·综述·

β-淀粉样蛋白被动免疫治疗阿尔茨海默病的现状与策略

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【摘要】 β-淀粉样蛋白(Aβ)既是阿尔茨海默病发病机制中的重要病因,又是治疗的关键靶点之一。采取被动免疫途径清除脑组织Aβ是目前颇受临床关注的治疗策略。然而,各项临床试验至今尚未获得一致性的结论。对其研究现状的分析表明,Aβ被动免疫治疗失败的原因可能与Aβ-IgG免疫复合物所固有的糖基化修饰有关。因此,改良Aβ-IgG Fc片段N-糖基化修饰、采取促炎症反应-抗炎症反应序贯给药模式,可能是一种有效的被动免疫治疗策略。

【关键词】 阿尔茨海默病; 淀粉样β肽类; 免疫法,被动; 综述

The situations and strategies of amyloid-β-directed passive immunotherapy for Alzheimer´s disease

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【Abstract】 It is widely believed that amyloid β-protein (Aβ) plays a core role in the pathogenesis of Alzheimer´s disease (AD). Thus Aβ is one of main targets in the therapeutic explorations for AD. Currently, clearance of Aβ by passive immunotherapy is an important strategy for the treatment of AD. However, no consistent conclusions have been obtained from various clinical trails. We summarize the current situations of Aβ-directed passive immunotherapy for AD, and speculate that the failure of Aβ-directed passive immunotherapy for AD may be related to the intrinsic characteristics of Aβ-IgG glycosylation. Therefore, modifications of N-glycosylation on the Fc domain of Aβ-IgG and using a sequential administration mode of proinflammation-antiinflammation may be an effective strategy for passive immunotherapy for AD.

【Key words】 Alzheimer disease; Amyloid beta-peptides; Immunization, passive; Review
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阿尔茨海默病(AD)是老年性痴呆的常见病因,随着人口老龄化的进程其患病率呈急剧上升趋势,目前在我国65岁以上人群中的患病率为3.21%[1],约有6×10^6例患者,预计到2020年,患病人数将突破8×10^6例。在美国全民死因中,阿尔茨海默病位列第6,而在65岁以上人群死因中位居第5,过去的10余年间,美国脑卒中、心脏病和前列腺癌死亡率呈不同程度下降趋势,但阿尔茨海默病死亡率却增加了71%[2]。同样,我国的阿尔茨海默病进展程度亦不容乐观,已经由原来的全民死因第8位跃升至第5位[3],患病人数不断增加,形势十分严峻。然而,现有治疗方法仍停留在对症治疗层面,疾病修饰药物匮乏,亟待建立针对病因的有效预防措施和治疗方案。目前研究认为,神经元胞外β-淀粉样蛋白(Aβ)沉积和胞内过磷酸化tau蛋白形成的神经原纤维缠结(NFTs)是阿尔茨海默病的主要病理学特征,其中,Aβ级联学说是主要的机制学说,也是重要的治疗靶点。然而,在轻度认知损害(MCI)、阿尔茨海默病临床前期或临床期的机制研究中可能会混

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杂其他病因，因此美国国家老龄化研究所-阿尔茨海默病学会（NIA-AA）2011年公布的诊断标准指出，在所有的阿尔茨海默病生物学标志物中Aβ相关生物学标志物居重要地位，而在2018年颁布的新的研究框架中，不仅确立了由Aβ定义的阿尔茨海默病连续体，而且进一步强调Aβ作为必需的生物学标志物在明确诊断中的重要性[4]。Aβ是神经元β-淀粉样前体蛋白（APP）经β-和γ-分泌酶水解所产生的包含39～43个氨基酸的多肽，人体内最为常见的Aβ类型是$Aβ_{40}$和$Aβ_{42}$，以$Aβ_{42}$神经毒性最强，易聚集，是阿尔茨海默病的核心致病物质[5]；$Aβ_{42}$单体可自发聚集形成可溶性寡聚体，然后进一步聚集形成Aβ纤维沉积于神经元胞外，引起神经元突触功能障碍、tau蛋白过磷酸化并继发炎症反应，导致神经元死亡，最终引起痴呆[6-7]。由于可溶性Aβ寡聚体是Aβ代谢过程中产生的最具神经毒性的代谢产物[6-7]，因此，降低脑组织Aβ表达水平业已成为目前预防和治疗阿尔茨海默病的重要策略，尤其是下调可溶性Aβ寡聚体的表达是取得治疗效果的关键环节[8]。

