· 综述 ·

阿尔茨海默病神经炎症损伤中 miRNA 介导 TLR4 信号通路的作用机制及其中西医防治的研究进展

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【摘要】 阿尔茨海默病(AD)是一种严重威胁老年人群健康的神经系统疾病，发病率逐年上升，尚无治愈方法。因此，深入研究致病机制并寻求防治策略意义重大。神经炎症被认为是 AD 的重要病理特征与病因，微 RNA(miRNA)可影响 Toll 样受体 4(TLR4)信号通路的上、中、下游相关因子，调节机体神经炎性水平。大量研究表明，miRNA 以及 TLR4 信号通路在神经炎症中发挥重要作用，其中 miR-34a-5p、miR-107-5p 和 miR-146a 等几种特异性 miRNA 可靶向 TLR4 信号通路，参与 AD 的神经炎症损伤。本文重点关注 miRNA 如何通过调控 TLR4 信号通路影响 AD 的神经炎症损伤，并总结针对这一信号通路的中西医治疗途径，以期为 AD 防治提供新思路。

【关键词】 阿尔茨海默病；　miRNA；　TLR4；　神经炎症；　中西医结合治疗；　综述

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Mechanism of miRNA-mediated TLR4 signaling pathway in neuroinflammatory injury in Alzheimer disease and its research progress on Chinese and western medicine prevention and treatment

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【Abstract】 Alzheimer's disease (AD) is a neurological disorder that poses a serious threat to the health of the elderly population, with the incidence increasing every year and no cure available. It is of great significance to conduct in-depth research on the pathogenic causative mechanisms and to seek preventive and curative strategies. Neuroinflammation is considered to be an important pathological feature and cause of AD, and microRNAs (miRNAs) can affect upstream, midstream, and downstream factors associated with the Toll-like receptor 4 (TLR4) signaling pathway to regulate the level of neuroinflammation in the body. Numerous studies

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have shown that miRNAs as well as the TLR4 signaling pathway play important roles in neuroinflammation, and several specific miRNAs, including miR-34a-5p, miR-107-5p, and miR-146a, can target the TLR4 signaling pathway and participate in neuroinflammatory injury in AD. This paper focuses on how miRNAs affect neuroinflammatory injury in AD by regulating the TLR4 signaling pathway, and summarizes the Chinese and Western medicine treatment pathways targeting this signaling pathway, with a view to providing new ideas for AD prevention and treatment.

【**Key words**】 Alzheimer disease; miRNA; TLR4; Neuroinflammatory diseases; Combined treatment of traditional Chinese medicine and western medicine; Review

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AD是以认知功能障碍为主要表现的神经退行性疾病[1]，为最常见的痴呆类型，占所有痴呆病例的60%～80%[2]。由于人口老龄化和增长，预计到2050年全球将有1.58亿痴呆症患者[3]，然而该病尚无根治之法，给全球医疗、社会带来严峻考验。神经炎症被视为AD发生、发展的重要部分[4]。Toll样受体4(Toll-like receptor 4, TLR4)表达于小胶质细胞、星形胶质细胞和神经元[5]，其介导的信号通路在AD神经炎症损伤中有重要意义[6]。微RNA(microRNA, miRNA)是AD的重要调节因子和治疗靶点[7]，同时对TLR4信号通路[8]与炎性反应[6]具有显著调节效应。本文围绕AD的神经炎症机制，介绍miRNA介导TLR4信号通路在AD中产生的影响并寻找靶向这一通路进行中西医治疗的可能方案，致力于为AD的临床防治提供理论依据。

