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自身抗体介导的神经免疫性脑疾病及精准诊疗

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摘要: 抗N-甲基-D-天冬氨酸(简称NMDA)受体脑炎是一种由自身抗体穿透血脑屏障, 靶向神经细胞膜蛋白导致其功能障碍的神经自身免疫性疾病, 常表现出认知障碍、癫痫、精神行为异常等症状。该病以患者的脑脊液及血清中检出抗NMDA受体自身抗体为关键生物标志物。本文系统回顾了抗NMDA受体脑炎的临床发现历程, 重点阐述自身抗体介导疾病发生发展的致病机制, 概述靶向性治疗研究的新进展, 展望神经与免疫的交互研究将成为连接临床神经病学及基础神经科学的前沿交叉领域。

关键词: 自身抗体; NMDA受体; 发病机制; 精准诊疗

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Pathogenesis and precision therapy in autoantibody-mediated neuroimmune brain disorders

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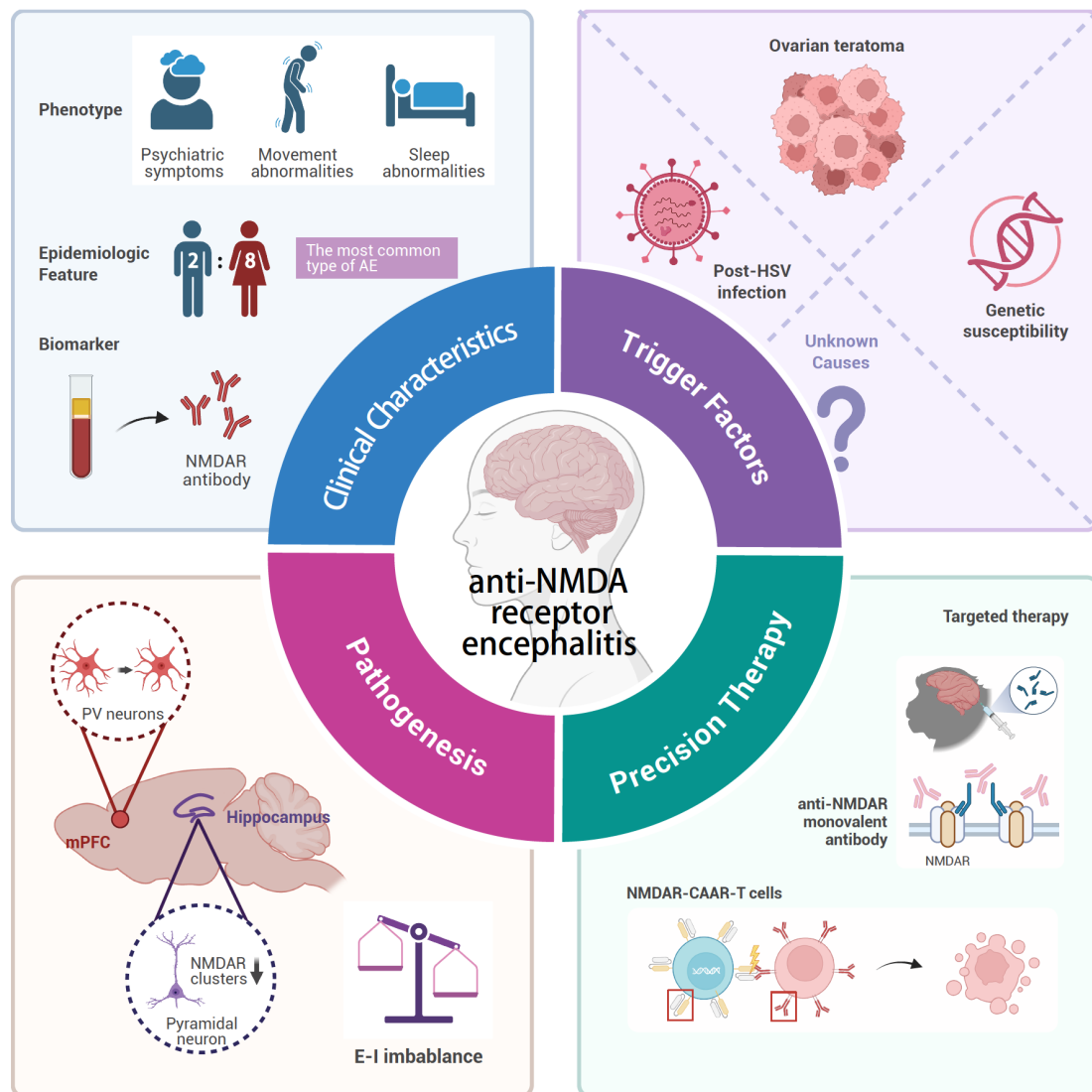
Abstract: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune neurological disorder characterized by pathogenic autoantibodies that cross the blood-brain barrier and target NMDA receptors on the neuronal cell surface. Clinically, patients present with a range of neuropsychiatric symptoms, including cognitive dysfunction, seizures, and prominent psychiatric and behavioral abnormalities. The detection of anti-NMDA receptor autoantibodies in cerebrospinal fluid and serum serves as the primary diagnostic biomarker. This review summarizes the clinical identification and discovery of anti-NMDA receptor encephalitis. Although anti-NMDA receptor encephalitis was initially recognized as an atypical neuropsychiatric disorder, its autoimmune etiology was subsequently established through multiple complementary approaches, including brain tissue immunostaining, neuronal labeling, and cell-based assays, ultimately effectively identifying NMDA receptors as the specific target antigen. Regarding clinical management, early first-line immunotherapy combined with tumor resection improves prognosis, while the initiation of second-line immunotherapy

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in patients with an inadequate response to first-line treatment can further reduce the recurrence. Furthermore, we highlight the pathological and neuronal mechanisms underlying the initiation and progression of anti-NMDA receptor encephalitis. Various triggering factors have been implicated in disrupting immune tolerance and promoting the production of pathogenic autoantibodies, including tumor-associated immune responses and infection-induced immune dysregulation. Both *in vitro* and *in vivo* evidence supports the central pathogenic role of anti-NMDA receptor autoantibodies. These antibodies induce NMDA receptor cross-linking and internalization, disrupt excitatory synaptic transmission, and impair neural network function, thereby contributing to the diverse clinical manifestations observed in patients. Finally, we discuss recent advances in precision therapies, including neutralizing antibodies that competitively inhibit autoantibody function, as well as innovative cellular therapies utilizing chimeric autoantibody receptor (CAAR) T cells to selectively eliminate the B cells expressing pathological antibodies. We anticipate that the interdisciplinary research on the nervous and immune systems will bridge the gap between clinical neurology and fundamental neuroscience, ultimately reshaping clinical treatment strategies for antibody-mediated neurological diseases.



