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An Overview of Alzheimer's Disease Pathogenesis and the Outlook for Its Treatment

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Abstract

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases and its prevalence is closely related to aging, and also the most common cause of dementia. AD is clinically characterized by cognitive deficits and behavioral disorders like language disorders, memory loss, agitation and depression. AD is pathologically characterized by senile plaques (SPs) composed of *β*-amyloid (A*β*), neurofibrillary tangles (NFTs) caused by hyperphosphorylated Tau proteins, and neuronal loss. AD pathogenesis is not well understood yet, but a body of evidence shows that A*β* plays a critical role in AD pathology. In this paper, we review the role of A*β*-induced oxidative stress, neuroinflammation and neuronal apoptosis in AD pathology, aiming to provide new ideas for the development of new therapeutic drugs against AD.

Keywords

AD, A*β*, Oxidative Stress, Neuroinflammation, Neurofibrillary Tangles

阿尔兹海默病发病机理概述及治疗策略展望

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摘　要

阿尔兹海默病(Alzheimer's disease, AD)是最常见的一类的神经退行性疾病，也是最常见的一类痴呆病，

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高发于老龄群体。AD临床症状包括语言障碍、记忆丢失、易怒、抑郁等认知功能障碍及行为异常；AD病理特征主要包括神经元外*β*-淀粉样蛋白(*β*-amyloid, A*β*)沉积形成的老年斑(senile plaques, SPs)和神经元内Tau蛋白过度磷酸化形成的神经原纤维缠结(neurofibrillary tangles, NFTs)、神经元丢失等。尽管AD发病机理至今尚不清楚，但越来越多的证据表明A*β*与AD病理紧密相关，本文综述A*β*诱导的氧化应激、炎症反应及神经元调亡与AD病理的相关性，以期为AD新药研发提供新的思路。

关键词

阿尔兹海默病，A*β*，氧化应激，神经炎症，神经原纤维缠结

1. 阿尔茨海默病

阿尔兹海默病(Alzheimer's disease, AD)是最常见的一类的神经退行性疾病，其发病与衰老紧密相关[1]；AD 高发于老龄群体，也是最常见的一类痴呆病[2]，其临床表现包括语言障碍、记忆丢失、易怒及抑郁等认知及行为方面的异常[3] [4]，其病理特征主要包括神经元外 *β*-淀粉样蛋白(*β*-amyloid, A*β*)沉积形成的老年斑(senile plaque, SP)、神经元内 Tau 蛋白过度磷酸化形成的神经原纤维缠结(neurofibrillary tangles, NFT)及神经元丢失[5] [6]。越来越多的证据表明 A*β* 诱导的氧化应激(oxidative stress)、炎症反应(inflammation)及神经元调亡(apoptosis)与 AD 病理紧密相关。

