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铁自噬介导铁死亡在阿尔茨海默病中的研究进展

张爱婷,钟健民,贾珮雯,董贤慧*
(河北中医药大学,河北省心脑血管病中医药防治研究重点实验室,石家庄 050091)

摘 要:铁自噬是一种选择性自噬,通过核受体辅激活因子4(nuclear receptor coactivator 4,NCOA4)将细胞内铁蛋白转移到自噬溶酶体中进行降解并释放出游离铁,以满足多种铁依赖性生理过程的需要。铁自噬作为铁死亡的上游调控机制,其介导的铁死亡在阿尔茨海默病(Alzheimer's disease,AD)中的重要作用引起广泛关注。故本文对AD的发病机制研究进展进行简单归纳,指出铁自噬和铁死亡在AD中的作用,讨论铁自噬介导的铁死亡在AD发病中的机制及两者之间的关系;在此基础上,对通过铁自噬介导铁死亡防治AD的研究前景进行了展望,以期为今后的研究提供方向。

关键词:核受体辅激活因子4;铁自噬;铁死亡;阿尔茨海默病
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Research progress on ferroptosis mediated by ferritinophagy in Alzheimer′s disease

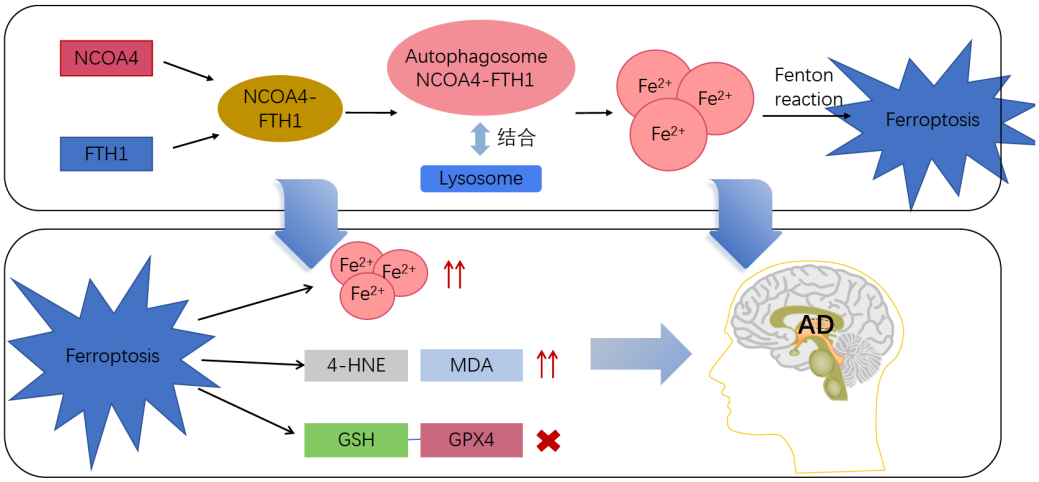
ZHANG Ai-Ting, ZHONG Jian-Min, JIA Pei-Wen, DONG Xian-Hui*
(Hebei Key Laboratory of Chinese Medicine Research on Cardio-cerebrovascular Disease, Hebei University of Chinese Medicine, Shijiazhuang 050091, China)

