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·综述·

β– 位点淀粉样前体蛋白剪切酶 –1 在阿尔茨海默病中的表达、作用及其抑制剂

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[摘　要]　阿尔茨海默病(Alzheimer's disease，AD)是引起老年性痴呆的常见神经退行性疾病，主要临床表现为学习记忆功能减退、认知功能障碍，最终导致患者死亡。β-淀粉样蛋白(beta-amyloid protein，Aβ)是目前公认的AD发病的中心环节，由淀粉样前体蛋白(amyloid precursor protein，APP)经β-位点APP剪切酶-1(β-site APP cleavage enzyme-1，BACE-1)和γ-分泌酶降解生成，BACE-1介导了APP的第1次剪切，是Aβ产生的关键酶和限速酶，故BACE-1的活性决定其剪切产物Aβ的产生。

[关键词]　阿尔茨海默病；β淀粉样蛋白；淀粉样前体蛋白；β-位点APP剪切酶-1

Expression and role of β-site amyloid precursor protein cleavage enzyme-1 in Alzheimer's disease and its inhibitor

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Abstract　Alzheimer's disease (AD) is a common neurodegenerative disease leading to dementia. Its main clinical manifestations are severe memory loss as well as cognitive and behavioral impairments, which eventually leads to death. Beta-amyloid protein (Aβ) is identified as a critical factor involved in the pathogenesis of AD. It is derived from amyloid precursor protein (APP) through the action of beta-site APP cleavage enzyme-1 (BACE-1) and γ-secretase. BACE-1 is beta-secretase 1. It mediates the first cut of APP and is the key and speed-limiting enzyme during the process of Aβ generation.

Keywords　Alzheimer's disease; β-amyloid protein; amyloid precursor protein; β-site APP cleavage enzyme-1

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人口老龄化是发展中国家包括我国面临的社会发展趋势。发达国家的疾病流行病学与临床资料[1]显示：年龄相关性神经退行性疾病将是老龄化社会的严峻医疗卫生与大众保健难题，绝大多数(95%以上)的AD患者属于散发性病例，年龄(65岁以上)是其最主要的危险因素。阿尔茨海默病(Alzheimer's disease，AD)是引起老年性痴呆的常见神经退行性疾病，占老年性痴呆病的60%~70%，主要临床表现为记忆力严重衰退、认知及行为能力障碍，最终导致患者死亡[2-3]。据国际阿尔茨海默病协会[4]最新统计，截至2016年，全球有近4 700万早老性痴呆症患者(我国约950万)，预计到2050年，这一数字将增加到1.31亿，随着全球老龄化加剧，AD患病率恐将达到流行病比例。AD已成为当今老年医学面临的最为严峻的课题之一。因此，研究AD的发病机制，探索防治AD的干预靶点，是神经科学的工作重点。AD病因复杂，目前有多种假说，其中胆碱能学说和淀粉样蛋白级联假说[4-6]备受学者们关注。β-淀粉样蛋白(beta-amyloid protein，Aβ)是目前公认的AD发病的中心环节，其致病片断主要包括$A\beta_{40}$和$A\beta_{42}$两种，由淀粉样前体蛋白(amyloid precursor protein，APP)经淀粉样代谢途径产生，其不同程度的聚集，对神经元造成毒性作用，以可溶性的Aβ寡聚体的毒性最强，能够促进AD的发生、发展[7-9]。最近研究[6]表明：铁能够选择性地通过降低$A\beta_{42}/A\beta_{40}$比值来增加$A\beta_{40}$的生成并抑制淀粉样蛋白的沉积，铁可作为降低AD中$A\beta_{42}/A\beta_{40}$比值和$A\beta_{42}$沉积的新方法。β-位点APP剪切酶-1(β-site APP cleavage enzyme-1，BACE-1)与γ-分泌酶参与APP降解为Aβ的过程，BACE-1的酶切点位于Aβ的N端met671和asp672之间，APP经切割后产生β-APP和C99肽，C99肽再经γ-分泌酶作用产生$A\beta_{40}$和$A\beta_{42}$两种亚型[10]，它们的异常聚集引发AD。