一、AD与神经炎症

目前，AD的病理机制包括β-淀粉样蛋白(amyloid β-protein, Aβ)沉积形成的淀粉样斑块与过度磷酸化tau蛋白聚集形成的神经原纤维缠结[9]。神经炎症也是AD的关键发病机制之一，而小胶质细胞和星形胶质细胞是AD神经炎性反应的重要细胞[10]。当急性神经炎症发生时，胶质细胞活化增生，外周炎性细胞浸润，炎性因子表达[11]。星形胶质细胞作为维持血脑屏障(blood-brain barrier, BBB)的核心部分，能促进BBB基膜的形成[12]，在神经炎症刺激下增多活化，导致渗透性增加，免疫细胞等易进入脑实质内释放神经毒性物质。Aβ和tau聚集体可激活小胶质细胞和星形胶质细胞参与AD的病理生理进程，这两类细胞兼具神经保护与促炎作用。在生理情况下，小胶质细胞[13]与星形胶质细胞[14]能够对Aβ进行吞噬或降解，阻碍Aβ沉积。然而在AD病理阶段，Aβ反而诱导小胶质细胞[15]与星形胶质细胞[16]释放促炎因子与细胞毒性因子，加剧神经炎症。此外，在对tau蛋白的反应中，小胶质细胞和星形胶质细胞启动炎症级联反应，造成神经元损伤[17]。神经毒性Aβ的沉积[18]与病理性tau蛋白积累[19]也会导致BBB损伤。在持续的炎症作用下，机体内逐渐发生突触功能障碍、神经发生抑制、神经元的死亡和tau磷酸化等[20]，在不断发展的恶性循环中，神经元逐渐损伤，导致认知障碍与记忆减退，最终发展为AD。

二、TLR4参与AD神经炎症损伤的机制

Toll样受体是免疫系统的重要组成部分，在天然免疫中具有识别作用，能够监视与识别各种不同的疾病相关分子模式(pathogen-associated molecular patterns，PAMP)，从而启动免疫应答。在人类细胞中，已知的TLRs家族成员有11个(TLR1～TLR11)，其中TLR4表达于神经元和非神经元神经胶质细胞，包括小胶质细胞、星形胶质细胞和少突胶质细胞，是调节中枢神经系统疾病中神经炎症的有效靶点[5]。

TLR4在小胶质细胞上表达，发挥双重作用。小胶质细胞通过TLR4信号通路传导，响应Aβ沉积而被激活和募集，以促进Aβ清除[21]。Aβ聚集体(低聚物)作用于小胶质细胞表面的TLR受体(包括TLR4)时，引发先天免疫系统的反应[16]。CD14与TLR4形成受体复合物表达于小胶质细胞时，与纤维状Aβ结合诱导炎症反应[22]。TAK-242治疗(TLR4特异性抑制剂)可能诱导小胶质细胞从炎性M1表型转变为保护性M2表型，并增加在AD中的吞噬功能，因此抑制TLR4可诱导M2小胶质细胞极化[23]。在星形胶质细胞中，张薇和曾常茜[24]研究认为，AD患者大脑中的Aβ淀粉沉积和炎性因子的浓度升高到一定程度时激活星形胶质细胞，使其分泌细胞毒素，吞噬能力减退时很可能与内源性分子激活TLR2和TLR4有关。综上所述，Aβ与TLR4联系紧密且复杂，对神经细胞的炎症反应具有重要调节作用。

TLR的信号传导途径包括MyD88依赖性和MyD88非依赖性2种，这2种途径在神经系统疾病的炎症反应过程中均发挥重要作用。MyD88依赖性途径是TLR4信号转导中最经典的途径，主要通过激活核因子-κB(activation of nuclear factor-κB，NF-κB)和促炎性细胞因子的产生引发下游炎性效应。非依赖性途径则主要是通过TLR4与跨膜接头分子(Transmembrane junction molecule，TRIF)以及TRIF相关分子(TRIF related molecules，TRAM)的相互作用实现。

三、miRNA调控TLR4信号通路参与AD神经炎症损伤

miRNA是一类长约22个核苷酸的内源性非编码RNA分子，主要参与基因的转录后调控，大脑中发现的miRNA中有70%在AD的发病中具有重要意义[9]。细胞核中的miRNA基因在RNA聚合酶的催化下转录形成初级miRNA转录本(pri-miRNA)[25]，经过微处理器复合体切割成为前体发夹(pre-miRNA)，并转入细胞质中被Dicer进一步剪切为具有特征性2-nt3'突出端的短RNA双链体，随后其中的一条链优先与Argonaute蛋白组合形成功能性miRNA诱导的沉默复合物(miRISC)，另一条链通常被降解[26]。装载入miRISC中的单链为成熟miRNA，其能通过“种子区域”与mRNA上主要位于3'-非翻译区(untranslatedarea，UTR)的位点碱基互补配对将miRISC定向至mRNA，发挥促mRNA降解或抑制mRNA翻译的作用[26-27]。

miRNA可以通过对TLR4信号通路上、中、下游相关因子的转录后基因调控影响TLR4信号通路的信号传导。下文总结miRNA对TLR4信号通路的调控机制及其与AD神经炎性机制之间的联系，以期探寻miRNA介导TLR4信号通路中与AD有关的潜在靶点。