Abstract: Alzheimer′s disease (AD), the leading age-related neurodegenerative dementia, is defined by cognitive decline, β-amyloid (Aβ) plaques deposit, and neurofibrillary tangles (NFTs) from hyperphosphorylated tau. Despite extensive research, its pathogenesis remains unclear, and no disease-modifying therapies exist. Ferritinophagy, a selective autophagy regulating iron homeostasis via nuclear receptor coactivator 4 (NCOA4)-dependent ferritin degradation, is a key upstream regulator of ferroptosis, an iron-driven programmed cell death caused by lipid peroxidation and reactive oxygen species (ROS) accumulation. Mounting evidence links dysregulated ferritinophagy and ferroptosis to AD's pathological cascades. This review synthesizes their molecular mechanisms, crosstalk with AD, and therapeutic potential, providing a framework for future research. AD's core pathologies and hypotheses (Aβ, tau, neuroinflammation, mitochondrial dysfunction) highlight iron imbalance and ferroptosis as critical contributors. Ferroptosis is driven by free Fe^{2+}-catalyzed Fenton reactions, generating ROS and lethal lipid peroxidation. The glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis is central: GPX4 suppresses ferroptosis by reducing lipid peroxides, with natural compounds like icariin-astragaloside IV-puerarin mixture and Bingchang Powder modulating this axis in AD models. Ferritinophagy maintains iron homeostasis physiologically: NCOA4 binds ferritin heavy chain 1 (FTH1), forming a complex degraded via autophagosome-lysosome fusion to release iron. Pathologically, disrupted ferritinophagy causes Fe^{2+} overload and ferroptosis. Key regulators include E3 ubiquitin ligase HERC2 (modulating NCOA4 stability) and the iron-responsive element (IRE)-iron regulatory protein (IRP) system (regulating FTH1 transcription). In AD, brain iron deposition enhances ferritinophagy, leading to iron overload. Excess iron promotes Aβ overproduction via amyloid precursor protein (APP) processing interference and accelerates tau hyperphosphorylation via glycogen synthase kinase-3β (GSK-3β) activation. Ferroptotic neuronal death exacerbates neuroinflammation, forming a vicious cycle. AD risk factors like APOEε4 (activating PI3K/AKT to alter autophagic flux) and cellular senescence (impairing ferritinophagy) further dysregulate this pathway. Potential therapeutic targets include JWA,

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***通信作者**:E-mail: dongxianhuitj@126.com;Tel: 0311-89926252

transmembrane protein 164 (TMEM164), and ELAVL1. Dysregulated ferritinophagy-mediated ferroptosis is a pivotal AD pathogenic target. Unresolved questions include Aβ/tau's regulatory mechanisms on ferritinophagy, HERC2-FTH1 competitive binding to NCOA4, and NCOA4-CD63-mediated ferritin secretion. Future research should validate these mechanisms using AD models and clinical specimens, develop specific ferritinophagy modulators (small molecules, traditional Chinese medicine), and explore nanocarrier-based targeted delivery. Elucidating crosstalk with other AD pathways and establishing relevant biomarkers will enable combination therapies. Targeting this pathway shows considerable potential for the treatment of Alzheimer's disease and warrants further translational investigation.

铁自噬介导铁死亡在阿尔茨海默病中的作用机制



Key words: NCOA4; ferritinophagy; ferroptosis; Alzheimer's disease

阿尔茨海默病(Alzheimer's disease，AD)是中枢神经系统退行性疾病，也是常见的老年性痴呆类型，核心特征为进行性认知能力下降、β淀粉样蛋白(β-amyloid peptide，Aβ)斑块沉积和过度磷酸化的微管相关蛋白(microtubule-associated protein tau，tau)病变引发神经纤维缠结(neurofibrillary tangles，NFTs)，其发病机制尚未完全明确，目前公认的主要有Aβ假说、tau蛋白假说、胆碱能假说、神经炎症假说和线粒体功能障碍等[1]。典型AD以缓慢进展的健忘症为初始表现，反映了内侧颞叶结构神经纤维缠结病理的早期分布，最终演变为遗忘为主的多域痴呆[2]。

铁死亡是一种程序性细胞死亡，由细胞中脂质过氧化物和活性氧(reactive oxygen species，ROS)过度积累诱发。随年龄增长，大脑中的铁积累会增加神经退行性疾病风险[3]。神经退行性疾病患者特定脑区铁沉积更为严重，可导致氧化应激和神经元死亡[4]。

AD病理进程与铁稳态失调及铁死亡密切相关[5]。在AD大脑的斑块、小胶质细胞和带有缠结的神经元中已观察到铁沉积[6]。脑内铁代谢失衡与内源性抗氧化系统功能障碍，均与AD发病机制紧密关联[7]。铁死亡的终产物4-羟基壬烯醛(4-hydroxy-2-nonenal，4-HNE)在AD中通过产生Aβ原纤维和神经原纤维缠结来促进炎症反应[8]。