Key words: autoantibody; NMDA receptor; pathogenesis; precision diagnosis and therapy

人类大脑是由数千亿个神经元及其突触构成的复杂网络,离子通道在其中承担着信号传递的关键功能。当自身抗体直接攻击神经元膜表面的离子通道并导致其功能障碍时,其介导的调控学习、记忆和情感神经环路也将会受到干扰,进而引发中枢神经系统炎症性疾病,称为自身免疫性脑炎。自身免

疫性脑炎于2018年被纳入我国首批罕见病名录,全球发病率约为十万分之一^[1,2]。迄今为止,研究人员已鉴定出超过25种神经元膜蛋白及相关蛋白的致病性抗体^[3]。例如,靶向N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体的抗体,常导致弥漫性脑炎综合征;靶向富亮氨酸胶质瘤失活蛋白1

(leucine-rich glioma inactivated protein 1, LGI1)的抗体,常引发表现为面-臂肌张力障碍发作的边缘性脑炎;靶向 γ -氨基丁酸(γ -aminobutyric acid, GABA)受体的抗体,则会造成以严重癫痫为主要表型的脑炎。在自身免疫性脑炎的多种亚型中,国内研究数据显示其发病特征与国际趋势一致^[4],抗NMDA受体脑炎最为常见,约占病例总量的54%~80%^[5,6]。《Brain On Fire》是纽约记者Susannah Cahalan根据亲身经历撰写的关于抗NMDA受体脑炎的回忆录。由于早期表现为剧烈的情绪波动、妄想及幻觉,她被误诊为精神分裂症,直至确诊为抗NMDA受体脑炎并接受免疫治疗后,病情才得以缓解。自身免疫性脑炎相关自身抗体的发现,重新定义了我们与免疫系统互作机制的认知边界。本文将抗NMDA受体脑炎为例,概述其发现历史、疾病发病机制、诊疗相关进展,并进一步探讨基于发病机制的自身免疫性脑炎精准治疗策略。

1 抗NMDA受体脑炎概述

1.1 NMDA受体是神经系统重要的谷氨酸门控离子通道

NMDA受体是在中枢神经系统中高表达的一类兴奋性谷氨酸门控的离子通道家族,是调控突触可塑性及学习记忆的“分子开关”,其功能失调与神经和精神疾病密切相关^[7]。功能性的NMDA受体通常组装成包含两种或三种不同亚基的四聚体,即二异四聚体或三异四聚体,均由两个结合甘氨酸的GluN1必需亚基,与两个结合谷氨酸的GluN2(GluN2A-D)亚基或结合甘氨酸的GluN3(GluN3A-B)亚基组成^[8-10]。近期,对成年大鼠大脑皮层和海马体的内源性NMDA受体纯化及结构解析表明,这些调控学习与记忆关键脑区的NMDA受体主要存在三种亚型:三异四聚的GluN1-N2A-N2B受体及二异四聚的GluN1-N2B和GluN1-N2A受体^[11,12]。

体外重组系统与内源纯化解析的NMDA受体结构共同揭示了该受体的组装模式:两个必需的GluN1亚基位于四聚体的外围,而调节性的GluN2或GluN3亚基则占据中心位置。这种外围分布使GluN1亚基的胞外结构域更加暴露于环境中^[8-12]。NMDA受体由四个功能结构域组成,分别是胞外负责变构调节和受体组装的N端结构域(N-terminal domain, NTD)^[13],介导激动剂(神经递质)识别与结合的配

体结合结构域,介导门控开关的跨膜结构域^[14],以及参与胞内信号转导的C端结构域^[15]。

1.2 抗NMDA受体脑炎的发现历史:从靶点鉴定到机制研究

自身免疫性脑炎的发现起源于对一类临床异常综合征患者的观察。这类患者表现出类似副肿瘤性中枢神经系统疾病的精神和神经症状,但未发现恶性肿瘤或针对细胞内抗原的自身抗体,且通常对免疫治疗反应良好^[16]。此外,尽管患者常伴随前驱病毒样症状,但脑脊液及脑组织病理学检测均未发现病毒感染证据^[17]。这一现象提示,这些患者可能携带类似于重症肌无力等疾病中所见的致病性自身抗体^[18,19]。

2007年,Dalmau团队首次系统报道了12名与卵巢畸胎瘤相关的脑炎患者。这些患者主要表现为行为异常、意识水平下降和记忆力减退等精神和神经系统症状。研究通过免疫组化技术证实,患者的脑脊液与大鼠脑切片孵育后,在海马区域呈现出特异性的免疫反应。HEK293细胞转染实验进一步证实,患者血清及脑脊液中存在特异性识别并结合NMDA受体的自身抗体。手术切除肿瘤并联合免疫治疗后,多数患者的症状显著改善甚至完全康复^[20]。这一工作首次明确界定了以NMDA受体为靶点的自身免疫性脑炎这一全新疾病。基于细胞底物的实验(cell based assay, CBA)检测表明,约90%的抗NMDA受体脑炎患者脑脊液或血清抗体的表位位于GluN1-NTD区域^[21,22]。随后,该团队及国内外多个中心的临床观察逐渐描述清晰了这一组患者的临床特征。抗NMDA受体脑炎常见于45岁以下的女性(中位年龄22岁;80%为女性)^[6,23]。约70%的患者在发病前出现头痛或发热等前驱症状^[20,24]。约90%的患者会出现一系列精神症状^[25],包括焦虑、失眠和妄想,常难以与原发性精神疾病区分。随着病情发展,大多数患者会出现癫痫发作、言语输出减少、意识水平下降、运动障碍和自主神经功能障碍。其中,癫痫发作、异常运动、失眠和易怒在儿童中更为常见^[6,26]。

多项体内外研究表明,致病性抗NMDA受体自身抗体是介导抗NMDA受体脑炎核心病理损伤的关键因素,在特定病理生理条件下(如血脑屏障受损、高抗体滴度及特异性表位识别等)对脑炎表型的发生是充分且必要的^[21,27-30]。抗NMDA受体脑炎患者

来源的IgG型自身抗体可特异性诱导神经元突触表面NMDA受体的内吞和密度下降,但不影响神经元存活、突触结构或树突棘数量^[27]。首个被动免疫小鼠模型显示,将患者脑脊液连续14天灌入小鼠脑室后,动物出现进行性记忆缺陷和抑郁样行为,同时突触NMDA受体水平下降。这些表型在灌注停止后的三周内可恢复,且脑组织内未见明显炎症细胞浸润和神经元细胞毒性损伤表现^[30]。此后,研究者通过流式细胞术分选出CD38⁺/CD27⁺抗体分泌细胞和CD38⁺/IgD⁺/CD27⁺记忆B细胞,利用单细胞测序与重组表达技术构建了抗NMDA受体单克隆抗体。这些单抗被证明可直接诱导海马突触NMDA受体内吞并降低NMDA受体电流,说明自身抗体(而非脑脊液其他混杂成分)本身足以发挥致病作用^[31]。

在临床治疗方面,多中心观察性研究显示,早期启动一线免疫治疗(糖皮质激素、静脉注射免疫球蛋白以及血浆置换),并尽可能在合并畸胎瘤患者中实施肿瘤切除,可显著改善临床症状。对一线治疗不佳者及时加用二线免疫治疗(利妥昔单抗、环磷酰胺等靶向B细胞的免疫清除或抑制策略)可进一步降低复发风险。约80%的患者在免疫治疗联合肿瘤切除2年内功能恢复良好^[23]。这为后续抗NMDA受体脑炎的治疗策略奠定了基础。随后,NEOS (anti-NMDAR encephalitis one-year functional status)评分被引入作为抗NMDA受体脑炎1年预后的评估工具^[32]。近年来,前沿研究聚焦于探索更为精准的靶向性治疗策略。例如,基于NMDA受体设计的chimeric autoantibody receptor (CAAR)-T细胞能够特异性清除表达抗NMDA受体自身抗体的记忆B细胞,在小鼠模型中成功耗竭该类B细胞并持续降低抗体水平^[33];新型中和单臂抗体ART5803也在猴脑炎模型中展现出治疗潜力^[34]。综上,抗NMDA受体脑炎从临床诊断到分子机制的研究历程(表1),揭示了患者自身抗体特异性靶向GluN1-NTD并导致神经细胞上NMDA受体功能障碍的核心病理特征。随着表位精确定位、抗体结合模式及精准免疫疗法的迭代发展,未来有望实现更高效、更个体化的治疗,从而缩短治疗周期,改善患者预后并降低复发率。

