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ApoE 与 β 淀粉样蛋白在阿尔茨海默病中相互作用的研究进展*彭羽瑶¹ 张浩然¹ 易明玉¹ 吴婷¹ 刘超² 肖乐^{2Δ} 李昌琪^{3Δ}

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摘要: 阿尔茨海默病(Alzheimer's disease, AD)是一种中枢神经系统神经退行性疾病,至今尚未明确其发病机制,但基于其典型的病理特征之一是 β 淀粉样蛋白(amyloid-beta, A β)聚集,A β 沉积假说一直都是研究的重点。近年来,载脂蛋白E(apolipoprotein E, APOE)对A β 代谢清除的影响备受关注。研究表明,APOE ϵ 4等位基因是散发性AD的危险因素,且APOE对A β 具有很高的亲和力,不同亚型的APOE对A β 的代谢有不同的影响,这为对AD的认识、防止及治疗提供了新的研究方向。

关键词: 阿尔茨海默症; β 淀粉样蛋白;载脂蛋白E;A β 沉积假说

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The Recent Advance in Interactions between Apolipoprotein E and Amyloid-beta in Alzheimer's Disease*

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ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disease of the central nervous system. Its pathogenesis is still incompletely understood. The accumulation of amyloid-beta (A β) is one of the typical pathologic symptoms, and the "amyloid hypothesis" has dominated Alzheimer research for a long time. Recently, the effect of apolipoprotein E (APOE) in A β metabolism attracts extensive concern. It suggests that ϵ 4 allele is a risk factor in sporadic Alzheimer disease. Apolipoprotein E has a high affinity with A β , while different isoforms of apolipoprotein E have different influences on A β metabolism. These results provide a new way for the identification, prevention and therapy of AD.

Key words: Alzheimer's disease; Amyloid-beta; Apolipoprotein E; Amyloid hypothesis

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阿尔茨海默病(Alzheimer's disease, AD)是一种主要在老年期发生的以进行性痴呆为主要特征的神经退行性疾病^[1]。在临床上,AD患者的主要症状是大脑的认知和功能功能障碍,常表现为渐进性的功能丧失,病变早期即出现短期记忆不牢,并由此逐渐发展为短期及长期的记忆缺失,有的患者甚至会表现出语言、行为障碍和人格改变。在病理特征方面,AD患者的脑部神经元减少,致使其大脑皮质出现弥漫性萎缩,脑沟回增宽且加深,脑室扩大。经切片染色处理后可见患者脑部神经元细胞外有大量老年斑(senile plaques, SPs)聚集,系由 β 淀粉样蛋白(amyloid-beta, A β)沉积而成^[2]。此外,在神经元细胞内,tau蛋白(τ 蛋白)过度磷酸形成神经元纤维缠结(neurofibrillary tangles, NFTs)。上述二者共同构成AD的典型病理改变^[3-5]。

AD不仅对患者个人的社交、职业与生活功能产生了严重的影响,还对患者的家庭以及社会造成了巨大的心理和经济负

担。其发病机制一直都是神经系统退行性疾病研究的热点之一,目前比较普遍的观点认为AD是一种多病因的疾病。关于AD的发病原因,有众多假说来解释,如胆碱能假说与其他神经递质因素^[6]、A β 沉积假说^[3]、应激适应性衰竭假说^[7,8]、自由基损害假说^[9]、炎症机制假说^[10]、铝中毒假说^[11]等。其中占主导地位的是A β 沉积假说。

尽管有相关研究推测,A β 沉积仅仅是AD的一个病理表证而不是根本的发病原因^[12],但是A β 沉积假说在AD的致病机制和治疗策略的研究中仍是一个重点。并且随着研究的深入,载脂蛋白E(Apolipoprotein E, ApoE)及载脂蛋白相关基因在AD中的作用开始受到关注^[13]。以下就目前关于ApoE与 β 淀粉样蛋白在阿尔兹海默病症中的相互作用的研究进展予以综述。