铁自噬常与铁死亡相伴而行，其平衡紊乱会释放大量Fe^{2+}，导致细胞内铁超载，诱导铁死亡的发生。铁自噬可以通过调节细胞内Fe^{2+}数量抑制铁死亡的发生，改善心脑缺血再灌注损伤，参与肿瘤发病过程并调控神经退行性疾病[9]。本文就铁自噬机制、铁自噬与铁死亡的关系以及铁自噬在AD中的作用作一综述，以期为治疗AD提供新靶点和新思路。

1　铁死亡是AD发病的重要致病机制

细胞铁死亡的主要形态特征为线粒体畸形、嵴减少，外膜浓缩、破裂，生化特征包括铁代谢异常、谷胱甘肽代谢紊乱、ROS累积及脂质过氧化，其中脂质过氧化是铁死亡复杂机制网络中的关键一环[10]。其核心机制为细胞内过量游离Fe^{2+}通过芬顿(Fenton)反应产生高活性ROS，诱发脂质过氧化链式反应，破坏

细胞内的氧化还原平衡,导致脂质过氧化物堆积并损害细胞膜完整性,最终引发细胞死亡[11]。

1.1 铁死亡的关键机制

谷胱甘肽(glutathione,GSH)-谷胱甘肽过氧化物酶4(glutathione peroxidase 4,GPX4)轴在限制脂质过氧化中发挥重要作用。脂质过氧化物大量积累至致死水平是铁死亡的必要信号[12]。在正常生理状态下,胱氨酸在胱氨酸/谷氨酸反向转运体(cystine/glutamate antiporter,System Xc^-)相关基因溶质载体家族7成员11(solute carrier family 7 member 11,SLC7A11)的调控下,通过System Xc^-进入细胞内,在胱氨酸还原酶和还原性辅酶——主要为烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate,NADPH)的作用下被还原为半胱氨酸。GSH是由谷氨酸、半胱氨酸和甘氨酸组成的三肽化合物,半胱氨酸是其合成的关键原料,同时GSSH也在NAPDH的作用下被还原为GSH。GSH-GPX4构成细胞内重要的氧化还原系统,GPX4以GSH的硫醇基团为电子供体,将脂质过氧化物还原为无毒脂质醇,减少过氧化物的蓄积,阻断脂质过氧化链式反应,从而抑制铁死亡的发生。

GSH依赖的GPX4的活性在调节神经元铁死亡中起着重要作用。神经元特异性敲除GPX4基因导致脂质过氧化物和细胞内ROS的积累,最终导致神经元铁死亡,证实GPX4是神经元细胞铁死亡的关键调控因子[13]。淫黄葛合剂可以上调γ-谷氨酰半胱氨酸连接酶催化亚基和谷氨酰胺酶2的表达,促进GSH合成,减轻脑铁沉积[14];冰菖散可以激活核因子E2相关因子2(nuclear factor erythroid 2-related factor 2,NRF2)/血红素加氧酶-1(heme oxygenase-1,HO-1)通路,增加GPX4的表达,通过抑制Keap1来增强NRF2的转录活性,进而提高SLC7A11的表达并恢复GSH的含量,有效对抗铁死亡[15]。

1.2 AD中的铁死亡

在AD发病过程中,神经元细胞内脂质过氧化物水平显著升高[16]。铁代谢紊乱是Aβ沉积的关键因素[17]。铁可以直接与淀粉样前体蛋白(amyloid precursor protein,APP)相互作用,抑制弗林蛋白酶(furin)的表达,而furin调控裂解APP的α-分泌酶和β-分泌酶,α-分泌酶被抑制,β-分泌酶被激活;同时,ROS增加引发的氧化应激可以激活β-分泌酶1(beta-secretase 1,BACE1),BACE1是Aβ生成的关键酶,最终促进APP异常加工、Aβ生成增多,导致突触损伤和认知功能减退[18]。Aβ的沉积可能会干扰细胞内正常的铁代谢,引发细胞内铁超载,进一步增加铁死亡发生风险。

铁死亡与tau蛋白磷酸化同样密切相关。糖原合酶激酶-3β(glycogen synthase kinase-3β,GSK-3β)活化是tau异常过度磷酸化的原因,铁死亡可以通过激活GSK-3β和抑制蛋白酶体促进tau聚集[19]。异常的tau病理与神经退行性疾病患者大脑中铁积累密切相关,铁可以通过激活多种促进tau过度磷酸化的激酶,或影响蛋白质磷酸酶2A活性,调控tau磷酸化进程[20]。细胞内铁沉积增加与细胞外铁含量升高相互作用,共同推动AD的发生发展。

