研究显示，AD 小鼠模型中 GPX4 蛋白及其 mRNA 的表达均呈现下调趋势，这暗示了 GPX4 功能

异常可能与 AD 的起病及进展密切相关[86]。此外，有研究者提出，额叶和海马体中的 GSH 水平可作为 AD 及轻度认知障碍的潜在生物标志物，其水平的降低可能预示着 AD 发病风险的上升[87]。在铁死亡进程中，生成的脂质过氧化物及活性氧(ROS)会对神经元的细胞膜、蛋白质及核酸等重要生物分子造成攻击，损害神经元的正常构造与功能，最终导致神经元凋亡[88] [89]。通过抑制铁死亡的发生，能够有效减轻 AD 模型小鼠的神经病理损害及认知功能障碍，为 AD 治疗提供了新的潜在干预途径[90]。

5.2. 铁死亡与 PD

帕金森病(PD)位列全球范围内第二常见的神经退行性疾病，对众多人群造成了广泛影响[91]。伴随着全球老龄化趋势的加剧，PD 的发病率正逐年攀升，对中老年群体的健康状况及生活质量构成了严峻挑战。

PD 的典型症状包括静止性震颤、运动迟缓、肌强直和姿势平衡障碍等运动症状，以及嗅觉减退、睡眠障碍、自主神经功能紊乱、认知障碍等非运动症状[92]。帕金森病(PD)的病理学特征核心在于黑质中多巴胺能(DA)神经元的显著减少，这是引发患者运动症状的关键因素[93]。黑质内多巴胺能神经元的大量凋亡，直接导致纹状体中多巴胺浓度的大幅下降，进而破坏了大脑多巴胺能神经通路的正常运作[94] [95]。此外，PD 患者还伴随着持续的神经炎症反应，炎症细胞的浸润及炎症因子的释放加剧了神经元的损伤，加速了疾病的恶化进程[96]。线粒体功能障碍亦是 PD 的重要病理特征，线粒体结构与功能的异常引发能量代谢失衡，产生过量活性氧(ROS)，诱发氧化应激，对神经元造成损害[97]。同时，以路易体形式广泛存在的 α-突触核蛋白蛋白质聚集体，是 PD 的标志性病理改变。α-突触核蛋白的异常蓄积干扰了神经元的正常生理功能，最终导致神经元凋亡。

PD 的病理特征决定了多巴胺能神经元对铁死亡具有内在易感性。黑质区域本身富含铁离子，且多巴胺能神经元对铁摄取更为活跃[98]。多巴胺的代谢过程中可自身氧化产生醌类和 ROS，消耗细胞内抗氧化物质[99]。线粒体复合物 I 缺陷是 PD 的典型特征，导致线粒体 ROS 生成增加，促进脂质过氧化[100]。研究发现，帕金森病(PD)患者的黑质区域中，转铁蛋白受体 1 (TfR1)表达水平上调，促进了铁离子的摄入[101]。与此同时，膜铁转运蛋白(Fpn)的表达却呈现下降趋势，阻碍了铁离子的外排，进而导致细胞内铁离子积累过多。这些过量的铁离子通过芬顿反应，催生出大量活性氧(ROS)，这些 ROS 随即攻击细胞膜上的多不饱和脂肪酸(PUFAs)，触发脂质过氧化反应。脂质过氧化过程中生成的脂质过氧化物具有极强的细胞毒性，它们会破坏细胞膜的完整性，扰乱细胞内离子平衡，最终诱导细胞死亡。此外，PD 患者的抗氧化系统也处于失衡状态，使得神经元对氧化应激的易感性增强。谷胱甘肽过氧化物酶 4 (GPX4)，作为细胞内关键的抗氧化酶，能将脂质过氧化物转化为无害的脂质醇，从而抵御氧化损伤。然而，在 PD 患者的黑质中，GPX4 的活性降低，导致脂质过氧化物无法及时清除，进一步加剧了脂质过氧化的进程[102]。一项针对 PD 小鼠模型的研究发现，抑制铁死亡能显著减少黑质中多巴胺能神经元的凋亡，并改善小鼠的运动功能障碍[103]。这一发现进一步佐证了铁死亡在 PD 发病机制中的核心作用，并为 PD 的治疗提供了新的潜在靶点。