1 β 淀粉样蛋白(A β)沉积假说

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β 淀粉样蛋白沉积假说是基于大量的尸检资料而提出的。对 AD 患者进行解剖发现,在 AD 患者的脑部,特别是海马及其基底核区域聚集着较多的老年斑和神经元纤维缠结。在此基础上开展的许多研究认为,由 $A\beta$ 构成的 SPs 和过度或异常磷酸化的 τ 蛋白构成的 NFTs 是 AD 的重要发病原因^[14]。AD 患者脑部聚集的 $A\beta$ 来源于神经元细胞膜上的淀粉样前体蛋白 (amyloid precursor protein, APP), APP 是一种单次跨膜蛋白,广泛存在于全身各处的组织细胞上,常集中分布于中枢神经系统各神经元的突触中。在正常人的大脑内, APP 经 α - 分泌酶水解后释放到胞外区,这一过程将 $A\beta$ 裂解为两半,进而阻止 $A\beta$ 的形成。但是在病理条件下,例如当 APP 基因发生突变后产生新的酶切位点, APP 则在 β - 分泌酶和 γ - 分泌酶的共同作用下剪切形成胞外游离的 $A\beta$ ^[15,16]。 $A\beta$ 作为一条肽链,包含的氨基酸越多,其毒性作用就越强。这是因为越长的 $A\beta$ 越容易在胞外聚集到足够多的 $A\beta$ 装配成不溶性的共聚体沉淀,此即为 $A\beta$ 神经毒性的结构基础^[17]。由胞外 $A\beta$ 聚集形成不可逆的不溶性沉淀,最终将构成 SP 进而引发 AD。

$A\beta$ 作为一条在结构上以 β - 片层为特性的多肽链,其在氨基酸组成上多为含有 39~43 个氨基酸残基的 $A\beta$ 39~43。其中,人体中存在的 $A\beta$ 亚型主要是含有 40 或 42 个氨基酸残基的 $A\beta$ 40/42。研究证实, $A\beta$ 42 更容易发生沉积,是 AD 患者脑内的老年斑即淀粉样蛋白的主要成分^[18]。而 AD 患者脑内沉淀的淀粉样蛋白多数是由于其自身原因引起的,随着年龄的增长、遗传信息表达的改变、神经系统与免疫系统的功能出现异常,患者脑部的 $A\beta$ 产生量超出正常生理指标范围,且其清除 $A\beta$ 的速率下降,过量的 $A\beta$ 与相应的聚集因子发生作用,加剧胞外 $A\beta$ 的游离态单体聚集为不可溶性的沉淀,进而形成斑块^[19]。但是老年斑不仅仅存在于 AD 患者脑部,在正常生理状态下,健康的老年个体也会由于年龄的增大而产生老年斑。

目前学术界普遍认为,在 AD 的发病过程中起着至关重要的作用的是 $A\beta$ 42 与 $A\beta$ 43^[20]。在此基础上提出的 $A\beta$ 沉积假说即阐明, $A\beta$ 本身就具有一定的神经毒性,其能破坏细胞膜的完整性,引起细胞内超载,扰乱细胞的内环境,使得细胞内氧自由基 (reactive oxygen species, ROS) 的代谢紊乱,引起一系列氧化应激反应,进而诱发中枢免疫炎症反应和神经毒性级联反应、促使 NFLs 形成,最终导致神经元广泛变性,甚至是坏死^[21,22]。

大量的解剖学实验证实, AD 患者脑内 NFTs 主要由螺旋纤维 (paired helical filament, PHF) 和少量的直纤维构成,而构成这两种纤维的正是过度或异常磷酸化的 τ 蛋白^[23]。有研究发现, τ 蛋白与硫酸葡聚糖 (肝素或硫酸肝素) 的相互作用能够形成 NFTs, 并且 $A\beta$ 25-35 片段能够激活 τ 蛋白激酶,加速 τ 蛋白的磷酸化。脑内注射 $A\beta$ 纤维可加速 τ 蛋白转基因小鼠 NFTs 的形成。体外实验表明,聚集态的 $A\beta$ 41~42 可降低细胞内 τ 蛋白的可溶性,促进 τ 蛋白纤维的形成,诱导 NFTs 的产生^[19]。