一、抗β-淀粉样蛋白自身抗体

阿尔茨海默病和健康人体内均存在抗Aβ自身抗体[9]。许多学者最初均认为，抗Aβ自身抗体与阿尔茨海默病的发生有关，因此针对患者外周血抗Aβ自身抗体相继开展了大量临床研究，但这些试验并未获得预期的一致性结果[10-17]。其中有多数研究证实阿尔茨海默病患者血清游离抗Aβ自身抗体水平显著低于同龄健康人群，提示抗Aβ自身抗体水平降低可能是导致脑组织Aβ清除减少、促进阿尔茨海默病发生与发展的原因[10-14]；然而，另外一些研究结论则完全相反，指出阿尔茨海默病患者血清抗Aβ自身抗体水平与同龄健康人群并无显著差异，与痴呆的发生无关联性[15-17]。造成这种研究结论完全相悖的原因，可能与不同临床研究所采用的检测方法和所检测的抗体的形式不同有关，因为抗Aβ自身抗体在外周血中既可以游离状态存在亦可以抗原-抗体复合物的形式存在，故针对不同状态的抗Aβ自身抗体进行检测，自然无法得出一致性的结论。在一项队列研究中，通过酶联免疫吸附试验（ELISA）检测阿尔茨海默病患者血清抗Aβ自身抗体的表达变化，其结果显示，阿尔茨海默病组患者表达水平高于正常对照组，且抗体滴度与认知功能呈正相关关系[18]。但是针对外周血中抗Aβ自身抗体的检测结果可受多种因素的影响，例如抗原片段、病程等，采用不同的Aβ抗原片段检测其相对应抗体，结果存在显著差异：Gruden等[19]采用$Aβ_{25～35}$寡聚体作为抗原，对阿尔茨海默病患者血清中抗$Aβ_{25～35}$寡聚体自身抗体的表达变化进行检测，显示阿尔茨海默病组的表达显著高于正常对照者；但王延江等[20]采ELISA法检测不同的抗原片段，发现血清抗$Aβ_{19～30}$和$Aβ_{31～42}$自身抗体水平低于正常对照者，而抗$Aβ_{1～12}$自身抗体占所有抗Aβ自身抗体的比例均高于正常对照者。此外，王延江等[20]还发现，阿尔茨海默病患者的外周血抗Aβ自身抗体水平呈增龄性变化，即外周血中抗Aβ自身抗体水平随着患者年龄的增长呈现逐渐升高之趋势，但其总体水平和针对不同表位的抗体水平均低于正常对照组。抗Aβ自身抗体水平升高可能还与痴呆程度的加重有关，Gruden等[19]发现，轻至中度痴呆患者血清抗$Aβ_{25～35}$自身抗体表达上调，而中至重度痴呆患者表达下调。