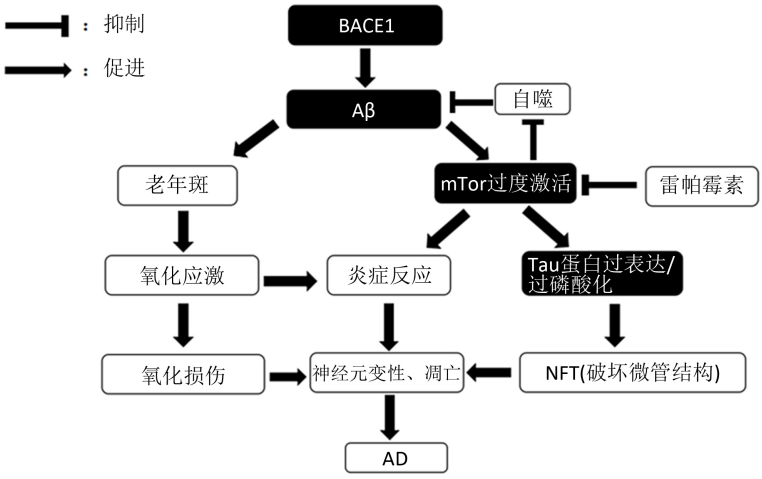
2. A*β* 与氧化应激

氧化应激是指因机体氧化-抗氧化内稳态(oxidant-antioxidant homeostasis)受损，导致自由基过量积累，对机体造成氧化损伤的现象；氧化应激可导致生物大分子脂质、蛋白质、DNA 及 RNA 的过氧化损伤[7] [8]。越来越多的研究结果显示，氧化应激与 AD 发病密切相关[9] [10] [11]。A*β* 是由 39~43 个氨基酸残基组成的多肽，是老年斑的主要组成部分[12]；诸多研究表明，A*β* 沉积可诱导氧化应激反应、引起神经元凋亡[13] [14] [15]，A*β* 诱导的氧化应激在 AD 发病中起关键作用[16] [17]。研究表明，A*β* 可显著提高 AD 老鼠脑组织脂质过氧化水平，致使 NO、MDA 水平显著上升[18]。Montine T 等的研究显示，A*β* 可促进自由基的生成，损伤学习能力和记忆能力[19]；Soodi M 等的研究显示，大鼠海马区注射 A*β* 可显著提高大脑脂质过氧化水平，导致大鼠认知功能损伤[20]；Hayeon J 等的研究显示，A*β* 可显著提高细胞活性氧簇(reactive oxygen species, ROS)的生成水平，促进细胞染色质固缩和细胞凋亡[21]；而使用抗氧化剂可改善 A*β* 诱导的氧化损伤和认知功能损伤[22] [23] [24]。另有研究证明，A*β* 寡聚物能降质膜的流动性，质膜流动性的下降反过来又刺激 A*β* 的生成[25]，A*β* 聚集形成的可溶性聚集体可伸入质膜，促进 ROS 的生成，继而加剧氧化应激反应[26] [27]，ROS 对生物大分子 DNA、蛋白质、脂质以及细胞内小分子的氧化，导致细胞损伤[27] [28]。研究显示，线粒体功能障碍与神经退行性病变紧密相关，且神经元对线粒体功能障碍和氧化应激非常敏感[29]。ROS 是线粒体电子传递链(electron transport chain)的主要中间产物，如过氧化氢和羟自由基，在正常生理状态下，ROS 具有维持内稳态、调节与细胞生长、增殖、存活相关的信号转导的功能[30]，线粒体功能障碍可导致 ROS 过度生成[31]，ROS 过度生成进一步加剧氧化应激对线粒的损伤，破坏电子传递链、降低 ATP 合成，形成“ROS-线粒体损伤-ROS”恶性循环[32]。大脑是高度耗

能器官，耗氧量达机体总量的 20%，且大脑中多不饱和脂肪酸的含量高于其他器官，这使得大脑更易遭受氧化应激损伤[33]。因此，Aβ 诱导的氧化应激已被广泛认为是导致 AD 重要因素之一[34]。Aβ 的生成源自 β-分泌酶(β-secretase，BACE1)对 Aβ 前体蛋白(amyloid precursor protein, APP)的酶切，因此 BACE1 被认为是 Aβ 生成的关键因素[35]，抑制 BACE1 也因此被认为是治疗 AD 的关键环节[36] [37]。综上所述，本文推测 Aβ 可能通过与质膜相互作用诱导氧化应激，对线粒体及脂质、核酸、蛋白质等生物大分子造成氧化损伤，最终引起神经元凋亡。因此 BACE1 和 Aβ 可作为 AD 的重要治疗靶点(如图 1)。