2 ApoE 概述

ApoE 是一种具有多态性的载脂蛋白,最初是在正常人的极低密度脂蛋白 (very low density lipoprotein, VLDL) 中被发现

的。后来人们依次在人体的乳糜微粒 (chylomicron, CM) 及乳糜微粒残基 (chylomicron remnants, CMR) 中发现了 ApoE 的存在^[24]。 ApoE 由 299 个氨基酸组成,其相对分子质量为。编码 ApoE 的基因位于人类的第 19 号染色体长臂 3 区,基因全长为 3.7kb,系由 4 个外显子和 3 个内含子组成。由于 ApoE 基因的第 4 个外显子表现为基因多态性,故可将其分为 ApoE ϵ 2、ApoE ϵ 3、ApoE ϵ 4 三个等位基因,在人体内的正常比例分别为 10%、75%、15%^[25],对应编码 ApoE 2、ApoE 3 和 ApoE 4 这三种不同的载脂蛋白。对 ApoE 载脂蛋白分子的这三种异构体进行氨基酸组成分析的结果表明,在分子水平上, ApoE 基因的多态性表现为其编码的蛋白质分子的一级结构差异性。 ApoE 2、ApoE 3 和 ApoE 4 分子中的第 112 位和第 158 位上氨基酸的种类不同。 ApoE 2 分子的这两个位置上均为半胱氨酸; ApoE 3 分子的第 112 位氨基酸为半胱氨酸,而第 158 位氨基酸则是精氨酸; ApoE 4 分子的这两个位置上则均为精氨酸^[24]。 ApoE 这三种异构体其本质上是基因选择性表达的产物,即 ApoE 的同一基因位点上三个不同等位基因 ApoE ϵ 2、ApoE ϵ 3、ApoE ϵ 4 在不同条件下选择性表达,分别对应产生 ApoE ϵ 2、ApoE ϵ 3、ApoE ϵ 4,它们作用于胆固醇和三酰甘油代谢过程的中心环节。 ApoE 三种基因中任意两种表达导致其具有 6 种表型,其中纯合子和杂合子各占 3 种。纯合子的表型有: ϵ 2/2、 ϵ 3/3、 ϵ 4/4; 杂合子的表型有: ϵ 2/3、 ϵ 3/4、 ϵ 2/4^[26]。大量的研究发现,在 3 个等位基因中, ApoE ϵ 4 是散发型 AD 的危险性因素^[27],约 40%~50% 的早发性 AD 及 80% 的晚发性 AD 与 ApoE ϵ 4 相关^[28]; 而 ApoE ϵ 2 和 ApoE ϵ 3 可使 AD 发病率降低,发病年龄延迟,是一种保护性因素^[29,31]。

人体内的 ApoE 主要是在肝脏和脑中合成的,其他组织细胞也有一定的合成能力,例如肾上腺细胞、卵巢颗粒细胞以及单核细胞 (含巨噬细胞) 等^[32]。肝脏是 ApoE 的第 1 大合成器官,经肝脏合成的 ApoE 进入血液循环,随血液运输广泛分布于全身,是血浆中重要的载脂蛋白之一,在胆固醇和甘油三酯的运转和代谢中发挥着举足轻重的作用^[33]。脑是 ApoE 的第 2 大合成器官,神经系统中的 ApoE 主要是由星形胶质细胞和少突胶质细胞产生的^[34]。 ApoE 负责脑内胆固醇和脂质蛋白的转运,实现细胞间的物质交换,进而调节突触的重塑。此外, ApoE 对 $A\beta$ 的聚集和清除有调节作用^[35-37],但是这一理论尚存在争议。目前的研究主要认为, ApoE 在多种中枢神经系统疾病中扮演负面的角色^[38-43]。已有调查显示, ApoE ϵ 4 携带者可能要比无 ApoE ϵ 4 携带者提前 10~20 年患上阿尔茨海默症^[44,45]。且有统计学结果证实, ApoE ϵ 4 携带者脑卒中的预后效果更差^[46-49]。

3 ApoE 与 β 淀粉样蛋白的相互作用

上个世纪九十年代初,针对日本老年人群的一项调查较为明确地揭示了 ApoE 与 $A\beta$ 的关系。该研究表明, ApoE 对大脑中枢神经系统中的 $A\beta$ 具有很高的亲和力,并由此推论 ApoE ϵ 4 是散发性 AD 的危险因素之一^[50]。随后有实验发现,在适宜的条件下,大鼠体内的 ApoE 4 通过改变可溶性 $A\beta$ 多肽的溶解度,进而加速淀粉样蛋白沉积的形成并诱导 AD 的产生^[51]。近年来有研究进一步证实, ApoE ϵ 4 携带者更易患 AD,而 ApoE ϵ 2 却能降低携带者患该病的风险^[52]。虽然 ApoE 4 对 AD