2 抗NMDA受体脑炎的触发因素和发病机制

抗NMDA受体脑炎的病因复杂,部分与环境因素和遗传易感性相互作用有关。其发病过程可概括

表1 抗NMDA受体脑炎研究历程的重要发现
Table 1 Key achievements of anti-NMDA receptor encephalitis research

年份	发现内容	参考文献
2007	明确NMDA受体作为抗NMDA受体脑炎靶抗原	[20]
2010	抗NMDA受体脑炎自身抗体致病性研究	[27]
2012	GluN1-NTD中的关键抗原决定簇	[22]
2013	多中心临床队列显示早期免疫治疗及肿瘤切除改善预后	[23]
2015	建立首个被动免疫小鼠模型,验证抗体致病性	[30]
2016	抗NMDA受体脑炎单克隆抗体的克隆及致病性验证	[31]
2019	NEOS评分作为抗NMDA受体脑炎1年功能预后评估工具	[32]
2023	CAAR-T细胞疗法选择性清除表达抗NMDA受体的致病B细胞	[33]
2024	揭示自身免疫单克隆抗体结合的抗原表位及致病机制	[35,36]
2025	新型中和抗体ART5803在灵长类动物模型中显示潜在疗效	[34]

为三个关键步骤。首先是触发因素,病毒感染、肿瘤、免疫疾病等诱因能刺激外周免疫系统,诱导抗NMDA受体自身抗体的产生^[20,37]。其次,在免疫激活或炎症状态下,血脑屏障通透性增加^[38-40],记忆B细胞或自身抗体进入大脑。最终,这些特异性自身抗体结合到神经元表面的NMDA受体,引起受体内吞或通道功能障碍^[2,26],改变突触神经传递和可塑性,从而导致认知下降、行为及精神异常等症状。

2.1 诱发因素

抗NMDA受体脑炎最常见的诱因包括肿瘤和病毒感染。年轻女性患者中约50%伴有畸胎瘤^[23]。多项临床研究和大型队列分析表明,早期切除合并的卵巢畸胎瘤可显著促进神经症状改善、功能恢复,并与良好长期预后相关^[21,23]。目前认为,畸胎瘤中异位高表达NMDA受体的神经组织可能作为抗原来源,破坏外周免疫耐受并诱导自身抗体的产生,但该机制仍需直接证据(图1)。与未合并脑炎的卵巢畸胎瘤相比,伴抗NMDA受体脑炎的卵巢畸胎瘤中含有更高比例的神经组织(96% vs. 38%),且GluN1在畸胎瘤神经胶质细胞中的表达更为丰富(73% vs. 29%)^[17]。此外,这类畸胎瘤中可见由T细胞、B细胞和成熟树突状细胞构成的三级淋巴结构,神经胶质组织常与B细胞聚集形成生发中心,并伴随明显的免疫球蛋白沉积^[17,41]及炎症细胞浸润^[42]。这些现象提示卵巢畸胎瘤可能是自身免疫反应发生的外周启动源头。除卵巢畸胎瘤外,乳腺癌也是女性高发

的肿瘤类型。癌症基因组图谱数据库分析显示,超过90%乳腺癌亚型的肿瘤细胞中普遍表达GluN1亚基,而GluN2B亚基的表达升高与三阴性乳腺癌(triple negative breast cancer, TNBC)的预后不良、高复发风险以及远处转移密切相关^[43]。近期研究进一步发现,18%的TNBC患者血浆抗NMDA受体抗体升高;在表达GluN1-N2B受体的TNBC荷瘤小鼠模型中,也观察到了相应的体液免疫反应;但是在抗体滴度升高的TNBC患者中,并未观察到典型抗NMDA受体脑炎的临床表现^[44]。这一现象提示,乳腺癌诱导的抗体反应与自身免疫性脑炎的致病机制之间可能存在尚未揭示的联系。

病毒性脑炎,尤其是单纯疱疹病毒(herpes simplex virus, HSV)感染,被认为是抗NMDA受体脑炎的另一重要诱因(图1)。研究显示,27%的HSV脑

炎患者会发展成自身免疫性脑炎,其中以抗NMDA受体脑炎最为常见^[37,45]。在临床表现上,儿童患者多以舞蹈样动作和运动障碍为主,而成人患者则更常表现为精神症状及认知功能改变^[46]。纵向队列分析显示,在感染数周内的多数HSV患者脑脊液和血清中可检测到针对NMDA受体的新生自身抗体^[46-48]。动物模型研究进一步发现,经鼻内接种HSV-1并接受抗病毒治疗的小鼠,约三分之二产生了抗NMDA受体自身抗体,感染8周后小鼠海马突触NMDA受体簇数量和总体NMDA受体水平均减少约50%^[49]。目前,HSV诱发抗NMDA受体的自身免疫反应的具体机制尚未厘清,推测HSV脑炎导致神经元破坏及血脑屏障通透性增加,使原本局限于中枢神经系统的抗原(如NMDA受体)暴露给外周免疫系统,引发自身免疫反应^[50,51]。近年来也有SARS-CoV-2感染后发生

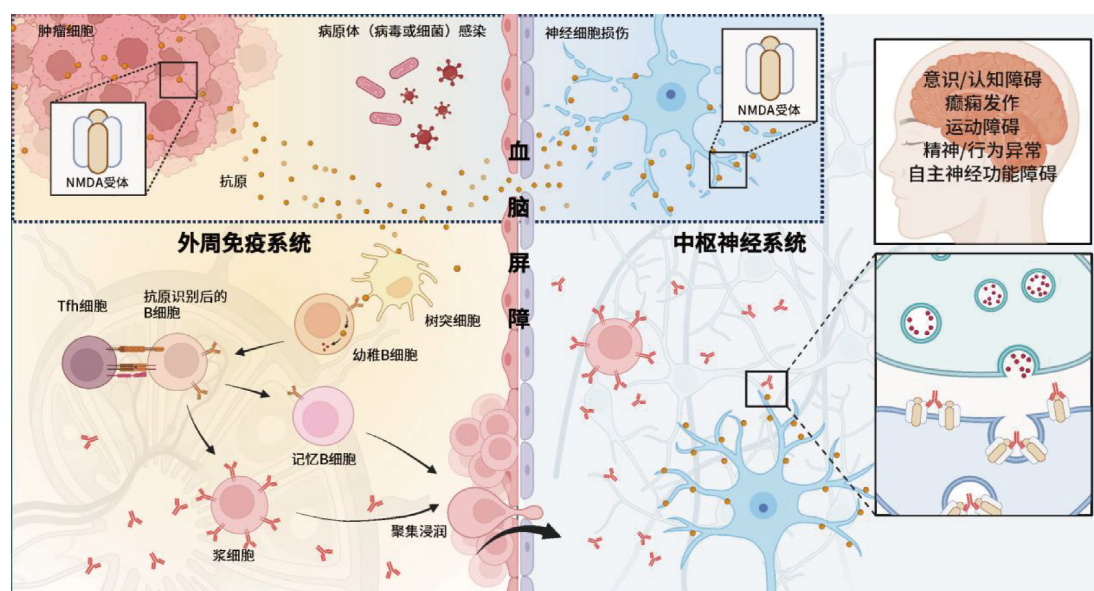


图1 抗NMDA受体脑炎的免疫学诱发机制

图中虚线框内展示了主要的免疫触发因素:肿瘤组织异位表达NMDA受体及病原体感染。肿瘤组织表达的NMDA受体抗原或病毒诱导释放的受体碎片,由树突状细胞提呈至局部淋巴结,激活幼稚B细胞并在滤泡辅助性T(Tfh)细胞辅助下分化为记忆B细胞和分泌抗体的浆母细胞。这些细胞和抗体跨越受损的血脑屏障浸润至中枢神经系统,经克隆扩增分化为浆细胞并在原位持续合成抗体。抗体与神经元NMDA受体结合后介导受体内吞,导致突触功能障碍,临床表现为意识障碍、癫痫发作及运动障碍等症状。本图采用了BioRender(<https://biorender.com>)的绘图素材。