1 BACE-1 在 AD 脑中的表达、分布

BACE-1 mRNA在胰腺组织中表达最高，其次为脑组织和一些外周组织，BACE-1表达在神经元，定位于突触前海马苔藓纤维末端[11]，在脑组织中的活性最强。BACE-1介导了APP的第1次剪切，是Aβ产生的关键酶和限速酶[12]，故BACE-1的活性决定其剪切产物Aβ的产生。起初，研究者[13]对AD患者进行了分子遗传学分析，未发现其遗传连锁、致病性突变或与BACE-1的遗传相关性，认为BACE-1与AD的病因无关，BACE-1与AD脑内Aβ产生和淀粉样斑形成没有必然联系。但最近研究[14-16]发现两者之间密切相关：与正常小鼠比较，AD模型小鼠脑的皮质和海马内BACE-1表达和活性均明显上调且与年龄呈正相关[14-15]，AD模型小鼠血脑屏障BACE-1表达也上调[16]。BACE-1和γ-分泌酶在AD脑组织中的表达均上调且BACE-1蛋白表达水平是正常组的2.7倍[17]。BACE-1酶活性和蛋白表达水平在AD脑额叶皮质分别增加63%和14%，颞叶皮质分别增加了13%和15%[18]。在AD患者和AD模型小鼠脑皮质、海马内，BACE-1定位于淀粉样斑块周围的神经元内且BACE-1表达上调先于淀粉样斑形成与神经元丢失[19]。表明AD患者脑BACE-1与Aβ过量产生密切相关，为AD的早期预防、治疗以及延缓AD病程提供了一个新的方向。

2 BACE-1在AD脑神经突起失营养性病变中的作用

神经突起失营养性变(dystrophic neuritis，DN)是指神经元树突或轴突呈现退行性改变的病理过程，表现为突起肿胀、树突棘丢失、曲度变形及树突茎变细、轴突葡萄样肿胀和玫瑰花瓣样芽生，其内可见溶酶体、线粒体等膜性细胞器。有研究者[20]对APP/PS1双转基因AD模型小鼠脑海马齿状回21 507个树突棘的形态、密度进行分析，发现海马齿状回分子层神经元呈现“神经突起失营养性变”表现。DN常常在AD中出现，并参与胞外老年斑的构成[21]。研究者[21]在对不同年龄AD转基因小鼠、AD患者及老年恒河猴脑内老年斑的形成机制进行研究时发现：DN并不是像传统观点认为的由老年斑的主要构成成分Aβ毒性作用所致。恰恰相反，从淀粉斑的动态发展过程中发现，早期可见Aβ产生相关的分子(如BACE-1，APP和PS1)在肿胀的神经轴突内表达上调且已证实这部分肿胀的神经突起为轴突成分，随着这些轴突的芽生、肿胀和分支，逐渐有少量的Aβ分泌到轴突外并沉积。当这些失营养性神经轴突进一步芽生长大形成典型玫瑰花瓣样外观时，花瓣中心已堆积大量致密的Aβ阳性产物，即典型老年斑形成。结果提示AD时淀粉斑的形成最先开始于轴突末梢，并随着DN病理改变的进一步加重而逐渐增加[22]；进一步研究发现：普通C57B/6J小鼠给予匹鲁卡品处理后，海马CA1及颞叶一过性出现BACE-1阳性的DN，而PBS对照组未见这种改变。3xTg-AD转基因小鼠经匹鲁卡品处理后也观察到海马及颞叶内有少量BACE-1阳性DN簇及Aβ阳性斑块的出现(9月龄

开始出现)，但同年龄转基因小鼠对照组(即未给予匹鲁卡品处理)脑内则没有以上现象出现。这些结果显示DN病变可能促进了Aβ的形成，它在AD的发病过程中处于比Aβ形成为淀粉斑更早的阶段。基于此，DN可能在AD病中Aβ蓄积及淀粉斑形成的发生发展中起诱导作用，而淀粉斑的形成将进一步加剧DN的形成[23-24]，最终形成恶性循环。

全基因组关联单核苷酸多态性的研究确定了与AD相关的Contactin-2蛋白由CNTN2基因编码[25]。Contactin-2是一种可溶性的细胞黏附蛋白，最初表达在神经元轴突和突触膜上[26-27]。它属于免疫球蛋白超家族，并且有6个成员(Contactin-1~6)[27]。Contactin-2表达于海马锥体细胞、小脑颗粒细胞、有髓神经纤维的近节区[28]额叶和颞叶[26,29]。Contactin-2是一种多功能蛋白，在发育过程中能够促进轴突生长并介导轴突生长方向[30]、神经纤维的成束化和轴突的髓鞘化[31]。

研究[32-35]表明：突触丢失和功能障碍是AD病理过程的早期事件。与正常老年人相比，Contactin-2在AD病理过程中发生变化，AD患者脑组织海马、颞叶皮质内老年斑周围的Contactin-2蛋白质减少，在脑脊液中Contactin-2蛋白减少，且与APP和BACE-1发生相互作用[36]。Contactin-2与tau蛋白、BACE-1和神经颗粒素(neurogranin)之间呈正相关，Contactin-2与APP的结合增强了胞质溶液中APP胞内结构域的产生，同时导致Aβ的生成[37-38]。在死后的AD患者脑组织中较高的BACE-1活性伴随着较低水平的Contactin-2[29]。因此，Contactin-2与BACE-1和APP蛋白之间的相互作用可能影响Aβ的产生和淀粉样斑块的形成。

