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评 述

阿尔茨海默病血浆和肠道菌群中生物标志物的研究进展

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摘要 阿尔茨海默病(Alzheimer's disease, AD)是一种常见的神经退行性疾病, 在老年人中患病率高. 但目前其发生机制尚不明确, 而且缺乏便捷的早期诊断手段, 因而难以在疾病早期进行干预和治疗. 近几年, 随着质谱、免疫学方法等新技术的发展, 外周血Aβ、P-tau、外泌体、miRNA、肠道细菌等成为AD早期诊断及病情监测的潜在生物学标志物. 本文就目前AD外周血生物标志物及AD相关肠道菌群生物标志物现况进行了综述, 旨在为AD的早期诊断和预测疾病进展提供参考.

关键词 阿尔茨海默病, 血浆生物标志物, 肠道菌群, 诊断, 生物标志物

阿尔茨海默病(Alzheimer's disease, AD)是一种中枢神经退行性病变, 主要表现为记忆力减退[1], 是痴呆最常见的类型[2]. AD的典型脑部病理改变为淀粉样蛋白沉积形成的细胞外老年斑和微管相关tau蛋白过度磷酸化形成的神经纤维缠结(neurofibrillary tangles, NFTs), 同时伴有神经元丢失及其突触变性、胶质细胞激活和神经炎症[3]. 2018年1月, 美国食品药品监督管理局(U.S. Food and Drug Administration, FDA)推荐AD的诊断标准——ATN(amyloid, tau, and neurodegeneration)标准, 明确了AD生物标志物的诊断意义[4]. 标准中的生物标志物包括: Aβ(A)、病理性tau蛋白(T, 包括总tau蛋白和磷酸化tau蛋白)以及神经变性(N). 随着生物标志物相关研究的发展, 脑脊液(cerebrospinal fluid, CSF)、磁共振成像(magnetic resonance imaging, MRI)、正电子发射断层扫描(positron emission computed tomography, PET)成像对于AD的早期诊断有重要作用. 但由于CSF难以获取并且有侵入性, PET价格昂贵, MRI特异性差等原因, ATN标准难以普遍推广. 目前AD临床诊断仍然主要依赖于病史、神经心理测试以及随着时间的推移对症状的评估[5]. 亟需侵入性更小、成本效益更高、更容易获得的生物标志物. 越来越多研究者将目光投向血浆生物标志物和肠道菌群

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(gut microbiota, GM)的研究. 本文就AD外周生物标志物(血浆生物标志物、肠道菌群)进展进行综述.

1 血浆生物标志物

由于大脑神经元等细胞分泌的蛋白会直接进入脑脊液, 所以CSF能够更好地反映脑内的情况. CSF中Aβ、总tau(total tau, T-tau)蛋白和磷酸化tau(phosphorylated tau, P-tau)蛋白作为核心生物标志物, 对于AD早期诊断的准确度可达85%以上[6]. PET能提前2.5年确诊AD, 其准确度在90%以上[7]. 针对Aβ的匹兹堡复合物B(Pittsburgh compound B, PiB)等PET成像技术引起了广泛关注, PiB-PET阴性被许多临床研究列为排除AD的影像学依据[8~11]. 但脑脊液的获取具有侵入性、创伤较大, PET价格昂贵, 且较难在短时间内多次检测. 血液易于采集, 更有利于临床诊断或筛选. 然而, 大部分研究表明开发AD的血液生物标志物比较困难. 因为其通过物质交换, 只有一小部分进入外周血, 且血液的复杂成分使低丰度蛋白质的检测变得困难[12]: 进入血液的微量脑蛋白必须在含有非常高水平的血浆蛋白(如白蛋白和IgG)的基质中进行测量; 其次, 除了被稀释, 释放到血液中的脑蛋白可能会被蛋白酶降解, 在肝脏代谢或被肾脏清除; 而在血浆中, 血小板也分泌APP并产生Aβ[13], 这增加了寻找AD血浆生物标志物的难度.

因此, 血浆的中枢神经系统疾病生物标志物的测量方法需要具备极高的灵敏度和特异性, 以降低其他分子干扰的风险[14]. 从最早使用单分子阵列(single-molecule array, SIMOA)、数字酶联免疫吸附试验(enzyme-linked immunosorbent assay, ELISA)技术对血浆神经丝轻链(neurofilament light chain, NfL)进行定量检测[15], 到目前基于质谱、免疫学方法及其组合等手段对血浆多种蛋白质进行大规模测量, 已经报告了AD的多种血浆生物标志物. 本文将展示AD的主要血浆生物标志物及其产生机制(图1).