Figure 1 Immunological triggering mechanisms of anti-NMDA receptor encephalitis

The dashed boxes indicate the primary immunological triggers: tumor tissue with abnormal expression of NMDA receptors (e.g., ovarian teratoma) and pathogenic infections (e.g., HSV). NMDA receptor antigens expressed by tumor tissues or released during viral infection are captured by dendritic cells (DCs) and transported to regional lymph nodes. Within the lymph nodes, these antigens, with the assistance of follicular helper T (TFH) cells, trigger the activation and differentiation of naïve B cells into memory B cells and plasmablasts. These cells subsequently cross the compromised blood-brain barrier to infiltrate the central nervous system (CNS). Once inside the CNS, they undergo clonal expansion and differentiate into plasma cells, leading to the *in situ* synthesis of anti-NMDA receptor antibodies. The binding of these antibodies to NMDA receptors on neurons mediates receptor internalization, resulting in synaptic dysfunction. This process ultimately manifests as clinical symptoms, including impaired consciousness, seizures, and movement disorders. The figure was created using drawing materials from BioRender.

NMDA受体脑炎的个案报道^[52,53],但现有荟萃分析尚未支持二者之间存在明确的特异性关联^[54]。

全基因组关联研究(genome-wide association study, GWAS)提示,多种遗传变异亦可能增加抗NMDA受体脑炎的发病风险。Mueller等^[55]对96名患者和1 194名健康对照进行分析,发现HLA-I类B*07:02等位基因与疾病呈弱相关性,且主要见于成年起病患者。Shu等^[56]在中国汉族人群中发现HLA-II类DRB1*16:02等位基因在患者中显著富集。除HLA区域外,不同人群研究还鉴定出多个非HLA易感位点:中国汉族患者中IRF7、BANK1和TBX21基因多态性与疾病相关^[57],而欧洲人群的GWAS发现LRRK1及ACP2/NR1H3区域为新的风险位点^[58]。这些结果共同提示B细胞发育、Th1反应及I型干扰素信号通路在抗NMDA受体脑炎发病中可能发挥重要作用,但相关多态性的功能机制亟需更多的细胞或动物实验验证。

目前,环境触发因素启动外周免疫后如何导致中枢神经系统内抗体的产生仍不完全明确。现有研究表明,中枢神经系统本身可作为活跃的免疫反应场所,抗NMDA受体自身抗体可在鞘内局部合成,且鞘内抗体产生在神经自身免疫性脑炎的发病机制中具有重要作用^[58]。主要依据包括:脑脊液中存在克隆性扩增的抗体生成性B细胞和浆细胞^[31,59];患者的活检和尸检组织显示含有明显的浆细胞脑炎性浸润^[60];患者病程与脑脊液抗体滴度的相关性优于血清抗体滴度^[21,61]。基于以上发现,有假说认为无论是NMDA受体在周围肿瘤神经组织中的异常表达^[41],还是嗜神经病毒诱导的神经元损伤后释放^[17,62],相关抗原均可以可溶性形式或由抗原提呈细胞摄取并转运至区域淋巴结。在该部位,抗原提呈细胞将NMDA受体抗原暴露并呈递给幼稚B细胞,并在滤泡辅助T细胞的协同作用下进一步激活幼稚B细胞,使其分化为特异性记忆B细胞和浆母细胞。记忆B细胞、浆母细胞和抗体随后穿过损伤的血脑屏障进入大脑。到达大脑后,这些记忆B细胞会经历再刺激、抗原驱动的亲合力成熟、克隆扩增,最终分化为产生抗NMDA受体自身抗体的浆细胞^[2,26,50,51](图1)。

2.2 抗NMDA受体脑炎的致病机制

2.2.1 抗NMDA受体自身抗体介导的受体内吞及突触功能障碍

抗NMDA受体自身抗体是抗NMDA受体脑炎的

特征性标志物。体外研究表明,患者来源的抗体可在海马区域呈现显著的免疫反应性富集^[20,21,27,29]。在原代培养的海马神经元中,抗体可在24 h内诱导突触NMDA受体簇的滴度依赖性下降^[27,29];并且可选择性降低NMDA受体介导的微小兴奋性突触后电流,同时显著抑制海马CA1区NMDA受体依赖的长时程增强^[28,63]。此外,抗体处理还可导致兴奋性神经元上抑制性突触的密度明显降低^[29]。不同脑区对抗体的易感性存在明显差异,在皮层中主要表现为抑制性神经元功能受损^[64,65],而在海马中则以兴奋性神经元NMDA受体功能障碍为主^[65]。这些结果提示,抗NMDA受体自身抗体可能通过诱导稳态性调节异常而破坏神经环路的兴奋/抑制平衡。当前普遍认为,抗NMDA受体自身抗体通过交联表面NMDA受体触发受体内吞,是抗体导致受体功能障碍进而引发突触功能障碍的核心机制^[27-29,66-68](图1)。内吞后的NMDA受体通过循环内体和溶酶体途径被降解,该过程与药物诱导的NMDA受体内吞相似^[29]。

在分子机制层面,抗体可破坏NMDA受体与Eph B型受体2(Ephrin type-B receptor 2, EphB2)的相互作用,导致NMDA受体及锚定伴侣EphB2从突触解离并发生内吞。而Ephrin-B2作为EphB2受体的关键配体,可通过激活EphB2信号,部分逆转这一过程^[28,66]。进一步研究显示,抗体介导的内吞具有一定的亚基选择性:抗体孵育海马神经元24 h后,含GluN2B的NMDA受体纳米簇减少程度显著高于含GluN2A的受体(79% vs 55%)^[66]。近期研究认为抗NMDA受体自身抗体在发病早期优先作用于突触外NMDA受体^[69],促进突触外受体的侧向扩散,破坏其与蛋白伴侣形成的纳米级互作网络,从而抑制突触内NMDA受体的动态补充与更新,最终导致受体流失和神经功能障碍。该模型扩展了以内吞和突触锚定障碍为核心的观点,并为靶向受体膜动态稳态的治疗策略提供了新的理论依据。

除介导受体内吞外,抗NMDA受体自身抗体是否直接调控NMDA受体通道活性导致突触功能障碍仍无定论。目前领域内共识认为,抗体介导的受体内吞与突触表达下调是其核心致病机制;而抗体对通道功能的直接调控作用存在显著的抗体异质性,与抗体的靶向表位、亲和力和亚型密切相关,是当前领域内的重要争议点。有研究发现急性抗体处