在AD中,铁死亡导致的脂质代谢物大量堆积会引发炎症,炎症通过加剧铁沉积反过来促进铁死亡,形成恶性循环。连翘苷A可以通过调控铁死亡以及抗炎途径发挥AD防治作用[21]。综上,铁死亡与AD的发病及防治关系密不可分,抑制铁死亡是防治AD的重要策略。

2 铁自噬是铁死亡的上游调控机制

2.1 铁自噬的发生机制

铁自噬是铁死亡的上游调控机制,由Mancias等[22]在2014年首次提出,是一种以NCOA4为受体介导的选择性自噬,常见于铁过载、氧化应激以及营养匮乏的细胞。在正常情况下,NCOA4与铁蛋白特异性结合形成复合物,该复合物被自噬体包裹后与溶酶体融合,最终被降解释放Fe^{2+},维持细胞内铁稳态。铁蛋白是细胞内储存铁的主要蛋白,其主要由重链(ferritin heavy chain,FTH)和轻链(ferritin light chain,FTL)组成。NCOA4因子存在多个转录变异体,其中NCOA4α的C端有多个结合FTH的位点,两者特异性结合形成NCOA4-FTH1复合物。自噬相关基因(autophagy-related gene,ATG)、自噬受体与货物依次相继作用[23]:在自噬准备阶段,ATG8样蛋白质微管相关蛋白1轻链3(microtubule-associated protein 1 light chain 3,LC3)由前体状态活化成胞质可溶形式的LC3-I;自噬信号进一步触发后,LC3-I在多种ATG蛋白酶的协同作用下,与磷脂酰乙醇胺结合形成脂化的LC3-II。LC3-II特异性定位于铁蛋白所在区域,参与自噬体与溶酶体的识别和融合,协同自噬体包裹NCOA4-FTH1复合物,促进铁蛋白的降

解和Fe^{2+}的释放，完成铁自噬[24]。在病理状态下，铁自噬平衡被打破，细胞内过多游离Fe^{2+}离子被释放，引起铁超载，游离铁作用于细胞膜发生Fenton反应，导致ROS大量释放，GSH-GPX4轴等氧化还原轴失代偿，过氧化物在细胞内大量堆积，最终诱发铁死亡。

2.2 细胞内NCOA4水平是调控铁自噬的关键

NCOA4蛋白在铁自噬中起着关键作用，其细胞内水平与铁自噬通量密切相关。E3 泛素连接酶HERC2(HECT and RLD domain containing protein 2)是调控细胞内 NCOA4 水平的关键蛋白，其蛋白结构中包含CPH(Cullin-7-PARC-HERC2)与INBD(铁硫簇依赖的NCOA4 结合域)两个关键功能区域。NCOA4的HERC2结合域(HBD)可结合 2Fe-2S 簇，该结构作为响应细胞内铁浓度变化的分子开关，介导NCOA4与HERC2的特异性结合。当细胞内铁含量较高时，NCOA4与2Fe-2S簇结合，并通过双位点作用模式与HERC2两个结构域相互作用：NCOA4 HBD的N端结合2Fe-2S簇后，继续与HERC2的INBD结构域结合；其C端直接结合HERC2的CPH结构域。当细胞内铁含量较低时，铁硫簇合成减少，不含2Fe-2S簇的NCOA4无法被HERC2有效识别，NCOA4含量上升，进一步诱导铁自噬以提升细胞内的铁水平[26]。

E3泛素连接酶TRIM21(tripartite motif-containing protein 21)[27,28]能够识别HERC2特定的氨基酸序列或结构域，将泛素分子共价连接至HERC2，或直接泛素化HERC2中与酶活性相关的关键结构域，使其丧失与NCOA4结合的能力。当细胞内铁充足时，HERC2与NCOA4结合增强，细胞内NCOA4含量减少，与FTH1结合减弱，铁离子储存于铁蛋白中；当细胞内铁浓度下降，NCOA4与FTH1结合增强，释放更多游离Fe^{2+}，与HERC2结合减弱(图1)。目前，与NCOA4结合的HERC2与FTH1这两个因子之间是否存在竞争关系，尚未明确。