1. miRNA对TLR4信号通路的调控机制：(1)miRNA靶向TLR4信号通路上游信号因子。在AD的发展进程中，TLR4炎性通路具有多个潜在上游因素，如Aβ、tau和高迁移率族蛋白B1(high mobility group box-1 protein，HMGB1)等。Aβ在胶质细胞上靶向TLR4诱导神经炎症的机制在前文已阐述，而tau聚集体激活胶质细胞的机制目前尚不清晰。当使用在体外自组装的过度磷酸化tau聚集体处理人巨噬细胞时，发现该聚集体能够触发钙信号升高和活性氧产生，引发TLR4依赖性炎症反应[28]。另有实验结果表明，细胞外tau蛋白通过激活TLR4受体和中性鞘磷脂酶刺激小胶质细胞对活神经元的吞噬[29]。根据上述实验可猜测，细胞外tau蛋白聚集体可能通过TLR4受体诱导胶质细胞活化引发炎症反应。miRNA能够调节Aβ以及磷酸化tau蛋白的产生与聚集，如miR-137[30]、miR-331-3p[31]与miR-9-5p[31]分别靶向Aβ前体蛋白APP、自噬受体Sqstm1和Optn，阻碍Aβ的生成或清除，进而影响AD中的Aβ水平。miR-485-3p诱导tau过度磷酸化和裂解型tau积累及炎症反应，并通过调节CD36的表达阻碍小胶质细胞对Aβ的吞噬[32]。与miR-485-3p相反，miR-128[33]和miR-142-5p[34]能有效抑制AD中Aβ的积累和tau病理性改变。HMGB1是一种染色质结合蛋白，释放到细胞外后可作为损伤相关分子模式驱动炎症[35]，其为诊断AD的特异性生物标志物。研究发现，miR-142-5p[36]、miR-142[37]、miR-216a-5p[38]能够直接靶向HGMB1 mRNA的3'-UTR区，降低HGMB1的表达，从而阻断HGMB1/TLR4/NF-κB通路激活，发挥神经保护作用。上述研究说明，miRNA通过靶向TLR4信号通路的上游信号因素间接影响细胞膜上TLR4受体的激活，从而参与TLR4信号通路的调控，对神经炎症发挥不同效应。(2)miRNA靶向TLR4信号通路中游分子蛋白。TLR4受体接收、识别并转导外界刺激信号，是通路信号传导的枢纽部位。部分miRNA如miR-451[39]和miR-7[40]等可与TLR4 mRNA的3'-UTR区域结合，直接抑制TLR4基因的表达。TLR4水平的下调能够影响胶质细胞活化与神经炎症。研究表明，miR-451[39]和miR-7[40]靶向并降低TLR4水平，可分别缓解脑缺血再灌注和脑出血诱导的脑部炎症，且均能减轻脂多糖(lipopolysaccharide，LPS)激活的小胶质细胞介导的炎症反应[40-41]。另外，miR-16[42]、miR-140-3p[43]、miR-424[44]等亦可以作用于TLR4发挥抗炎作用。除直接靶向TLR4受体发挥神经保护作用外，miRNA还可以通过介导TLR4/NF-κB通路中游的其他成分如肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6，TRAF6)、CD14、IL-1受体相关激酶(tinterleukin 1 receptor associated kinase，IRAK)等调节神经炎症。TRAF6是TLR4两种途径中共有的蛋白结构。实验表明，脑组织中miR-146a以TRAF6为靶标，抑制TRAF6/NF-κB并降低TNF-α的表达水平，改善脑缺血后的炎症反应[45]。CD14作为TLR4辅助受体可与LPS[46]和Aβ[22]等配体结合，驱动TLR4通路信号传导。研究发现，miR-124能够显著增加小胶质细胞上CD14的表达，并可能因此引发TRAM/TRIF信号通路的激活和IFN-β表达上调[47]。IRAK参与TLR4经典通路的信号转导。miR-146b-5p[48]与miR-27a[49]可分别与IRAK1和IRAK4 mRNA的3'-UTR区域