对血清结合或游离抗Aβ自身抗体表达变化的研究发现，阿尔茨海默病患者血清抗Aβ自身抗体总水平[18,21]，以及血清和脑脊液Aβ-IgG免疫复合物水平均高于正常对照者[22]，而血清游离抗Aβ自身抗体水平则低于正常对照者，尤其在65岁以上的患者中这种差异更为明显[23]。阿尔茨海默病患者外周血游离抗Aβ自身抗体水平降低的原因，可能是由于其与Aβ抗原结合而消耗过多所致，从而形成大量的Aβ-IgG免疫复合物，使外周血中Aβ-IgG免疫复合物水平升高；当外周血游离抗Aβ自身抗体水平降低，脑组织Aβ清除率下降，继发小胶质细胞激活，即可使阿尔茨海默病发生与发展。此外，来自治疗方面的证据也支持升高血清游离抗Aβ自身抗体对阿尔茨海默病具有预防作用。Sha等[24]尝试通过输注健康年轻人（18～30岁）血浆的方法以改善轻至中度阿尔茨海默病患者的认知功能和日常生活活动能力（1次/周），持续治疗4周后，与安慰剂组相比，阿尔茨海默病组患者认知功能和日常生活活动能力出现改善趋势[24]，可能与健康年轻人血浆中游离抗Aβ自身抗体水平较高有关，该项试验结果发表在2019年*JAMA Neurol*。对阿尔茨海默病小鼠模型的观察发现，天然抗Aβ寡聚体抗体的疗效明显优于静脉注射免疫球蛋白（IVIg）[25]，表明外周血游离抗Aβ自身抗体水平对脑组织Aβ清除率具有重要影响。

总而言之，外周血游离抗Aβ自身抗体作为机体对Aβ自然应答的产物，在阿尔茨海默病的发生与发展过程中很可能扮演重要保护角色，通过提高外周

血游离抗Aβ自身抗体水平以清除脑组织中Aβ、减少沉积，今后有望成为具有应用前景的治疗途径。

二、β-淀粉样蛋白被动免疫治疗现状

过去20余年间，不断有学者尝试通过免疫治疗途径清除脑组织中的Aβ，包括主动免疫（Aβ疫苗接种）[26]和被动免疫（直接静脉注射Aβ-IgG）[27-28]。然而，在动物模型上观察到的被动免疫治疗效果并未在临床试验中得到验证[29-31]，主动免疫治疗的临床试验亦因频繁发生的严重不良事件而被终止[32]。分析存在的问题，可能与以下原因有关：（1）治疗时机过晚，受试者在接受被动免疫治疗时，中枢神经系统退行性变已经处于疾病晚期阶段，而针对Aβ的免疫治疗，唯有在认知损害的早期阶段实施才能够更好地发挥延缓痴呆进展的作用[29]。（2）诊断缺乏精准性，绝大多数受试者的诊断都是采用阿尔茨海默病临床诊断标准，极少通过生物学标志物[如脑脊液Aβ或^{11}C-匹兹堡复合物B（^{11}C-PIB）PET]检测获得精确诊断，因此许多受试者很可能并非真正的阿尔茨海默病患者，其脑组织中甚至可能不存在试验药物作用的靶点——Aβ蛋白。（3）抗Aβ单克隆抗体针对的抗原表位单一且多为线性表位，在体内倾向于与Aβ单体结合，故对可溶性Aβ寡聚体和Aβ纤维的清除作用十分有限。此外，一旦抗原表位破坏或隐藏，抗体效能则难以发挥，尤其是针对Aβ中间区域的抗体（如Solanezumab）和针对羧基端（C端）区域表位的抗体（如Gantenerumab）更易受空间隐藏的影响[33]。而抗Aβ多克隆抗体（如静脉注射免疫球蛋白）除具有线性表位外，还具有构象表位，可以与Aβ谱中的多种聚集形式相结合[34]，理论上较抗Aβ单克隆抗体对Aβ的清除作用更强[35]，但是静脉注射免疫球蛋白中所含天然Aβ-IgG的生物活性受限于其自身的固有糖基化修饰特点。