2.3 调控FTH1的相关因子

铁蛋白mRNA和转铁蛋白受体(transferrin receptor，TfR)mRNA上均含有铁反应元件(iron-

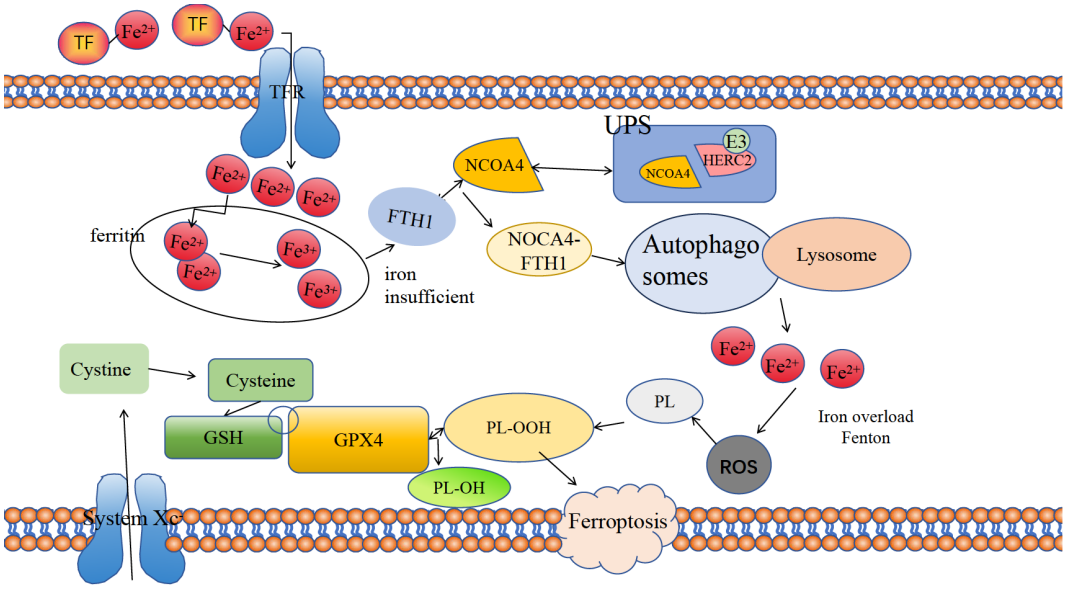


图1 铁自噬介导铁死亡信号通路

Fe^{2+}与转铁蛋白结合形成复合物，通过转铁蛋白受体介导进入细胞；在铁蛋白的亚铁氧化酶活性中心作用下Fe^{2+}被氧化为Fe^{3+}并储存于铁蛋白内部；在铁缺乏状态下，铁自噬处于激活状态，NCOA4与FTH1结合形成复合体，被自噬-溶酶体包裹，释放出游离Fe^{2+}，大量游离Fe^{2+}引发细胞内铁超载，发生芬顿反应，产生大量ROS，参与脂质过氧化过程，而脂质过氧化物堆积引发细胞铁死亡。

Figure 1 Ferroptosis signaling pathway mediated by ferritinophagy

Fe^{2+} binds to transferrin to form a complex, which is oxidized to Fe^{3+} by the ferroxidase active center of ferritin via transferrin receptor and stored in ferritin; under iron deficiency, ferritinophagy is activated, and NCOA4 binds to FTH1 to form a complex that is encapsulated by autophagolysosomes, releasing free Fe^{2+}. A large amount of free Fe^{2+} induces intracellular iron overload, triggers the Fenton reaction, generates a large amount of ROS, participates in the lipid peroxidation process, and the accumulation of lipid peroxides induces cellular ferroptosis.

responsive element,IRE)序列[29]。IRE与铁调节蛋白(iron regulatory protein,IRP)的结合可调控FTH1基因的表达。正常细胞内铁充足时,铁离子与IRP1结合重建铁硫簇,使其处于无活性状态,无法与铁蛋白mRNA上的IRE结合,核糖体可正常结合FTH1 mRNA并启动翻译,FTH1蛋白合成增加,与FTL组装成功能性铁蛋白,螯合胞内多余游离铁。