3. Aβ 与神经炎症

研究认为，神经炎症(neuroinflammation)是 AD 的病理特征之一[38]，神经炎症是 Aβ 诱导神经元死亡的重要介导因素之一，是除氧化应激外诱导 AD 病理的另一重要因素[39]，越来越多的证据表明，Aβ 诱导的炎症反应是 Aβ 神经毒性的重要组成部分[40]。研究显示，Aβ 可在细胞水平诱导炎性细胞因子 TNF-α 和 IL-6 的表达水平显著升高[41]，在 AD 发病早期，炎性细胞因子基因相关转录因子 NF-κB 可被 Aβ 沉积激活[42]，炎性细胞因子在 AD 的各个阶段都呈高水平表达，提示神经炎症与 AD 病理有着紧密的相关性[43]，也有研究证明 TNF-α 和 IFN-γ 能促进 Aβ 生成[44]，因此炎症反应与 AD 病理紧密相关。哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)是一类丝氨酸/苏氨酸激酶(serine/threonine kinase)，属磷脂酰肌醇相关激酶家族[45]，广泛参与细胞生长、增殖、脂质合成等细胞活动的调控[46]。越来越多研究表明，mTOR 与 AD 病理密切相关[47]；诸多研究表明，AD 脑组织存在 mTOR 过表达和过度激活的现象，如 Siman R 等在 AD 动物模型中观察到，Aβ 累积可上调 mTOR 的表达水平[48]；Liu Y C 等在老鼠海马区注射 Aβ，观察到海马组织 TNF-α 表达水平显著上调、mTOR 表达水平显著上调和激活的现象[49]。研究表明，mTOR 具有调控炎性细胞因子如 IL-1β，TNF-α 及 IFN-γ 的作用[50]，如 Dhingra R 等的研究显示，mTOR 能激活 NF-Kb [51]，而 Mengke N S 等的研究显示，mTOR 抑制剂雷帕霉素可下调脂多糖诱导的 IL-1β 和 IL-6 的 mRNA 表达水平[52]，提示脂多糖可能通过激活 mTOR 促进炎性细胞因子表达，炎性细胞因子 IL-1β 和 IL-6 的释放可破坏正常的神经生理功能[53]。因此，mTOR 被认为是 AD 治疗的重要靶点(如图 1)。



注释：1) BACE1 的过表达促进 Aβ 的生成和沉积，过量的 Aβ 通过某种机制促进氧化应激，对神经元造成氧化损伤；2) Aβ 沉积导致 mTOR 过度激活，继而促进神经炎症及 tau 蛋白过磷酸化形成 NFT，最终引起神经元变性死亡。

Figure 1. Overview of the pathogenesis of AD
图 1. AD 发病机理推理概述

4. Aβ 与神经原纤维缠结、自噬

Tau 蛋白是一类微管相关蛋白，主要表达于神经元轴突，对微管组装和维持微管稳定具有重要作用[54]，AD 的主要病理标志之一 NFT，则由 Tau 过度磷酸化与微管脱离形成，研究发现，异常过磷酸化的 Tau 蛋白，无论在溶解状态还是凝聚状态，都不能与微管蛋白相互作用[55]，NFT 的形成导致神经元细胞形态异常、轴突运输功能丢失及突触功能丢失等神经退性病变[56]。大量研究显示，mTOR 过度激活与 AD 发病紧密相关[57]，mTOR 信号通路的激活可促进 Tau 蛋白病变，而抑制 mTOR 信号通路则可缓解 Tau 蛋白病变[58]；有研究证明，Tau 蛋白可被 mTOR 直接磷酸化，且 Tau 蛋白的聚集、表达都受 mTOR 影响[59]，而体内外研究表明，mTOR 抑制剂雷帕霉素可降低 Tau 蛋白水平[60]，且能改善 AD 模型鼠的认知功能缺陷并能降低 Aβ 水平[61]；另有研究表明，mTOR 的过度激活可抑制自噬作用(autophagy)，从而降低自噬作用对 Aβ 的清除、加剧 Aβ 的沉积[62]；诸多研究显示，自噬功能损伤与 AD 发病密切相关[63]。神经元由于高度分化失去分裂能力，因而不能通过细胞分裂稀释不断积累的毒性物质，只能通过自噬作用清除胞内毒性物质或是受损的细胞器以维持细胞内稳态。mTOR 的异常过度激活与自噬作用、Tau 蛋白过磷酸化密切相关，提示 mTOR 可作为 AD 治疗的重要靶点(如图 1)。