结合沉默基因的表达，最终均改善下游炎症反应。(3)miRNA靶向TLR4信号通路下游分子蛋白。TLR4信号通路的下游成分如转录因子NF-κB和炎性细胞因子TNF-α、IL-1β、IL-6等也直接受miRNA调节。NF-κB的激活被认为是TLR4信号通路发挥炎性作用的重要环节[6]，其在活化后从细胞质内释放并转运至细胞核，上调炎性介质的转录和合成[50]。有实验表明，miR-9参与脑缺血再灌注损伤的炎症反应，并通过与NF-κB1 mRNA的3'-UTR区特异性结合，改善神经功能缺损[51]。miR-183同样能靶向NF-κB基因发挥脑保护作用[52]。炎性细胞因子的释放是炎症反应的关键，miR-130b可直接靶向3'-UTR调节TNF-α水平，并进一步调控TNF-α/NF-κB信号通道[53]。miR-27b[54]和miR-26a-5p[55]可分别结合IL-1β和IL-6的mRNA的3'-UTR区抑制对应炎性细胞因子的表达。

2. miRNA-TLR4通路与AD神经炎症：已有较多实验证实miRNA能够直接或间接介导TLR4信号通路影响炎症反应，这一机制已被证实可以在辐射损伤[56]、牙周病[57]、哮喘[58]等疾病中发挥作用。在AD中，目前确切说明miRNA可通过调控TLR4信号通路参与AD神经炎症损伤的miRNA有miR-34a-5p[59]、miR-107-5p[60]和miR-146a[61]等。姬令山等[59]在大鼠侧脑室注入$A\beta_{1\sim42}$寡聚体建立AD动物模型，发现与模型组相比，在其基础上进一步处理的miR-34a-5p抑制剂组与地黄饮子高、低剂量组AD大鼠的空间学习记忆能力增强，神经病变程度减轻，且海马miR-34a-5p、TLR4、MyD88、NF-κB p65、IL-1β和TNF-α mRNA的表达水平均下降，表明地黄饮子治疗AD可能与miR-34a-5p调控TLR4/MyD88/NF-κB信号通路，进而改善海马胶质细胞炎症反应有关。Hu等[60]的实验结果显示，AD大鼠内miR-107-5p过表达能有效抑制TLR4/NF-κB通路的激活，并减轻海马神经损伤、氧化应激和免疫反应，双荧光素酶测试证实TLR4 3'-UTR为miR-107-5p的靶标。Yang等[61]的研究表明，miR-146a可诱导AD中小胶质细胞的LPS/Aβ耐受性，同时能够改变炎症性AD风险基因和TLR信号相关基因的表达。除上述3种miRNA外，还存在某些与AD神经炎症以及TLR4信号通路分别关联的miRNA，如miR-140-5p[62]、miR-125b-5p[63]在AD中异常表达，前者的抑制剂可能靶向肽基脯氨酰顺反异构酶1(peptidyl-proplyl isomerase, Pin1)抑制Aβ寡聚体诱导的AD大鼠海马中IL-1β和TNF-α的mRNA表达[64]，其中Pin1能够改善tau病理及减少Aβ产生；后者在小胶质细胞、星形胶质细胞和神经元中均高表达[65]，可靶向BACE1减弱Aβ诱导的神经毒性[63]。miR-124同样与AD关系密切，其能靶向APP和BACE1[66]调控Aβ的合成进而调节AD。另外，miR-124的靶标还有Rela和蛋白酪氨酸磷酸酶非受体1型(protein tyrosine phosphatase non receptor type-1, PTPN1)。靶向Rela时，外泌体中的miR-124-3p被转移到海马神经元中，通过Rela/ApoE信号通路促进Aβ水解分解，缓解神经变性[67]；靶向PTPN1时，与AD突触功能障碍及记忆缺陷有关[68]。此外，miR-140-5p[64]、miR-125b-5p[69]、miR-124[70]皆被研究确定与AD的tau病理学有关。上述miRNA均具有抑制TLR4炎症信号通路的作用[71-73]，能够影响AD的Aβ及tau病理学，而Aβ与tau聚集体又可作为上游信号物质刺激TLR4通路信号传导。因此，猜测上述miRNA对AD神经炎症的调控可能通过TLR4信号通路进行。然而目前确切论证miRNA通过介导TLR4信号通路调节AD神经炎症的实验较缺乏，可作为AD防治的新方向。