理可降低NMDA受体介导的整体电流幅度,提示抗体可能直接抑制受体通道功能^[36,70]。亦有研究报道抗体加入后电流增强,提示抗体可能通过改变通道开放概率或解除镁离子阻断促进通道活性^[22];另有研究未观察到抗体对单通道或宏观电流特性的显著影响,认为抗体的致病作用不在于直接调控通道动力学^[29,35]。这些数据表明抗NMDA受体自身抗体在致病机制上的异质性,不同抗体可能通过直接调节和间接下调等多种途径共同致病。

近年来的抗原表位鉴定为深入理解抗体与NMDA受体结合的细节提供了新的见解。在明确GluN1-NTD区域是抗NMDA受体脑炎患者抗体的主要表位后^[21],Gleichman等^[22]通过点突变及CBA实验指出,GluN1-NTD中的N368/G369区域对于抗体识别NMDA受体较为关键。近期通过冷冻电镜解析其高分辨率结构,发现这些致病抗体主要结合在GluN1-NTD顶部和侧面暴露的结构域^[12,35,36]。NMDA受体和抗体呈现出1:1、1:2、2:1或2:2等多种化学计量比。结构显示GluN1的 $\alpha 1$ 、 $\alpha 1$ - $\beta 2$ 环、 $\alpha 8$ 和 $\beta 10$ - $\beta 11$ 环上的残基是自身抗体识别的抗原热点,而非先前推测的深部结合口袋^[22]。N368/G369区域的突变可能通过糖基化变化影响蛋白构象,从而影响抗体的结合^[35]。与位于中心的GluN2/GluN3亚基相比,外围分布的GluN1亚基的胞外结构域更易暴露,因而成为自身免疫攻击的主要靶点。

2.2.2 抗NMDA受体脑炎认知障碍的病理机制

记忆与认知功能受损是抗NMDA受体脑炎的核心临床表现之一,主要表现为近事记忆下降和学习能力受损。被动免疫模型研究表明,持续向小鼠脑内灌注抗NMDA受体脑炎患者脑脊液两周,可诱导记忆障碍及抑郁样行为,其病理基础包括海马突触NMDA受体簇显著减少,并伴随NMDA受体依赖性长时程增强严重受损^[30,67]。体内给予ephrin-B2蛋白可阻断抗体介导的致病作用,部分恢复突触NMDA受体水平,改善记忆功能并保护突触可塑性,进一步支持抗体介导的受体功能障碍在认知损伤中的关键作用^[67]。Ceanga等^[71]从神经网络层面揭示了抗NMDA受体自身抗体的致病机制:抗体破坏了海马CA3-CA1前馈通路中的兴奋/抑制平衡,从而导致CA1网络去抑制及病理性伽马振荡增强,而增强AMPA受体介导的兴奋性传递可部分恢复网络同步性并纠正异常振荡。

除海马外,内侧前额叶皮层(medial prefrontal cortex, mPFC)在抗NMDA受体脑炎相关认知表型中的作用逐渐受到关注。Feng等^[64]通过在小鼠mPFC中连续注射患者来源IgG,发现抗NMDA受体自身抗体可损害mPFC中小清蛋白(parvalbumin, PV)阳性的抑制性中间神经元,导致神经元形态异常、突触功能下降及低伽马频段神经振荡紊乱,从而引发认知缺陷。利用光遗传学或化学遗传学手段激活mPFC PV神经元可显著逆转上述认知障碍的表型。在海马中亦观察到类似的PV神经元功能改变,提示PV神经元功能受损可能是抗体介导认知障碍的关键机制。目前,抗NMDA受体自身抗体为何对皮层PV神经元表现出功能层面的选择性易损性仍不完全清楚。一种可能的解释是,PV神经元对NMDA受体介导的兴奋性输入具有高度功能依赖性。药理学研究显示,腹腔注射NMDA受体通道阻断剂MK-801可诱发皮质30~50赫兹波段伽马振荡异常激活。然而,在PV神经元特异性敲除*Grin1*的小鼠模型中,MK-801无法诱导伽马振荡增强^[72]。因此,在抗体介导的受体内吞或功能障碍下,PV神经元相较于其他神经元更易陷入功能失衡,进而导致神经网络的去抑制及认知缺陷。

2.2.3 自身抗体致病性的多模型证据及潜在致病机制

约70%的抗NMDA受体脑炎患者在急性期会经历癫痫发作^[23],儿童更为常见^[73]。多种动物模型已证实抗NMDA受体自身抗体具有明确的致病性。在被动免疫小鼠模型中,抗体介导的受体内吞虽然不直接引发自发癫痫,但可显著降低发作阈值并增加对促惊厥药的敏感性^[74]。在更长时程的连续视频-脑电监测中,则可直接观察到自发电生理发作的出现^[75]。将患者脑脊液注射入斑马鱼脑室后,同样也能观察到癫痫阈值降低,发作倾向显著提高。这些结果共同支持抗NMDA受体自身抗体可通过降低神经网络稳定性来促进癫痫发生^[71]。癫痫的网络层级失稳可能源于抑制性中间神经元功能减退引起的去抑制效应及兴奋/抑制失衡^[71],但相关直接证据仍有限。

近期研究进一步揭示炎症信号也参与抗NMDA受体脑炎相关癫痫的发生发展。临床队列分析显示,儿童患者中NLRP3水平与癫痫发作风险独立相关;在主动免疫小鼠模型中,戊四唑(pentylenetetrazole,

PTZ)诱发条件下可观察到癫痫潜伏期缩短和发作加重,并伴随小胶质细胞激活及NLRP3-ASC-Caspase1-IL-1 β 通路上调,而NLRP3特异性抑制剂MCC950可显著提高癫痫阈值^[76]。此外,基于人前脑类器官的研究发现,抗NMDA受体自身抗体诱导的受体内吞可引起神经元低活动状态,而患者脑脊液中异常上调的IL-17则可驱动神经元高兴奋性并诱发癫痫样放电;中和IL-17显著抑制了小鼠模型中患者脑脊液诱发的癫痫活动^[77]。上述结果提示,抗体介导的突触功能障碍与炎症通路之间的协同作用,可能共同塑造了抗NMDA受体脑炎相关癫痫表型的病理基础。

2.2.4 主动免疫模型揭示抗NMDA受体脑炎的致病机制

为了更好地模拟人类抗NMDA受体脑炎的发病过程,研究者采用主动免疫方法,构建了相关小鼠模型。Jones等^[78]通过注射搭载GluN1-N2B蛋白的脂质体,成功诱导出高发病率的小鼠模型。该模型表现出多动、癫痫及筑巢能力丧失等显著行为异常,同时伴有明显的血管周围性细胞浸润,并可见T细胞、B细胞及浆细胞等多系免疫细胞的聚集。2020年,Wagnon等^[79]则利用GluN1亚基关键表位(GluN1³⁵⁹⁻³⁷⁸)的肽段进行免疫,证明了针对该表位的自身抗体足以引发血脑屏障损伤及脑内IgG沉积,而清除B细胞显著缓解了症状,进一步揭示了B细胞反应在致病中的核心作用。2023年,有研究构建了幼年小鼠主动免疫模型,通过多次免疫诱导内源性抗体产生,再现了认知障碍、突触NMDA受体表达下调以及癫痫样放电等关键病理特征^[80]。上述研究表明,主动免疫模型能有效模拟从血脑屏障破坏到自身抗体介导的神经功能损伤的完整病理过程,为深入解析相关机制和开发治疗策略提供了重要工具。