1.1 Aβ

Aβ是APP经过一些列酶切作用裂解形成的多肽, 表达过量, 则沉积形成老年斑(senile plaque, SP). Aβ的可溶性寡聚体被认为是产生神经毒性并最终造成AD神经元丢失的主要形式[16]. Aβ在CSF和血液中都能检出[17], 是AD的首选标志物之一. 不同酶的切割可以产生长度可变的多肽, 如Aβ40, Aβ42等[18]. Aβ42比Aβ40更容易聚集, AD患者脑组织SP中的Aβ42/Aβ40通常是升高的, CSF中Aβ水平则降低[19]. Palmqvist等人[20]发现, CSF Aβ42变化最大, 其次是Aβ42/Aβ40, P-tau和T-tau. Nordberg[21]的一项纵向研究表明, CSF中T-tau/Aβ42和P-tau181/Aβ42在AD临床症状出现前15年显著升高, 而Aβ42水平仅在预期症状出现前10年左右才开始下降.

虽然血浆中Aβ不能反映脑内Aβ代谢, 但CSF和血液之间Aβ能通过双向运输达到动态平衡, 因此血浆Aβ水平能在一定程度上帮助鉴别和检查AD. AD早期血浆Aβ42水平会显著降低, 使用质谱法测量血浆Aβ浓度, 也显示了其与脑β淀粉样变性之间的显著相关性[22~24]. 2018年, 日本和澳大利亚的学者[24]结合免疫沉淀反应和质谱分析技术检测外周血中的Aβ, 结果发现, 与PIB-PET作为金标准比, (APP)669-711, Aβ42和Aβ40三者结合诊断AD的AUC值为94.1%, 准确率超过了90%. Janelidze等人[25]使用超灵敏分析也获得了类似的结果. 相关文献表明, 结合血浆Aβ42/Aβ40和P-tau181/Aβ42比只用单一指标鉴别和预测AD进展更准确[24,26,27]. Kim等人[28]用阵列式碳纳米管检测外周血的tau和Aβ, 将复合生物标志物(T-tau/Aβ42, P-tau181/Aβ42和Aβ42/Aβ40)作为biomarker进行评估, 区分AD和正常对照的AUC为0.93, 敏感性达到0.90. 与昂贵的质谱仪分析技术相比, 该碳纳米管传感器阵列可以很容易地被开发成带有集成传感器和读出电路的小型便携式设备, 且能极其灵敏地检测血浆中的多个AD生物标志物.

1.2 tau

tau蛋白是一种分子量为50~75 kD的微管相关蛋白, 主要分布在神经元的轴突上. 正常情况下, tau蛋白呈可溶性, 与微管蛋白结合以促进微管的聚合和稳定. 但在AD患者中, 过度磷酸化使tau蛋白由可溶变为不可溶, 从而发生病理性聚集导致NFTs, 并最终导致神经细胞丧失功能, 甚至死亡[19,29]. tau和P-tau在细胞内生成, 大部分是细胞变性死亡后释放到脑、CSF及外周血[30]. 与健康对照组相比, AD患者脑组织中有大量的tau蛋白聚集[31], NFTs的数量与临床痴呆程度呈正相关[32,33]. CSF中T-tau水平作为神经元损伤标志物, 在许