四、靶向miRNA介导TLR4炎性通路的防治方法

目前，AD临床治疗以药物为主，辅以康复治疗，临床药物以胆碱酯酶抑制剂为主，只能缓解一定症状，无法阻止病情进展，且常伴有恶心、呕吐等不良反应。因此，寻找更高效的AD治疗方法迫在眉睫。神经炎症的治疗对改善AD有积极作用。下文总结了有关靶向miRNA介导的TLR4/NF-κB炎性通路改善神经炎症损伤的研究进展，为该途径在AD防治领域的探索提供参考。

1. 西药靶向miRNA-TLR4防治AD：目前发现有西药可以通过miRNA-TLR4信号通路参与神经炎症调控。右美托咪定是一种α2肾上腺素能受体激动剂，在缺血性脑损伤、脑外伤和其他持续急性神经损伤中具有神经保护作用[74]。研究发现，右美托咪定可过表达miR-140-3p，抑制小胶质细胞活化[43]，上调miR-17-5p的表达，调控TLR4通路，减轻细胞炎症[75]。另外，其能促进神经元活动并阻碍神经元凋亡，改善行为和认知障碍[76]。阿格列汀对减少与神经炎症和淀粉样变形成相关的认知能力下降有益，并可作为AD的一种潜在治疗药物[77]。采用阿格列汀[20 mg/(kg·d)；口服]处理小鼠进行一系列实验，发现阿格列汀通过调节TLR4/MYD88/NF-κB和miRNA-155/SOCS-1信号通路对脂多糖诱导的小鼠神经炎症和认知障碍具有神经保护作用[77]。上述研究提示阿格列汀对神经炎症的调控与TLR4及miRNA-155介导的信号通路有关。

2. 中药靶向miRNA-TLR4防治AD：AD属中医学“呆病”“痴呆”范畴。中医辨证认为AD本虚标实，以肾虚精亏为本，痰浊、瘀血为标。中药治疗AD研

究起步较晚，目前还处于动物模型与体外实验阶段，但与单靶点拮抗剂相比，其多靶点、多成分的特点为治疗 AD 提供了优势[78]。因此，利用相关研究方法分析中药对于 AD 的作用靶点很有必要。(1) 中药单体。人参功擅大补元气、复脉固脱、安神益智，其活性成分人参皂苷 Rd1 单体可有效改善 AD[79]。病理学研究表明，人参皂苷 Rb1 可促进 miR-130b-5p 的表达，抑制 TLR4/NF-κB 激活，减少促炎细胞因子的分泌，同时减弱激活的小胶质细胞诱导的神经元损伤[80]。姜黄破血行气，通经止痛，其成分姜黄素可通过抗氧化、促神经干细胞增殖分化等作用机制改善对 AD 的认知与记忆功能[81]，并且能够通过上调 miR-218-5p[82]、miR-362-3p[83] 阻碍 TLR4/NF-κB 炎性通路，同时对小鼠小胶质细胞损伤发挥保护作用[83]。牛蒡子具有宣肺祛痰之功，其成分牛蒡子苷元通过上调 miR-16 和 miR-199a 的表达减轻炎症反应，常用于炎症的治疗[84-85]。另外，开窍药麝香提取物麝香酮干预脑缺氧损伤的细胞模型后，miR-142-5p 的表达增加，降低了 HMGB1 的表达，从而导致 TLR4/NF-κB 通路失活，最终促进缺氧/复氧损伤暴露的细胞损伤得到改善[36]。黄芩苷[86]、金雀异黄素[87]、淫羊藿[88] 等均可干扰 TLR4/NF–κB 信号通路，减轻 AD 的神经炎症反应。(2) 中药复方。黄芪汤具有益气滋阴养血之功，可上调 miR-140-5p 和下调 miR-93，影响 TLR4/MyD88/NF-κB 信号通路，抑制其下游的炎症级联反应[89]。地黄饮子滋肾阴、补肾阳、开窍化痰，其通过抑制该条通路减缓炎症反应，进而改善 AD 的机制已在前文介绍[59]。安神定志方可能通过抑制 miR-103a-3p 介导的 tau 蛋白中 Ser396 和 Thr231 位点的磷酸化，提升 AD 大鼠学习记忆能力并修复神经元损伤[90]。综上可知，部分补肾益髓、活血化瘀、化痰开窍醒神的中药可能通过 miRNA-TLR4 通路抑制神经炎症，发挥神经保护作用。