5.3. 铁死亡与 HD

亨廷顿氏病(HD)是一种常染色体显性遗传的神经退行性疾病，表现为进行性运动、行为和认知能力下降，最终引起死亡。亨廷顿舞蹈症(Huntington’s Disease, HD)的病理特征主要表现为基底节纹状体的广泛神经退行性变，其中中型多棘神经元和帕瓦布明中间神经元进行性丢失尤为显著[104]。这些神经元的死亡破坏了大脑相关神经回路的正常功能，进而引发一系列临床症状。研究显示，HD 患者的大脑纹状体体积显著缩小，神经元数量大幅减少，这与患者的运动和认知障碍密切相关[105]。此外，HD 还可导致大脑其他区域的病变，如大脑皮层萎缩和神经元连接减少等，这些变化进一步加重了患者的病情。

在 HD 中，突变的亨廷顿蛋白(mHTT)通过多种机制增强神经元对铁死亡的敏感性。mHTT 可干扰转录调控，下调抗氧化酶 GPX4 的表达[106]。mHTT 影响线粒体动力学和自噬过程，导致铁蛋白降解增加，释放游离铁[107]。研究显示，R6/2 HD 小鼠纹状体神经元中铁在核周细胞质中积累，铁调蛋白(IRPs)水平下降，铁摄取受体 TfR 和铁输出蛋白 FPN 表达发生适应性改变[107]。线粒体复合物 II 抑制剂 3-NP 通过 NOX2 介导的 ROS 生成，在携带 mHTT 的纹状体细胞中增强铁死亡[108]。同时，mHTT 可促进炎症反应，通过炎症小体激活和促炎因子释放，间接影响铁代谢[109]。这些改变使得纹状体神经元易于发生铁死亡。研究发现 ALOX5 失活可抑制 HD 小鼠纹状体神经元发生铁死亡，显著改善认知减退并延长寿命[110]。这一发现强调了铁死亡在 HD 发病机制中的关键作用，为 HD 治疗提供了新的潜在靶点。

6. 焦亡与神经退行性疾病

6.1. 焦亡与 AD

近年来众多研究表明焦亡在阿尔茨海默病(AD)的发病和进展中起关键作用。临床研究显示，AD 患者大脑及脑脊液中胱天蛋白酶-1 (caspase-1)、Gasdermin D (GSDMD)和白细胞介素-1β (IL-1β)水平显著升高[111]。此外，GSDMD 水平的升高与淀粉样 β 蛋白(Aβ)和 tau 蛋白水平呈正相关[112]。这一发现揭示，Aβ 和 tau 蛋白的聚集可能通过促进小胶质细胞和神经元等细胞的焦亡，推动 AD 的发生和进展。研究表明，Aβ 可通过 NLRP3/caspase-1 信号直接作用于小鼠皮质神经元诱导其焦亡，抑制神经元焦亡可改善 AD 模型小鼠的认知能力[113]。在 AD 模型中，小胶质细胞和星形胶质细胞中表达的 NLRP3 可被 Aβ 激活，进而通过 caspase1/GSDMD 轴诱导细胞焦亡，引发的炎症介质释放又可促进 Aβ 的募集、溶酶体损伤等，从而加剧炎症和神经退行性变[114]，抑制 caspase-1 活性可降低淀粉样蛋白 Aβ 的积累、大脑炎症和认知障碍[115]。