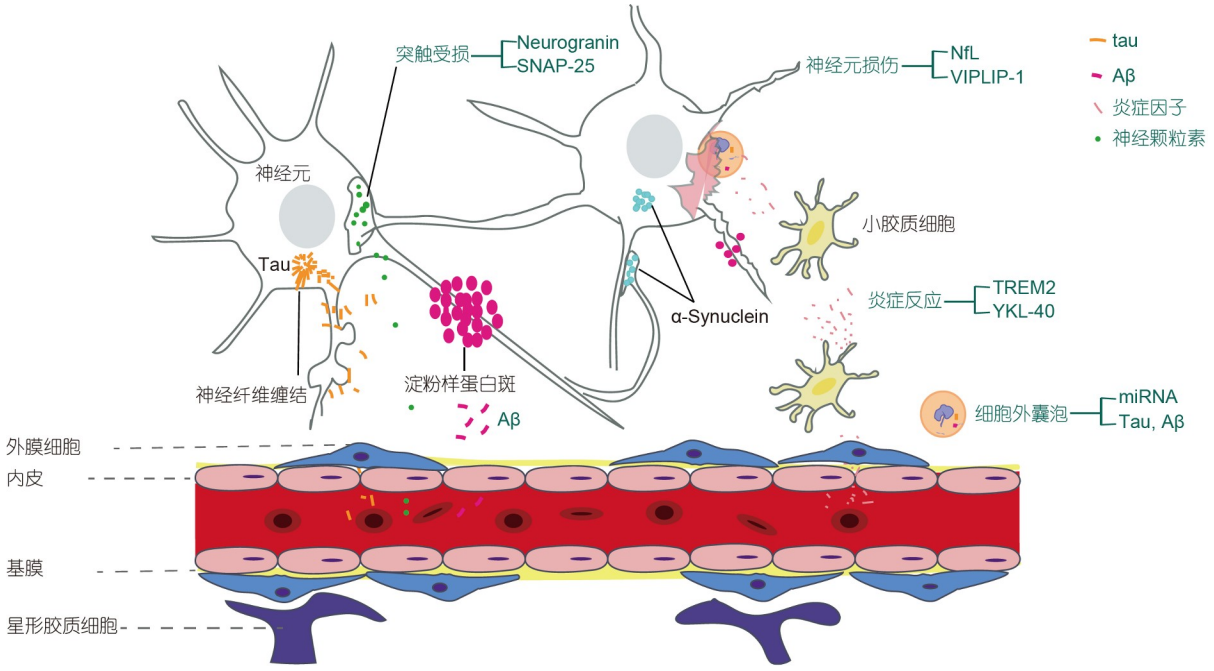

图 1　本文所涵盖的AD血浆生物标志物产生机制(神经元和AD生物标记物产生的物质通过血脑屏障或血脑脊液屏障进入外周血)

Figure 1　Mechanisms of the generation of plasma biomarkers for AD. Substances produced by neurons and AD biomarkers pass through the blood-brain barrier or the blood-cerebrospinal fluid barrier into the peripheral blood

多神经退行性疾病均升高, 如Creutzfeldt-Jakob病[34]、AD、路易体痴呆(dementia with Lewy bodies, DLB)、血管性痴呆(vascular dementia, VaD)和额颞痴呆(frontotemporal dementia, FTD)[35]等. 与T-tau相比, P-tau水平升高在AD中具有更高的特异性, 能反映NFTs病理改变[36]. 脑脊液中P-tau181或P-tau231水平在AD比在其他神经退行性疾病中升高更明显, 对于鉴别诊断具有重要意义[37].

由于血浆中的tau水平远低于脑脊液中的tau水平, 传统方法在轻度认知障碍(mild cognitive impairment, MCI)和AD患者血液中很难检测到tau蛋白[38], 需要借助血浆tau蛋白超灵敏定量检测的方法[39](表1). 2013年, Zetterberg等人[40]开发了一种基于数字阵列技术的超灵敏检测方法, 该方法比常规免疫分析的灵敏度高1000多倍, 他们发现, 与对照组或MCI患者相比, AD患者血浆中T-tau水平升高. 随后, Mattsson等人[33]使用超灵敏数字酶联免疫吸附方法进行了前瞻性队列研究和横断面研究, 报告了血浆T-tau可能部分反映了AD的病理, 但单独血浆T-tau不足以作为AD的生物标志物. Tatebe等人[41]开发了一种新的超灵敏免疫分析方法, 用于血浆P-tau181定量, 结果表明, 与正常对照组相比, AD患者的血浆P-tau181显著升高.

2020年, 有多项血浆P-tau相关的重要研究发表[42~46]. 使用电化学发光免疫分析技术、单分子免疫阵列技术等, 可以极大提高血浆P-tau检测的灵敏度, 而且与VaD、FTD、帕金森病性痴呆等神经系统变性疾病也有很好的区分度(AUC 80%~100%). 最新研究显示, 仅检测到Aβ的细微变化(如PET阳性)时, 血浆P-tau181, P-tau217以及P-tau231等新型tau生物标志物在临床前AD初始阶段即显著升高[47].