3. 针灸与运动调控 miRNA-TLR4 治疗 AD：在 AD 治疗中，药物治疗联合针灸与运动等非药物疗法更有益于患者的病情恢复。目前，针灸治疗 AD 的经脉选择以督脉居首，涉及足阳明胃经、手少阴心经等十四经[91]，具有活血通络[92]、醒脑开窍[92] 等功效。在 Wang 等[93] 的研究中，针灸通过抑制 miR-93 介导的 TLR4/MyD88/NF-κB 信号通路减轻与炎症相关的认知障碍。有氧运动可改善 AD 大鼠的学习记忆能力[94]，能够通过激活 TLR4/miR-223/NLRP3 信号通路轴上调 miRNA-223，调控 TLR4/NF-κB 信号通路抑制小鼠海马组织功能并发挥抗炎作用[95]。

4. 细胞外囊泡 (extracellular vesicles，EVs) 介导 miRNA-TLR4 治疗 AD：EVs 是生物源性纳米颗粒，通过携带 RNA、DNA 和一些细胞因子实现细胞间信息交流。EVs 穿过 BBB 的能力以及抗炎特性和调节功能为治疗神经系统疾病提供了新思路[96]。激活小胶质细胞分泌组的间充质干细胞 (mesenchymal stem cells，MSCs) 分泌的 EVs 可上调 miRNA，过表达的 miRNA 靶向 TLR4 信号通路上的关键基因，并增强免疫调节潜力，能够对抗神经炎症[96]。EVs 可以将 miR-124 传递到中枢神经系统，显著降低炎症标志物 TLR4、MYD88、STAT3 和 NF-κB 的表达，减轻小胶质细胞活化[97]。外泌体是常见的携带 miRNA 的一类 EVs。在 Xiong 等[98] 的实验中，从骨髓间充质干细胞中提取的外泌体可能通过提高 miRNA129-5p 的水平猝灭 HMGB1-TLR4 通路的活性以缓解 SAH 后的早期脑损伤 (early brain injury，EBI)。此外，携带 miR-138[99]、miR-126[100]、miR-146a-5p[101] 的外泌体均可抑制炎症因子与炎症小体，减轻神经炎症。

五、小结与展望

中西结合是治疗 AD 的关键策略，可发挥多途径、多靶点的优势对 AD 患者的病情进行整体调节。神经炎症是 AD 的重要发病机制之一，miRNA 介导 TLR4 炎性通路影响神经炎性损伤调节的机制精细复杂，囊括多种因子、靶点及层面，探索在 AD 无症状期敏感的生物标志物以及不同时期各种手段调节该通路对 AD 的早期诊断与防治具有重要意义。然而针对该炎性通路的各项疗法研究尚显不足，关于其具体发生、发展过程还有待进一步探究。因此，进一步了解 AD 病因及其与 miRNA-TLR4 信号通路的相关机制，探索具备潜在治疗价值的 miRNA 分子，开发以 miRNA-TLR4 信号通路为干预途径的新型药物具有重要意义。同时，外泌体作为一种可穿过 BBB 发挥作用的纳米颗粒，也是一种极具潜力的治疗药物。近年来，已有使用固体脂质纳米颗粒、脂质体、聚合物纳米颗粒转载药物治疗中枢神经系统疾病的研究，设计能够通过 BBB 的纳米载体将 miRNA 递送到靶器官或将成为治疗 AD 的有效手段。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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