AD 患者大脑中，慢性神经炎症是其显著特征，这为焦亡的发生提供了基础。Aβ 和 tau 蛋白不仅直接激活炎症小体，还可通过诱导氧化应激和溶酶体损伤，增强 NLRP3 炎症小体的活化。此外，AD 中小胶质细胞和星形胶质细胞的持续激活状态，使其处于“预启动”状态，更易在次级信号刺激下发生焦亡。Li 等人的研究表明，tau 蛋白促进细胞焦亡是其神经毒性的重要部分，过度磷酸化的 tau 蛋白可以激活 caspase-1 及其他焦亡相关蛋白[116] [117]。使用 caspase-1 抑制剂能够显著减轻 tau 蛋白的神经毒性，改善细胞活力和模型大鼠的认知功能。进一步研究发现，tau 蛋白通过与接头蛋白 ASC 相互作用，促进 NLRP3 炎症小体的组装与激活，进而诱导细胞焦亡[118]。因此，针对 tau 蛋白引发的细胞焦亡通路进行干预，可能为 AD 的治疗提供新的策略。采用 siRNA-caspase-1 技术干扰 APP/PS1 小鼠脑组织中 caspase-1 的表达，结果显示，沉默 caspase-1 显著抑制了神经元的焦亡，降低了脑脊液及外周血中炎性因子的浓度，减轻了海马、纹状体及皮层等脑组织区域的神经细胞损伤程度，改善了小鼠的认知表现[119]。上述结果提示，靶向 caspase-1 及其相关信号通路可能为 AD 的治疗提供新的策略。红景天苷(Salidroside, Sal)作为一种天然化合物，通过抑制 NLRP3 炎症小体诱导的细胞焦亡过程，有效改善了阿尔茨海默病(AD)小鼠的认知功能障碍和神经病理状态。研究显示，Sal 能够下调 Aβ 诱导的 NLRP3、ASC、活化型半胱天蛋白酶-1 (cleaved Caspase-1)和活化型 GSDMD (cleaved GSDMD)等焦亡相关蛋白的表达，同时减少 IL-1β 和 IL-18 的释放，从而缓解炎症反应并抑制细胞焦亡[120]。该发现不仅揭示了天然化合物干预神经退行性疾病的新机制，更为开发以焦亡通路为靶点的 AD 治疗策略提供了重要理论依据，有望通过调控细胞焦亡途径来延缓 AD 的进展，提高患者的生活质量。

6.2. 焦亡与 PD

帕金森病(PD)是一种以多巴胺神经元进行性丧失为特点的神经退行性疾病。其发病机制与线粒体功能障碍、氧化应激和神经炎症密切相关。线粒体功能障碍是帕金森病(PD)的核心病理特征之一，导致细

胞能量代谢失衡并引发大量活性氧(ROS)的生成，从而诱发氧化应激[121]。线粒体的结构和功能损伤引发ROS过量产生，也会参与NLRP3的激活和诱导细胞焦亡，焦亡后释放的大量IL-1β会进一步损伤多巴胺能神经元，造成恶性循环，不断放大炎症反应[122]。

在PD患者大脑中，α-突触核蛋白的聚集可被小胶质细胞识别，激活NF-κB通路，上调NLRP3表达[123] [124]。同时，多巴胺能神经元本身因线粒体功能障碍产生大量ROS，作为第二信号激活NLRP3炎症小体[125] [126]。另外，黑质区域高浓度的铁离子也可能通过芬顿反应产生ROS，协同促进焦亡。这种“双重打击”使PD大脑更易发生焦亡。研究表明，NLRP3介导的小胶质细胞焦亡参与了PD大鼠的行为缺陷，焦亡相关蛋白caspase-1和GSDMD显著增加，炎症因子IL-1β和IL-18显著上调，抑制小胶质细胞焦亡能够有效减轻神经炎症，改善模型大鼠的行为缺陷[127]。此外，神经毒素1-甲基-4-苯基吡啶离子(MPP+)和鱼藤酮等能够破坏线粒体氧化呼吸链，增加ROS的生成，从而激活NLRP3炎性小体，诱导多巴胺(DA)神经元发生焦亡[128]。早期研究表明，在多种PD啮齿动物模型中，口服具有中枢神经系统穿透性的活性药物可有效抑制NLRP3炎症小体的活化，进而预防α-突触核蛋白的纤维化病理变化[129]。这些药物还能减少路易体样病变、改善线粒体功能，并缓解氧化应激所致的黑质纹状体多巴胺能神经元变性。研究显示，活性氧(ROS)抑制剂通过降低ROS水平，显著抑制caspase-1介导的IL-1β分泌，成为抑制细胞焦亡的重要途径。在帕金森病(PD)模型动物中应用ROS抑制剂后，大脑ROS水平显著下降，caspase-1的激活和IL-1β的释放得到有效控制，进而减轻神经炎症和细胞焦亡，改善运动功能障碍[130]。研究发现，人脐带间充质干细胞来源的外泌体(hucMSCs-Exos)能够穿越血脑屏障，显著抑制帕金森病小胶质细胞的激活，缓解运动障碍，减轻多巴胺能神经元损伤。这一作用可能归因于外泌体中携带的microRNAs或蛋白质成分，通过抑制小胶质细胞的焦亡过程发挥积极作用[131]。这些研究成果表明，减轻炎症、抑制细胞焦亡在未来有望成为PD治疗的重要策略，为PD的治疗开辟了新的思路并提供了潜在的治疗靶点。