3 抗NMDA受体脑炎的治疗策略

在抗NMDA受体脑炎的治疗中,尽管一线和二线治疗可显著改善患者预后,但激素及二线治疗引起的全身免疫抑制效应也增加了严重感染及ICU相关并发症的风险^[81],且治疗延迟也与预后不良密切相关^[82]。总体而言,目前临床诊疗中仍存在多方面局限:抗体检测存在假阴性、早期诊断率有待提高;部分急性期重症患者因机械通气、长期卧床及继发重度感染而难以耐受强化免疫抑制治疗;同时,免疫

干预主要经外周免疫调控间接作用于中枢神经系统,起效滞后,难以快速控制神经精神症状;此外,缓解期长期维持治疗伴随感染、肝功能损害、代谢紊乱、肿瘤风险及潜在生殖毒性等不良事件。目前一线和二线治疗均为经验性治疗方案,全球尚无任何获批用于靶向治疗抗NMDA受体脑炎的药物。

当前已有新型免疫治疗策略进入临床研究阶段,旨在提供疾病治疗的循证医学证据,从而提高治疗有效性。其中,伊奈利珠单抗是一种靶向CD19的人源化单克隆抗体,已获FDA批准用于视神经脊髓炎谱系疾病的治疗^[83]。相较于抗CD20疗法,CD19表达范围更广,涵盖浆母细胞。ExTINGUISH研究是一项Ⅱb期随机、双盲、安慰剂对照临床试验,旨在评估在标准一线治疗基础上,加用抗CD19单抗(伊奈利珠单抗)治疗中重度抗NMDA受体脑炎是否安全并存在持续性获益,其主要终点为mRS评分的改善情况^[84]。同时,我国也正在开展一项随机、对照、开放标签的Ⅲ期临床试验(RADIA, NCT06867991),以评估靶向CD20单抗(奥法木单抗)联合靶向CD38单抗(达雷妥尤单抗)在自身免疫性脑炎患者中的有效性,其主要终点为第16周时mRS评分为0~2分的患者比例^[85]。另一方面,研究显示抗NMDA受体脑炎患者脑脊液中多种炎症细胞因子(如IL-6、IL-17)水平升高^[86],提示炎症介质在疾病发病中的潜在作用。目前,一项国际多中心的Ⅲ期、随机、双盲、安慰剂对照临床试验(CIELO, NCT05503264)正在开展,以评估靶向IL-6通路的药物萨特利珠单抗在抗NMDA受体脑炎治疗中的疗效^[87]。此外,针对蛋白质合成活跃细胞(如浆细胞)的蛋白酶体抑制剂硼替佐米,以及通过加速IgG降解起效的新生儿Fc受体抑制剂罗泽利昔单抗,目前均处于评估其治疗自身免疫性脑炎疗效的临床试验中^[88]。

抗NMDA受体脑炎的未来研究将聚焦于发病机制的精准靶向治疗策略。Steinke等^[89]开发了一种NTD-Fc融合蛋白,它结合了NMDA受体的NTD与IgG的Fc片段。结果显示,该蛋白能高效中和患者体内的致病性抗体,防止受体内吞及突触电流受损,并成功逆转小鼠的记忆缺陷。然而,该融合蛋白体积较大,难以穿透血脑屏障,且可能引发免疫原性反应。NMDAR-CAAR-T细胞疗法(图2)通过将NMDA受体胞外抗原结构域工程化融合至T细胞嵌合抗原受体中,构建表达特异性嵌合自身抗体受体

的工程化T细胞。该嵌合受体使T细胞能够特异性识别并清除表达抗NMDA受体自身抗体的致病性B细胞,在被动免疫小鼠模型中成功耗尽了致病B细胞并持续降低抗体水平^[33]。与广泛清除B细胞的二线疗法相比,CAAR-T疗法具有抗原特异性,可在清除致病克隆的同时保留正常体液免疫功能。此外,单克隆抗体在脑脊液中的浓度通常仅为血浆的0.1%~0.5%,其中枢渗透性有限,可能难以清除位于中枢神经系统及其他免疫豁免部位的致病性B细胞,从而成为部分抗NMDA受体脑炎难治的重要原因^[90]。而NMDAR-CAAR-T细胞可迁移至抗体难以到达的部位,在体内亦可于软脑膜等区域检测到^[33],这一特性可能有助于提高对难治性患者的治疗效果。

然而,该疗法目前基于的是体外实验和产生自身抗体的B细胞被动转移模型,这些模型不能很好地模拟抗NMDA受体脑炎的完整表型,且缺乏海马神经元改变及认知功能缺陷的分子和细胞特征,因此CAAR-T细胞疗法在抗NMDA受体脑炎的主动模型及临床试验中的有效性有待系统性评估。此外,该疗法的安全性及潜在神经毒性也需进一步研究评估。传统靶向CD19或BCMA的CAR-T疗法会广泛清除正常B细胞/浆细胞,易引发细胞因子释放综合征(CRS)及免疫效应细胞相关神经毒性综合征(ICANS),有导致认知障碍等副作用^[91]。相比之下,CAAR-T仅靶向特异性分泌NMDA受体抗体的致病性B细胞亚群,该亚群在总体B细胞中占比较小^[35],理论上抗原负荷与激活强度更低,CRS和ICANS风险亦相对降低。类似策略的DSG3-CAART(NCT04422912) I期试验显示,在26例天疱疮患者中未见剂量限制性毒性及ICANS,仅1例在高剂量下出现CRS。这些人体试验数据表明DSG3-CAART总体耐受性良好(<https://www.cabalettabio.com/>)。此外,相对现行疗法,CAAR-T疗法需要针对患者的致病抗体表位进行个性化调整,存在成本和时间周期上要求较高的局限。

此外,新型中和单臂抗体ART5803提供了一种竞争性抑制策略:该抗体通过人源化改造以降低免疫原性,并将传统双价IgG结构改造为单臂构型,因而能避免受体交联的发生;又引入了LALA突变削弱Fc介导的效应功能,从而降低炎症相关风险。经上述工程优化后,ART5803能够高亲和力特异性结

合GluN1-NTD,在阻断致病抗体结合的同时不干扰NMDA受体的正常生理功能,也不会诱导受体内吞。狨猴模型中静脉注射ART5803后,行为和运动的异常能够快速地被逆转^[34]。目前该药物已进入I期临床试验阶段(NCT06575153)。与NMDAR-CAAR-T疗法相比,中和抗体ART5803治疗在有效且迅速缓解抗NMDA受体脑炎急性症状方面具有明显优势,且由于该策略不涉及免疫细胞的剧烈扩增,发生CRS和ICANS的风险较低。然而,ART5803治疗策略并未靶向免疫反应的细胞来源,无法清除持续存在的记忆B细胞或长寿浆细胞,一旦停止给药,持续产生的自身抗体可能导致病情反复。更重要的是,受血脑屏障通透性限制,ART5803脑脊液药物暴露量仅约为血清水平的0.1%,临床应用仍可能面临高剂量静脉给药的需求及长期治疗相关免疫原性风险等挑战(图2)。