当细胞处于铁缺乏状态时,IRP1-铁硫簇解离并激活,与IRE形成复合物,阻碍核糖体亚基与mRNA的结合,抑制FTH1 mRNA的翻译,促使铁蛋白释放更多游离铁;同时,IRP与TfR mRNA 3′UTR上的IRE结合,稳定TfR mRNA,防止其降解,使其持续翻译,导致细胞表面转铁蛋白受体表达增加,增强细胞摄取铁的能力。IRE-IRP通过调控铁蛋白表达间接影响NCOA4与FTH1的结合。此外,NRF2和BTB-CNC同源性1蛋白(BTB domain and CNC homolog 1,BACH1)在FTH1调节中起拮抗作用——NRF2激活FTH1的转录,BACH1则抑制其转录[30]。

2.4 调控铁自噬介导铁死亡

阻断自噬或敲低NCOA4的表达可抑制铁自噬,消除细胞内不稳定铁和减少ROS的积累,避免细胞铁死亡。在慢性阻塞性肺疾病模型中,NCOA4的体外和体内消融可减轻GPX4敲低诱导的铁死亡[31,32]。脂多糖、缺氧诱导因子等物质可以增强NCOA4 mRNA的表达,促进铁蛋白降解和细胞铁死亡[33,34]。E3泛素连接酶HECW1(homologous to E6-AP carboxyl-terminal domain and C2 region containing 1)可以通过转录抑制因子ZNF350影响NCOA4 mRNA转录,对NCOA4产生正向调节作用,促使某些细胞发生铁死亡[35]。补肾活血颗粒可通过调节NCOA4介导的铁自噬,抑制脑黑质神经元细胞铁死亡,改善多巴胺能神经元损伤[36]。上调受损神经元中的去泛素化过程,增加泛素特异性肽酶14表达能够有效降低NCOA4水平以保护神经元免受铁自噬介导的铁死亡[37]。在脓毒性呼吸窘迫综合征模型中,褪黑素可以降低LC3II/LC3I(增强自噬通量的特征)比率、抑制FTH1的表达,从而抑制铁自噬,减少细胞内Fe^{2+}的积累,同时增加GPX4的表达,发挥抗铁死亡的作用[38]。上述研究表明,NCOA4介导的铁自噬在调节细胞内铁稳态和铁死亡中发挥重要调控作用,为通过调控铁自噬介导铁死亡防治AD提供了新的方向。

3 铁自噬在AD中的作用

3.1 铁自噬防治AD

铁自噬介导的铁死亡是神经退行性疾病的关键致病机制之一,NCOA4介导的铁自噬诱导的铁死亡功能障碍可加速AD病理过程[39]。当前广泛研究发现AD中存在铁死亡,其发生的具体机制尚未明确。

调控载脂蛋白E(APOE)可有效改善铁自噬介导的铁死亡导致的AD认知功能障碍。APOE是一种34 kDa的脂质转运糖蛋白,其编码基因存在三种常见亚型,其中,载脂蛋白E-ε4(*APOEε4*)等位基因是AD最强的遗传危险因素[40]。*APOEε4*基因携带者的脑脊液(CSF)中APOE蛋白含量显著降低,而铁蛋白水平明显升高,提示该类人群更易因脑铁负荷异常累积,加速AD的病理进展。从分子机制来看,APOE蛋白可通过激活PI3K/AKT通路,上调LC3II/LC3I比率,抑制铁自噬,进而避免铁死亡导致的铁依赖性脂质过氧化损伤,延缓AD进展[41]。AD杜鹃假说揭示了铁自噬在AD铁死亡发生中的重要作用,该假说指出AD中存在铁隔离(可能被Aβ和tau蛋白隔离)以及溶酶体和自噬功能障碍现象,导致功能性铁缺乏,破坏细胞内正常的生化过程,引发铁稳态失衡,进而使细胞内不稳定铁异常升高,触发铁死亡[42]。