3 以 BACE-1 介导的 Aβ 减少为 AD 治疗的靶点

抑制BACE-1活性是治疗AD最有效的方法之一。研究[39]表明小鼠BACE-1基因缺失使Aβ的产生停止并改善动物认知功能，且有研究[40]发现：过度表达人类APP和PS1的5×FAD转基因小鼠存在明显的神经元死亡，BACE-1基因敲除不仅仅使Aβ淀粉样蛋白不能产生，且Aβ淀粉样蛋白沉积也被阻断，在淀粉样蛋白变性最严重的5×FAD转基因小鼠脑皮质显示没有神经元丢失。由于人类APP的673位点发生罕见突变，使得突变的APP不能完全被BACE-1剪切为Aβ，细胞外Aβ的产生减少40%，Aβ的聚集倾向显著降低，AD发生的风险显著降低，老年人的认知功能障碍得到改善[41-42]，这意味着APP的673位点对BACE-1介导的APP淀粉样变发生过程至关重要。再次，有研究[11,43]在突触活跃区附近发现了含有BACE-1的小囊泡。抑制BACE-1可直接降低Aβ介导的突触传递的损伤[43-45]。最后，小鼠BACE-1的缺失似乎对其生长或整体功能有轻微影响[43,46]。基于BACE-1，γ-分泌酶作用于APP生成的Aβ在AD的发生、发展中的重要生理作用，策略之一是直接抑制γ-分泌酶，减少Aβ生成。由于γ-分泌酶[47-48]不可或缺的作用，现已被认为是更具挑战性的，研究者把重点放在BACE-1抑制剂的开发上，该抑制剂在Aβ生成过程中作用于γ-分泌酶的上游分子。因此，BACE-1被认为是治疗AD的靶点。研究[49]发现：天然植物芦丁(IC_{50}：3.8 nmol/L)对BACE-1的抑制作用最强，其次是马鞭草苷(IC_{50}：6.3 nmol/L)和橄榄果提取物(IC_{50}：18 ng)，同时BACE-1抑制剂分子量从1 100 D减少到小于600 D，也更易于穿透细胞膜发挥良好效果。三嗪酮衍生物对BACE-1和GSK-3β有双抑制作用[50]。目前影响脑内BACE-1的表达/活性来降低Aβ的产生的物质，根据其来源，主要有以下几类：1)瘦素(leptin，LP)是一种由脂肪组织分泌的蛋白质类激素，机体能够自身合成，能够降低BACE-1的活性和表达水平，减少Aβ的产生[51]；2)天然药物。姜黄素类化合物的饱和度、碳骨架类型、官能团类型、疏水性等结构特征对BACE-1具有一定的抑制作用[52]；3)某些植物提取物，如二氢杨梅素(dihydromyricetin，DHM)是提取自葡萄科蛇葡萄属的木质藤本植物的一种物质，其活性成分主要为黄酮类化合物。有研究者[53]通过往APP/PS1双转基因AD模型小鼠腹腔注射DHM后发现：皮质、海马内活化的小胶质细胞数目减少，具有神经毒性的M1型小胶质细胞转换成具有神经保护作用的M2型小胶质细胞，增加M2型小胶质细胞对Aβ的清除，脑啡肽酶的表达增加；DHM通过抑制小胶质细胞介导的神经炎症反应，NLRP3炎症小体各组分及IL-1β各等促炎细胞因子的表达下调，降低BACE-1 mRNA表达或抑制其活性，从而改善APP/PS1双转基因AD模型小鼠的学习记忆和认知功能。雷公藤氯内酯醇(tripchlorolide)是雷公藤内酯醇氯化后的产物，过氧化物酶体增殖物激活受体γ(PPARγ)是BACE-1启动子的转录因子结合位点，调节BACE-1活性。雷公藤氯内酯醇增强核PPARγ与BACE-1启动子的结合，进而抑制BACE-1的转录和翻译，抑制BACE-1的活性，最终减弱Aβ的生成[54]。

综上所述，AD患者脑的Aβ过量产生和淀粉

样斑形成与BACE-1调节有密切的关系，BACE-1表达和活性也与许多AD的高危因素密切相关。以BACE-1介导的Aβ减少为AD治疗的靶点。尽管近年来，BACE-1研究领域取得了一些成果，但仍然存在许多问题，如BACE-1抑制剂不能广泛应用于临床AD患者的治疗，理想的小分子BACE-1抑制剂尚需进一步探索。

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