4 抗NMDA受体自身抗体与其他神经系统疾病

4.1 抗NMDA受体脑炎与脱髓鞘疾病的重叠综合征

值得注意的是,约有5%的抗NMDA受体脑炎患者会同时或先后出现脱髓鞘综合征。与单纯抗NMDA受体脑炎患者相比,此类重叠综合征患者伴发卵巢畸胎瘤的比例更低^[92]。约40%~60%的患者血清中可检测到髓鞘少突胶质细胞糖蛋白(MOG)抗体,25%~40%可检测到水通道蛋白4(AQP4)抗体。合并MOG抗体的患者多见于儿童,最常见的临床表现是癫痫发作(51%~72.7%)和精神症状(45.5%~72.7%),共济失调的发生率显著增高;典型的MRI影像特征为皮层、皮层下区域及视神经的广泛或多灶性脱髓鞘病变(T2/FLAIR异常高信号)。此类患者通常对单独使用皮质激素治疗反应良好,预后相对较佳^[92-94]。而合并AQP4抗体的患者除了有抗NMDA受体脑炎典型症状外,常表现为视神经炎、长节段横贯性脊髓炎及脑干综合征,MRI特征包括双侧脑室周围白质及纵向长节段脊髓T2高信号病灶^[93]。此类患者预后通常较差。虽然大多数患者在接受免疫治疗后病情有所改善,但与单纯抗NMDA受体脑炎相比,伴发脱髓鞘发作往往需要更高强度的免疫干预,也更容易遗留神经功能缺损^[92]。综上,抗NMDA受体脑炎合并脱髓鞘发作可能涉及相互交织的免疫学机制,是否同时存在共同驱动与相对独立的致病机制,仍有待进一步研究。

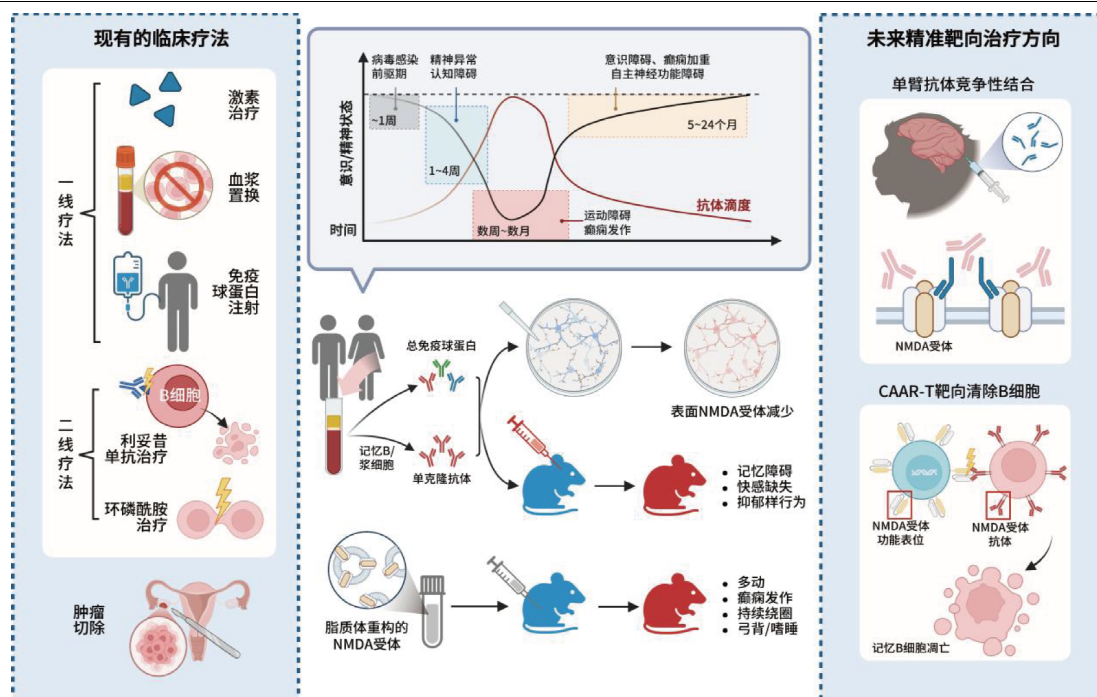


图2 抗NMDA受体脑炎的模型建立与诊疗策略

本图系统概述了抗NMDA受体脑炎的临床诊疗现状、致病机制、动物模型及前沿疗法。左侧展示了当前临床治疗策略,包括糖皮质激素、血浆置换和静脉注射免疫球蛋白等一线治疗,以及利妥昔单抗、环磷酰胺等二线免疫抑制疗法,强调了合并畸胎瘤患者尽早行肿瘤切除的重要性。中间展示了患者临床表型随抗体滴度变化呈现从精神行为异常到意识障碍的动态演变过程,并总结了体内外实验揭示的核心致病机制:抗体作用于神经元后诱导NMDA受体内存和表达减少,导致突触电流减弱和长时程增强受损;被动免疫小鼠表现出记忆障碍和抑郁样行为,而主动免疫模型则出现行为异常和癫痫发作等表型。右侧聚焦精准免疫治疗前沿,展示了单臂中和抗体以及CAAR-T细胞定向清除致病性记忆B细胞等新策略,体现了治疗模式从广谱免疫抑制向精准靶向干预的转变。本图采用了BioRender的绘图素材。

Figure 2 Model establishment and clinical treatment of anti-NMDA receptor encephalitis

This figure summarizes the clinical management, pathogenic mechanisms, animal models and emerging therapeutic strategies of anti-NMDA receptor encephalitis. The left panel shows current treatments, including first-line immunotherapies, second-line immunosuppressive agents, and early tumor removal in patients with teratomas. The central panel illustrates antibody-mediated disease progression and key pathogenic mechanisms, including NMDA receptor internalization, synaptic dysfunction, and behavioral abnormalities in experimental models. The right panel highlights advances in precision immunotherapy, including humanized monovalent neutralizing antibody and CAAR-T-mediated elimination of pathogenic B cells. The figure was created using drawing materials from BioRender.

4.2 抗NMDA受体自身抗体在其他神经系统疾病中的检出情况

除自身免疫性脑炎外,在精神分裂症、痴呆及其他神经精神疾病中也存在抗NMDA受体自身抗体。在不同精神分裂症队列中,约3%~10%的血清样本检测到低滴度抗NMDA受体自身抗体,以IgA和IgM亚型为主^[95,96]。然而,系统性筛查发现,健康对照者及其他疾病患者(如帕金森病、痴呆症)血清中同样存在比例相近的抗NMDA受体自身抗体,抗体的滴度和类型与精神分裂症患者相比无显著差异^[96-98]。精神分裂症患者血液中的抗NMDA受体自身抗体仅在血脑屏障功能受损时,才与严重的临床症状相关^[97]。近期TRAWINSKI临床试验数据显示,在急性动脉脑

卒中患者中,约9%在基线呈NMDA受体抗体(IgM/IgA)阳性,且7天内血清状态高度稳定,提示其作为急性期生物标志物具有一定可靠性^[99]。

此外,系统性红斑狼疮患者体内的抗双链DNA抗体可识别GluN2A和GluN2B NTD结构域中的保守五肽序列DWEYS,与GluN2亚基发生明确的交叉反应^[100-102]。这些抗体作为NMDA受体的正向别构调节剂,对含GluN2A亚基的受体具有高亲和力,可通过诱导神经元凋亡、小胶质细胞激活及树突修剪,导致空间记忆受损表型的发生。动物实验表明,敲除GluN2A或使用其特异性拮抗剂可有效预防此类神经损伤^[103]。与自身免疫性脑炎患者的抗GluN1抗体相比,SLE相关抗体表现出不同的病理机制。