衰老细胞中铁自噬异常也是AD的重要诱因。衰老细胞内会出现铁的大量累积,这一现象由受损的铁自噬驱动——铁自噬受损打破细胞内铁稳态,细胞中LC3-II大量积累,细胞膜上TfR受体显著增多,导致细胞内Fe^{2+}浓度显著升高[43]。同时,铁蛋白降解受损使铁被困于铁蛋白中,铁排出障碍导致细胞内铁离子浓度下降,使衰老细胞处于永久铁缺乏和持续铁获取的循环状态,对铁死亡具有高度抗性。动物体内研究显示[44],类黄酮作为一个抗氧化、抗细胞衰老、抗炎和抗肿瘤的因子,可以通过上调NCOA4表达水平,促进铁自噬从而诱导衰老细胞铁死亡,清除衰老细胞,同时也抑制亚铁螯合酶的表达以诱导铁死亡。

AD多发于老年人,衰老细胞对铁死亡的高度抗性使其发生铁死亡的阈值进一步提升,衰老细胞在患者体内的积累以及铁代谢紊乱可引发一系列症状与体征。铁自噬在AD中发挥重要作用,调控铁自噬

有望成为AD防治的新靶点。

3.2 调控铁自噬是改善AD认知功能障碍的潜在机制

动物实验研究表明,在帕金森病(Parkinson's disease,PD)模型中,*JWA*基因可抑制FTH1的表达,阻止FTH1向溶酶体易位,并与FTH1竞争NCOA4的结合位点,进而抑制铁自噬,同时抑制细胞内总铁水平和Fe^{2+}离子水平,最终抑制铁死亡的发生[45]。目前*JWA*基因与铁死亡其他相关因子的关联尚不明确,其有望成为调控神经退行性疾病的新靶点,尤其在调控AD中铁自噬介导的铁死亡方面。跨膜蛋白164(TMEM164)是铁死亡的正向调节因子,其通过选择性调节GPX4蛋白降解,参与FTH1、脂滴及LC3的形成,在脂质过氧化过程中推动自噬体形成,从而在自噬依赖性铁死亡中发挥关键作用[46]。TMEM164的产生机制及其具体作用路径尚未完全阐明,需进一步探究。临床研究指出[47],铁自噬相关基因*ELAVL1*在多发性骨髓瘤中呈高表达,且与MAPK信号通路密切相关,而该通路同样与AD的发生发展存在紧密联系,因此*ELAVL1*可作为AD潜在治疗靶点值得进一步深入研究。

4 总结及展望

当前,AD领域仍旧存在诸多值得深度挖掘的方向,持续探索AD的发病机制有助于揭示各假说之间的内在联系,阐明AD不同阶段的病因及病理表现,从而更全面地认识AD,并开发有效的预防及治疗方法。

铁自噬通过多种途径在AD中发挥作用,是铁死亡的上游调控机制。正常生理状态下,NCOA4与FTH1特异性结合于自噬体,自噬体与溶酶体相互作用,降解铁蛋白并释放Fe^{2+},维持细胞内铁稳态;但病理情况下,这一平衡紊乱可致细胞内铁超载,进而引发铁死亡。NCOA4可以与CD63蛋白结合将铁蛋白送入外泌体,再由外泌体送至细胞外或目标位置,该机制是否可以作为新的铁自噬相关机制,目前尚未明确[48]。此外,关于HERC2与FTH1之间竞争关系的探究意义重大:若该竞争关系成立,通过靶向增强HERC2表达适当抑制自噬通量,或可减少细胞铁死亡的发生,延缓AD进展。纳米颗粒联合靶向铁死亡的药物或物理方式是极具潜力的新型治疗策略。在胰腺癌研究中观察到,新型药物递送系统GDMCN2可携带靶向治疗药物,在超声刺激下触发细胞器严重损伤,激活LC3促进溶酶体自噬,在NCOA4辅助下诱导自噬依赖性铁死亡[49]。

铁自噬介导铁死亡的分子机制、结构基础和代谢过程在很大程度上仍不明确,尤其是其在AD中的调控机制及临床应用,亟需进一步探索。铁自噬和铁死亡作为AD研究的热点及防治AD的新方向,始终处于发展前沿,本文通过对铁自噬相关研究进行初步总结,希望能为读者提供一个深入探索的新思路。

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