5. AD 药物现状与展望

目前，运用最广泛的 AD 药物包括胆碱酯酶抑制剂(Acetylcholinesterase inhibitors, AChEI)：盐酸多奈哌齐(Donepezil)、加兰他敏(Galantamine Reminyl)、利凡斯的明(Rivastigmine)及兴奋性氨基酸受体拮抗剂美金刚(Memantine) [64]；然而，AChEI 类药物往往导致 Tau 蛋白磷酸化水平升高[65]，而且 AChEI 与美金刚存在不同程度的毒副作用。越来越多的证据显示，Aβ 沉积是起始 AD 的关键因素，因此大多 AD 治疗策略研究都聚焦在如何抑制或清除 Aβ。然而，2014 年，瑞士罗氏公司(Roche)发布公告称其在研的 AD 新药 Crenezumab 在二期临床实验中失败；2016 年，美国礼来公司(Eli Lilly and Company)也宣布其研发的新药 Solanezumab (一类靶向作用可溶性 Aβ 单体的疫苗)在三期临床试验中失败，这表明仅仅作用 Aβ 单个靶点难以到达理想的抗 AD 疗效。大量研究显示，Aβ 沉积导致氧化应激、炎症反应、神经原纤维缠结及神经元凋亡，最终导致认知功能障碍、行为异常等临床症状，现有的 AD 药物相关研究，也大多基于抗氧化、抗炎症的观点，且抗炎症、抗氧化类药物能在细胞水平及动物水平上取得理想的抗 AD 效果，表明氧化应激、神经炎症确与 AD 病理密切相关。越来越多的证据显示，AD 是一类多因素疾病，多靶点治疗无疑是当下和将来 AD 药物研发的新策略。

6. 结语

脑组织神经元外 Aβ 异常沉积被广泛认为是起始神经元突触丢失，并最终导致神经元死亡的关键因素[66] [67]。尽管存在多种 Aβ 诱导的神经毒性机制假说，但大量研究证明，Aβ 诱导的氧化应激是 AD 病理的重要促进因素，Aβ 引起神经元 ROS 水平上升，对脂质、DNA 以及 RNA 等生物大分子造成氧化损伤，最终导致神经元的变性死亡[7] [8]。线粒体是细胞的产能中心，机体吸收的氧气大部分作为电子传电链终端电子受体参与 ATP 的生成，是产生 ROS 的主要细胞器。在正常生理情况下，约有 2%的 O2 被电子传递链底物端漏出的电子还原生成 ROS [68]。低水平的 ROS，可作为细胞内氧化还原信使，并行使传递、调控细胞内信号的功能[69]，而过量的 ROS 则对细胞造成过氧化损伤，最终导致细胞凋亡[70]。因此 Aβ 诱导的氧化应激是 AD 病理的重要促进因素。

mTOR 的过度激活与过表达与 Tau 蛋白的过磷酸化紧密相关，Tau 蛋白的过磷酸化导致 NFT、微管结构不稳定、细胞形态异常及轴突运输功能紊乱，最终导致神经元死亡[56]。同时，mTOR 的过度激活与过表达与神经炎症紧密相关，mTOR 的过度激活促进炎性细胞因子的表达。此外，mTOR 的过度激活可

抑制自噬作用，从而减弱自噬作用对 Aβ 等毒性物质的清除，被认为是 Aβ 沉积的重要原因。尽管 AD 的确切病理机制仍有待探索阐明，但越来越多的证据表明，Aβ 过度沉积、mTOR 过度激活与过表达与 AD 病理密切相关；Aβ 累积可通过诱导氧化应激、Tau 蛋白过磷酸化、线粒体功能损伤导致神经退行性病变[71] [72]。研究显示，AD 患者脑组织存在 BACE1 过表达的现象[73]，BACE1 的过表达促进 APP 转变成 Aβ，过量的 Aβ 可能通过某种机制促进 ROS 的过度生成，加剧氧化应激；此外，Aβ 可能通过某种机制过度激活 mTOR，继而促进神经炎症、Tau 蛋白过磷酸化形成 NFT，最终引起神经元变性死亡，综上，Aβ 介导的氧化应激、神经炎症、微管结构异常均是 AD 病理的重要促进因素，Aβ、BACE1、mTOR 及 Tau 蛋白可作为 AD 药物研发的重要靶点。

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