未来,从不同临床表型及神经免疫疾病患者的脑脊液中克隆致病性抗体,仍将是阐明自身抗体相关疾病机制的重要途径。

5 其他自身抗体介导的神经系统疾病及致病机制

在抗体相关的神经系统疾病中,目前已发现超过25种针对神经元表面蛋白或突触相关蛋白的自身抗体,其致病机制呈现出高度的异质性,主要表现为直接影响受体功能、介导内吞以及激活补体反应^[3]。抗GABA_A受体和GABA_B受体脑炎中的自身抗体,主要靶向受体的配体结合相关结构域。这些抗体既可作为功能性拮抗剂,也可通过变构方式调节受体构象,从而干扰受体的正常激活与抑制过程^[104,105]。随后开展的功能学与结构生物学研究进一步证实,这类自身抗体的结合位点涉及GABA及苯二氮卓类药物的结合区域,直接或通过变构效应抑制GABA_A受体介导的离子电流。这种对受体功能的抑制是抗GABA_A受体自身免疫性脑炎发生的核心致病机制^[106]。

除了直接抑制受体功能外,受体内吞与突触重塑也是重要的致病机制。边缘性脑炎相关的抗AMPA受体抗体直接介导受体内吞,导致自发兴奋性突触后电流振幅降低^[107]。同样,引起脑脊髓炎和强直症状的抗GlyR脑炎抗体^[108],以及导致睡眠障碍的抗IgLON5^[109]脑炎抗体,均可通过促进受体内吞,减少受体在突触的分布密度^[3]。在抗LGI1脑炎中,抗体并不直接引起内吞,而是通过物理方式阻断LGI1与受体ADAM22和ADAM23的相互作用,重塑神经元表面Kv1.1和AMPA受体的分布,最终导致神经元的兴奋性增高和可塑性降低^[110,111]。此外,自身抗体也可以激活补体途径。在以视神经脊髓炎为典型表现的AQP4抗体相关疾病中,抗体与AQP4结合后形成的簇集可招募C1q并激活补体系统,产生直接的细胞毒性作用^[112,113]。综上所述,抗体介导的神经系统疾病中自身抗体的致病作用除了涉及受体功能的直接抑制,还包括受体内吞、突触重塑及补体介导的细胞损伤等多种机制,这种复杂病理特征为理解其临床异质性提供了基础。

6 讨论

抗NMDA受体脑炎是目前最常见的靶向神经细

胞膜蛋白的自身免疫性脑炎。研究表明,抗NMDA受体自身抗体通过介导受体交联,导致NMDA受体相关的突触功能紊乱,从而引发多种神经精神症状^[6]。然而,约40%~60%的患者没有明确的诱因^[6,23],上游免疫启动机制仍是该领域亟待解决的核心科学问题。尤其在无肿瘤背景患者中,触发自身免疫反应的初始抗原来源及相关免疫通路目前尚不清楚。已有研究发现,这类患者外周血中存在大量克隆性B细胞,免疫库多样性降低,并伴有高频体细胞突变,提示B细胞经历了强烈的抗原驱动选择和亲和力成熟^[114]。此外,有研究报道了克罗恩病患者长期使用英夫利昔单抗后罹患抗NMDA受体脑炎的病例^[115],西班牙的一项关于免疫检查点抑制剂相关神经不良事件的回顾性研究显示,该类抑制剂的使用可明确诱发脑炎、重症肌无力等综合征^[116]。这些发现提示抗原驱动的B细胞反应与免疫调节失衡在抗NMDA受体脑炎发病中发挥关键作用,亟须深入研究以揭示其机制。

此外,记忆B细胞跨越血脑屏障进入中枢神经系统的分子机制仍是神经免疫领域的重要未解问题。已有研究显示,趋化因子CXCL13与其受体CXCR5结合可激活B细胞表面的整合素VLA-4,增强VLA-4与内皮细胞VCAM-1的结合,从而促进B细胞在脑血管内皮表面的黏附与滞留^[117]。在多发硬化患者及EAE模型中,活动性脱髓鞘病灶及血管周围炎性浸润区域都存在CXCL13高表达^[118],而在CXCL13敲除的EAE模型中脑内脑膜异位淋巴滤泡生成受阻^[119]。B细胞特异性缺失VLA-4或应用那他珠单抗阻断该通路,均可显著减少中枢神经系统内B细胞的浸润水平^[120,121]。相比之下,在抗NMDA受体脑炎中B细胞是否同样依赖CXCL13/CXCR5和VLA-4/VCAM-1入脑,仍缺乏直接证据。临床数据显示,约70%的早期患者脑脊液CXCL13水平升高,并与鞘内抗体合成呈正相关^[122]。但与多发硬化不同的是,多数患者MRI增强信号并不显著,提示血脑屏障的整体结构性破坏可能并非主要入脑途径。近期研究发现,Ly6c1和碳酸酐酶IV可作为内皮转运受体介导AAV跨越血脑屏障^[123],这为细胞是否通过特异性跨内皮转运通路进入中枢提供了新的机制线索。因此,血脑屏障在炎症微环境中的动态调控机制及其在抗NMDA受体脑炎中的作用仍有待系统阐明。

抗体是疾病的核心致病因素,但抗体介导受体内存的具体分子机制尚不清楚。部分患者来源的单克隆抗体(如IgG-008-218和IgG-007-168)虽能快速抑制NMDA受体介导的突触后电流,但在24 h作用下并不降低突触NMDA受体表达水平^[36]。此外,靶向GluN1的鼠源单抗在培养神经元中孵育24 h未引起表面受体减少,表明其不诱导内存^[35]。这些结果表明,不同抗体即使靶向GluN1相近表位,但在诱导NMDA受体内存方面仍存在明显的功能异质性,这背后的分子决定因素仍需深入研究。抗NMDA受体抗体致病机制的复杂性和异质性,提示治疗和干预策略应根据不同抗体特性进行精准设计。目前,抗NMDA受体脑炎尚缺乏FDA批准的特异性治疗药物,研究方向正由广谱免疫抑制逐步转向精准靶向干预策略。近期开展的NMDAR-CAAR-T细胞疗法及中和抗体的临床前研究为靶向治疗提供了新的可能性,但这些治疗策略在复杂临床表型中的实际疗效仍有待系统、严格的评估^[33,34]。另外,体外功能实验显示这些疗法难以覆盖患者抗体谱的高度异质性,单一靶点策略的广谱适用性受限,多靶点联合干预或“鸡尾酒”方案可能更具有临床转化潜力。例如,通过中和抗体阻断致病抗体与NMDA受体的结合,联合B细胞清除策略抑制抗体持续产生,从而在快速缓解急性期症状后有效抑制免疫病理过程的进展,预防疾病的复发。在炎症反应显著阶段,结合抗炎治疗以减轻神经免疫损伤。而在疾病恢复期,则进一步联合促进突触功能恢复的干预手段,以改善神经功能重建。结合人工智能辅助分子设计,开发能够竞争性阻断自身抗体与NMDA受体相互作用的小分子或多肽抑制剂,也有望为精准治疗拓展新的路径。总体而言,围绕致病性抗NMDA受体自身抗体的精细化靶向干预策略,将成为该领域未来基础研究与临床转化的重要发展方向。

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