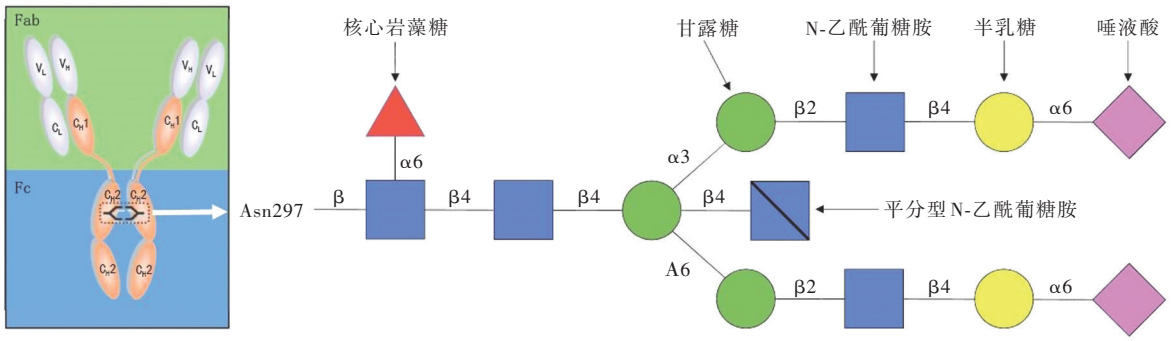
三、静脉注射免疫球蛋白中Aβ-IgG的固有糖基化修饰

人类免疫球蛋白有5种类型，即IgM、IgD、IgG、IgA和IgE，其中，IgG又进一步分为IgG1～4共4种亚型[36]。IgG是血清中含量最高的免疫球蛋白，由抗原结合片段Fab和可结晶片段Fc组成，Fc片段第297位天冬氨酸的N-糖基化位点在抗体效能中起重要作用，包括抗体依赖性细胞毒性作用（ADCC）和补体依赖性细胞毒性作用（CDC）[37]。静脉注射免疫球蛋白属于多克隆抗体生物制品，经血浆分离纯化制备而成，其中95%以上的成分均为IgG，主要为IgG1和IgG2（>95%），其中的天然Aβ-IgG免疫复合物倾向于与神经毒性最强的可溶性Aβ寡聚体相结合[38-39]，发挥抗体依赖性细胞毒性作用和补体依赖性细胞毒性作用。对阿尔茨海默病动物模型的观察显示，天然Aβ-IgG较静脉注射免疫球蛋白具有更佳的疗效[25]。同时，静脉注射免疫球蛋白还具有炎症调节作用[40]，但临床试验中并未显示出持久改善认知功能的作用，不过经静脉注射免疫球蛋白治疗的阿尔茨海默病患者血浆$A\beta_{42}$水平显著低于经安慰剂治疗者[41]，静脉注射免疫球蛋白后第1年，阿尔茨海默病源性轻度认知损害患者的认知功能有所改善，并可延缓阿尔茨海默病的进程，但这种治疗效果在治疗后第2年即明显减弱[42]。

几乎所有临床试验均证实，静脉注射免疫球蛋白对改善阿尔茨海默病患者认知功能无效[41,43-44]，除外与治疗时机过晚有关，可能还与Aβ-IgG免疫复合物的固有糖基化结构修饰有关。有学者采用亲和层析法分离获得经静脉注射免疫球蛋白中的天然Aβ-IgG免疫复合物，并对Aβ-IgG亚型和Fc片段N-糖基化的修饰特点进行分析，结果显示，Aβ-IgG以IgG1和IgG2为主；Fc片段N-糖基化修饰以核心岩藻糖形式为主，而半乳糖和唾液酸的修饰水平较低[45]，甚至缺乏α-2,6连接的唾液酸[46]。临床研究表明，阿尔茨海默病患者外周血复合型半乳糖糖基化和唾液酸化的IgG水平低于正常对照者[47]；体外实验表明，唾液酸化修饰对血-脑屏障（BBB）药代动力学具有重要影响，表面唾液酸化IgG抗体可通过抑制自身外排作用而促进抗体透过血-脑屏障[48]。因此推测，静脉注射免疫球蛋白治疗失败的原因可能与其中天然Aβ-IgG免疫复合物的固有糖基化修饰有关。