6.3. 焦亡与HD

尽管HD被视为一种基因缺陷性疾病，但近年来的研究提示，焦亡可能是其神经退行性病变的重要诱因之一。突变亨廷顿蛋白可诱发一系列细胞功能障碍，包括促凋亡蛋白的激活、线粒体功能受损、轴突运输障碍、转录调控失衡、兴奋毒性、代谢与能量水平变化以及钙离子调节异常等[132]。这些功能障碍在HD早期阶段即已显现，且先于纹状体细胞死亡发生，暗示细胞内环境的紊乱可能触发细胞焦亡。

在HD中，mHTT可通过直接与IκB激酶复合物相互作用，激活NF-κB信号，上调多种炎症因子和NLRP3的表达。此外，mHTT引起的溶酶体功能障碍和异常自噬可导致组织蛋白酶释放，激活炎症小体。这些机制共同促进了HD中焦亡的发生。研究发现，在亨廷顿舞蹈症(HD)患者的大脑及小鼠模型中，核因子κB (NF-κB)活性显著增强，NLRP3炎症小体的表达也明显上调[133]。这表明NF-κB和NLRP3通路在HD发病过程中被激活，可能与细胞焦亡的发生密切相关。研究显示在HD患者的大脑和HD小鼠模型中均检测到caspase-1的激活，近年来的研究结果也提示了HD动物模型中有部分神经元的变性可能是由焦亡引起的，如纹状体神经元内NLRP3炎症小体和caspase-1的表达上调，下调NLRP3可抑制caspase-1，减缓HD R6/2小鼠模型的疾病进展[134] [135]。这些研究表明，炎症小体介导的焦亡在HD的发展中扮演了重要角色。突变亨廷顿蛋白可能通过激活NLRP3炎症小体，导致caspase-1的激活和GSDMD的裂解，最终触发细胞焦亡，加速HD的神经退行性病变过程。当前，针对焦亡机制治疗亨廷顿病(HD)的研究已取得初步成效，为HD治疗领域开辟了新的潜在策略。研究证实了四环素衍生物米诺环素在治疗HD方面的潜力，其通过抑制caspase-1和caspase-3的表达，减少GSDMD的裂解，进而遏制细胞焦亡的发生，减轻神经炎症与神经元损伤有效延缓了疾病进展[136]。

7. 结论与展望

随着对新型程序性细胞死亡方式——铁死亡和焦亡等研究的持续深入，人们日益认识到这些独特死亡形式在特定生理与病理环境中的关键作用。它们不仅丰富了对细胞生命周期的认知，更为探究其在各类疾病发生发展机制中的角色开辟了新的研究路径，为临床实践提供了潜在的创新性治疗策略。

在神经退行性疾病这一复杂且严峻的研究领域，细胞生死平衡的精细调控对神经系统的正常发育、功能维持及疾病的发生发展具有至关重要的影响。神经退行性疾病的发病机制往往涉及遗传、环境、代谢等多重因素的相互交织与作用，使得其病理过程极为复杂[137]。近年来，诸多研究表明，多种程序性细胞死亡方式共同参与了神经系统疾病的发病过程，它们或独立作用，或相互协同，共同驱动着疾病的进展。值得关注的是，针对程序性细胞死亡通路的抑制剂在延缓疾病进展、改善患者预后方面已展现出一定的积极效应。这些发现不仅为神经退行性疾病的治疗提供了新思路，也进一步佐证了深入探究程序性细胞死亡机制的重要性。

因此，未来的研究应继续聚焦于各种程序性细胞死亡的特异性信号传导途径及其间的复杂相互作用，力求全面揭示它们在神经系统疾病中的具体作用机制。这不仅有助于更精准地评估疾病预后，还可能为开发针对神经退行性疾病的新型治疗药物提供坚实的理论支撑和实践指导。总而言之，对程序性细胞死亡的深入研究将是推动神经退行性疾病治疗领域取得突破性进展的关键。

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