发病的具体作用机制尚未完全阐明,但是目前普遍认为 ApoE 4 是 AD 是高风险因素^[53]。

随着科学技术的不断发展,关于 ApoE 与 A β 的相互作用的研究也逐步转移到基因层面。大量研究表明,人体内 APP 的分解代谢即 A β 的产生受 ApoE 基因多态性的影响^[54,55]。并且越来越多的学者开始致力于研究 ApoE 蛋白亚型与 ApoE 受体的联合作用对 APP 分解过程的影响^[56]。在进行体外实验探究时,将细胞与低密度脂蛋白相关受体 1(low density lipoprotein receptor-related protein 1, LRP1) 的受体拮抗剂受体相关蛋白(receptor associated protein, RAP)共同孵育后,检测细胞内 APP 和 A β 的含量,结果显示增加的是 APP 的表达量,而减少的则是 A β 的产生量。当 APP 与 LRP 基因共转染时,A β 的产生量比 APP 基因单独转染时 A β 的产生量高出 3 倍^[57]。同时也有人发现 ApoE 能增加 APP 的胞内吞作用,加速 APP 的水解过程,且这一作用效应在强弱上表现为:ApoE 4 > ApoE 3^[58]。随后有研究进一步证实,ApoE 与相应的受体结合后,尤其是与 ApoE 受体 2(ApoE receptor 2, ApoER2)结合之后,这一促进作用更强。且 ApoE 4 产生的效应较 ApoE 2、ApoE 3 更为明显,导致这种差异的原因可能与 ApoE 4 结合 ApoER2 的能力更强有关^[59]。

ApoE 基因多态性不仅影响着脑内 A β 的产生,还作用于 A β 的清除过程。以 ApoE 4 转基因小鼠为实验对象,用微透析的方式检测发现,其脑部清除 A β 的能力明显低于其他实验组以及正常对照组^[60]。事实上,大脑清除 A β 主要是依靠脑实质细胞上的受体介导,即星形胶质细胞和神经元细胞,因为脑内的 A β 绝大部分都是先与 ApoE 受体相结合,再转运至溶酶体内由蛋白水解酶进行降解,最后通过细胞间液或血脑屏障排出^[61]。由于 A β 和脂质结合 ApoE 的部位相同,故二者存在着竞争机制,当 A β 与 ApoE 结合后,便减弱了 ApoE 与脂质的结合^[62]。近年来的研究显示,当 A β 与 ApoE 4 结合后,其受体由 LRP1 转变为低密度脂蛋白受体(low density lipoprotein receptor, LDLR),而这种清除途径的速率明显慢于 LRP1。进而针对 apoE 在 A β 的清除过程中是否具有亚型特异性开展的一系列研究证实,在血脑屏障处各复合体的清除速率存在差异性,且其清除速率由大到小依次为:A β -ApoE 2 复合体、A β -ApoE 3 复合体、A β -ApoE 4 复合体^[63]。但是近年来也有研究发现,这种差异并没有显著性^[64]。

大脑清除 A β 的途径除了通过特异性受体将其转入至胞内溶酶体进行降解外,还能直接由内肽酶(neprilysin, NEP)和胰岛素降解酶(insulin-degrading enzyme, IDE)介导通过蛋白水解降解途径将其清除^[65]。有实验探究的结果显示,ApoE 在 NEP 和 IDE 对 A β 的降解过程中起促进作用,且不同亚型的 ApoE 作用的强弱程度不同,目前已明确 ApoE 3 产生的作用比 ApoE 4 作用更为强烈^[66]。此外,有研究进一步发现,ApoE 对 A β 水解的促进作用与 ApoE 自身的酯化状态密切相关。实验中通过激活肝 X 受体(liver X receptor, LXR),促进 ApoE 的酯化,其对 A β 的水解作用能够明显加强^[65]。

ApoE 不仅与 A β 在脑内的生成有关,而且还作用于 A β 的清除过程,在整个 A β 的代谢过程中起着至关重要的作用,且不同亚型的 ApoE 对于 A β 代谢的影响具有显著的差异性。

虽然其具体的机制尚有许多不明之处,但毋庸置疑的是 ApoE 与 A β 的相互作用启发了人们以新的视角探讨 AD 发病的本质。希望今后能有更多的研究来阐释并确定 AD 的发病机制,为预防和治疗 AD 提供有力的理论依据,造福于 AD 患者及其家属。

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