四、Aβ-IgG N-糖基化修饰效应

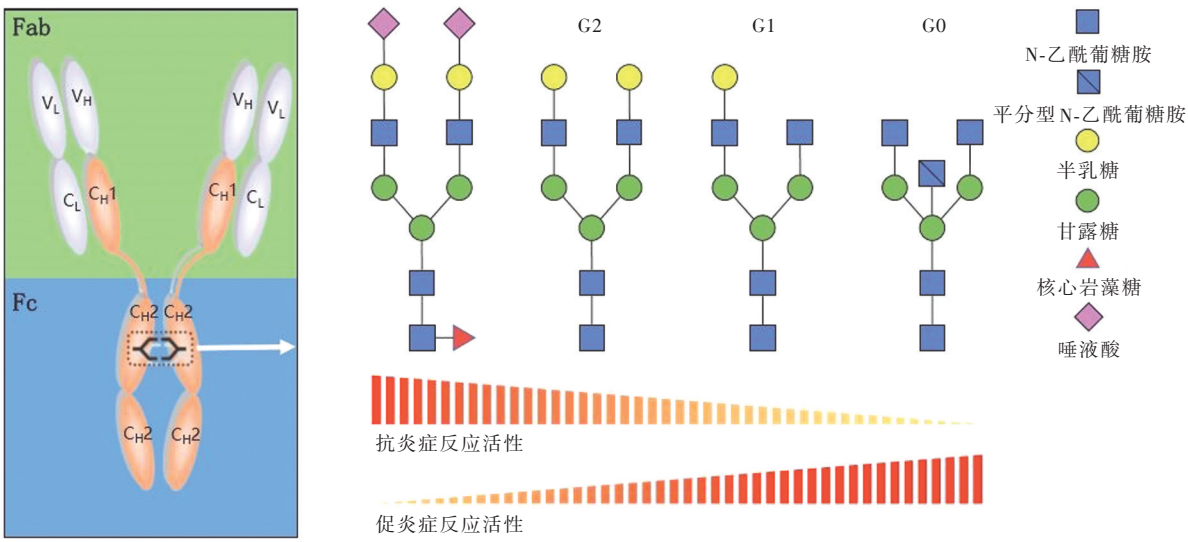
目前普遍认为，糖基化是蛋白质翻译后的重要修饰，受宿主细胞酶催化机制、高尔基体内转运时间、环境因素和所获得的活化形式的核苷酸糖的影响。IgG是抗体的核心成分，是具有糖基化修饰的重要血清糖蛋白，糖基化修饰结构可通过影响IgG与Fc受体或补体C1q的结合，而影响IgG的生物活性和功能。IgG的Fc片段C_H2区域有一共同核心结构，与第297位氨基酸位点结合形成氨基端（N端）连接的多聚糖结构，即由N-乙酰葡糖胺分出两条等长的分支，其分支上连接甘露糖，构成核心结构，该核心结构外连接核心岩藻糖、平分型N-乙酰葡糖



V，可变区；C，恒定区；L，轻链；H，重链

图1 人源IgG-Fc片段N-糖基化修饰结构

Figure 1 N-glycosylation modified structure of human IgG Fc segment.



V，可变区；C，恒定区；L，轻链；H，重链

图2 人源IgG-Fc片段N-糖基化修饰结构及其效应

Figure 2 N-glycosylation modified structure and effects of human IgG Fc segment.

胺、半乳糖和唾液酸（图1）[36]，根据N端半乳糖残基数目可以将糖基化修饰命名为G0、G1和G2。IgG的Fc片段通过糖基化修饰区域与受体结合，从而发挥效应子功能，人类效应子受体包括FcγRs（FcγRⅠ、FcγRⅡa、FcγRⅡb、FcγRⅢa和FcγRⅢb）、新生儿Fc受体（FcRn）和补体C1q[36]。IgG1的Fc片段N-糖基化修饰位点通常为免疫细胞（如小胶质细胞）Fc受体与补体C1q的结合位点，分别发挥抗体依赖性细胞毒性作用和补体依赖性细胞毒性作用。Huang等[49]以及Kubota等[50]采用化学酶法对N-糖基化修饰进行改良，以提高抗体与Fc受体和补体C1q的结合能力，以增强抗体依赖性细胞毒性作用和补体依赖性细胞毒性作用。在IgG的糖基化修饰中，岩藻糖、半乳糖和唾液酸是影响抗体生物活性（促炎症反应活性和抗炎症反应活性）的关键单糖（图2）。核心岩藻糖修饰可以降低抗体与FcγRⅢa的结合能力，使抗体依赖性细胞毒性效应减弱，此作用不依赖于唾液酸修饰状态[51-52]；而唾液酸修饰对抗体依赖性细胞毒性作用的影响却依赖于核心岩藻糖修饰。在核心岩藻糖修饰的状态下，唾液酸可显著降低抗体依赖性细胞毒性作用，而在去核心岩藻糖修饰的状态下，唾液酸对该效应并无影响[51]，但是唾液酸修饰和半乳糖修饰可提高抗体与补体C1q的结合能力，增强补体依赖性细胞毒性作用[52-53]。在抗炎症反应方面，唾液酸尤其是α-2,6连接的唾液酸对IgG发挥抗炎症作用至关重要[54-55]，但该作用依

赖于核心岩藻糖的修饰。唾液酸化的Fc片段主要通过树突状细胞特异性抗原呈递(DC-SIGN)途径发挥抗炎症作用[56-57],促进辅助性T细胞(Th)因子白细胞介素-33(IL-33)的产生,引起分泌IL-4的嗜碱性粒细胞数目增加,促进巨噬细胞表面的抑制性Fc受体FcγRⅡb的增加,实现抗炎症作用[56]。

五、Aβ-IgG被动免疫治疗策略

如前所述,基于核心岩藻糖和唾液酸对免疫球蛋白生物活性的限制,推测静脉注射免疫球蛋白治疗阿尔茨海默病的临床试验并未充分利用Aβ-IgG的促炎症反应或抗炎症反应作用。理论上讲,用于静脉注射的免疫球蛋白中所含的天然Aβ-IgG,其Fc片段经N-糖基化修饰后活性即受到影响,Fc片段经去唾液酸/去核心岩藻糖后其Aβ-IgG则可发挥更强的促炎症反应作用。但是阿尔茨海默病被动免疫治疗的临床试验更多关注的是IgG通过促炎症反应清除Aβ的能力,事实上,被动免疫治疗是一把双刃剑,在清除脑组织中Aβ的同时亦可激活小胶质细胞,由小胶质细胞释放的细胞因子可进一步造成神经元损伤,形成持久性的炎症环境,持续损伤神经元。阿尔茨海默病被动免疫治疗相关临床试验结果显示,通过IgG促炎症作用清除由Aβ所继发的中枢性免疫损伤并未得到干预,这可能是试验失败的重要原因。因此笔者认为,未来研究可以利用糖基化改良方法以Fc片段去唾液酸/去核心岩藻糖形式的Aβ-IgG,增强免疫复合物的促炎症反应活性,通过序贯给药模式,再以抗炎症活性如Fc片段唾液酸/核心岩藻糖形式的Aβ-IgG,即先予促炎症活性较强的Aβ-IgG,促进神经毒性Aβ的清除,然后再以抗炎症活性较强的Aβ-IgG治疗,以减轻继发性炎症反应和中枢性免疫损伤,为依靠Aβ精确诊断的阿尔茨海默病患者争取最佳的治疗效果。

利益冲突 无

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Spine Summit 2020: 36th Annual Meeting of the Section on Disorders of the Spine and Peripheral Nerves

Time: March 5–8, 2020

Venue: Lasvegas, US

Website: https://www.cns.org/

Spine Summit 2020, the 36th Annual Meeting of the Section on Disorders of the Spine and Peripheral Nerves will take place in Lasvegas, US on March 5–8, 2020.

Meeting highlights included eight special courses, special dinner for young neurosurgeons, hands-on cadaver course, Beer and Wine Happy Hour Debates: Orthopedic vs. Neurosurgeon, oral presentations, Charles Kuntz Scholarships, Mayfield Awards, and J.A. N.E. Award and Thursday APRN/PA Seminar offered complimentary for PAs and RNs who register for Spine Summit 2020.

This meeting also included two new courses. One was "Introduction to Spinal Coding: From Decompression to Deformity (Thursday)" and the other was "Spine Summit Grand Rounds: Difficult Cases—The Decision-Making Dilemma (Saturday)".