Palmqvist等人[46]研究发现, 血浆P-tau217将临床诊断的AD与其他神经退行性疾病区分开来, 并能区分AD患者不同的病理诊断水平. 此外, 血浆P-tau217准确性显著高于血浆P-tau181, NfL, CSF P-tau181, CSF Aβ42/Aβ40, PET tau和MRI测量, 而与CSF P-tau181, CSF P-tau217和tau-PET相比没有显著差异. 与非*PSEN1*突变携带者相比, *PSEN1*突变携带者血浆P-tau217水平显著升高. Brickman等人[48]也得出与其相似的结果, 测定血浆P-tau217的效果优于所有其他血浆生物标志物. 此外, Janelidze等人[49]的一项纵向研

表 1 阿尔茨海默病血浆生物标志物tau

Table 1 Plasma biomarkers for AD, tau

血浆生物标志(tau)	资料来源	检测方法	效能/结论
T-tau	Zetterberg等人[40] Mattsson等人[33]	数字阵列技术超灵敏检测技术; 超灵敏数字酶联免疫吸附方法	AD患者血浆中T-tau水平升高; 发生AD的MCI患者和稳定的MCI患者之间未发现差异; 血浆T-tau可能反映了AD的病理; 单独血浆T-tau不足以作为AD的生物标志物
P-tau181	Tatebe等人[41]	超灵敏数字酶联免疫吸附方法	AD患者的血浆P-tau181显著升高
P-tau217	Palmqvist等人[46] Brickman等人[48] Janelidze等人[49] Mattsson-Carlgren等人[50]	电化学发光免疫分析技术 超灵敏单分子免疫阵列技术	测定血浆P-tau217的效果优于所有其他血浆生物标志物; 将临床诊断的AD与其他神经退行性疾病区分开来; 能区分AD患者不同的病理诊断水平
P-tau231	Ashton等人[51]	超灵敏单分子阵列技术	区分Aβ阴性CU患者、Aβ阴性MCI患者、非AD神经退行性疾病患者; 能区分AD患者不同的病理诊断水平

究通过检测血浆P-tau217与CSF和PET AD病理生物标志物, 发现血浆P-tau217水平在AD早期升高, 且这种变化先于PET tau, 与脑脊液P-tau217类似. 在另外一篇纵向研究中, Mattsson-Carlgren等人[50]重复测量P-tau217长达6年, 发现血浆P-tau217水平在AD临床前期和前驱阶段加速上升. Ashton等人[51]开发了一种超灵敏的SIMOA, 定量测定血浆P-tau231, 发现血浆P-tau231能够高准确度地识别AD患者, 并将他们与Aβ阴性的认知能力未受损(cognitively unimpaired, CU)老年人(AUC=0.92~0.94)、Aβ阴性的MCI患者(AUC=0.89)、非AD神经退行性疾病患者(AUC=0.93)区分开来. 血浆P-tau231与血浆P-tau181一样能区别AD的临床分期和神经病理, 且P-tau231增加得更早, 但目前尚无直接比较血浆P-tau231和血浆P-tau217的研究. 因此, 血浆P-tau231适用于AD快速筛查, 也可能作为更好的AD病理分期生物标志物. 由于横断面研究的局限性, 需要进行更多纵向研究以确认疾病过程中新型P-tau生物标志物的变化, 并评估其预测认知障碍的能力.

1.3 miRNA

微小RNA又称microRNA(miRNA), 是一类由内源基因编码长度约为22个核苷酸的非编码单链RNA分子, 参与转录后基因表达调控. miRNA可通过调控AD中APP[52]、β-分泌酶1(BACE1)[53,54]、tau[55]等生物标志物的表达和神经炎症相关的胶质细胞的激活从而影响AD的发病机制.

miRNA可通过调节*APP*, *BACE1*等基因的表达致使Aβ异常沉积. Hébert等人[54]发现, 与同龄对照组相比, 散发性AD皮质中的miR-9表达下调, 且BACE1和PS1均被鉴定为miR-9的潜在靶点. 临床试验发现, 与同龄对照组相比, AD患者顶叶皮质中的miR-29a和miR-29b下调[56]. miRNA可通过参与调节tau蛋白过度磷酸化进程来影响AD的发展. miR-132/-212双敲除小鼠在识别、空间记忆以及新物体识别测试中表现出明显的认知缺陷[57]. miRNA可通过调节炎症因子和抗炎症因子的表达对神经系统发挥作用. miR-155是研究AD相关神经炎症最深入的miRNAs之一. miR-155的上调可增强小胶质细胞和星形胶质细胞的活化, 从而导致炎症. 近来, 有关mRNA的AD血浆生物标志物相关研究走进人们的视野.

Swarbrick等人[58]系统总结了2016年以前的外周血miRNA与AD的相关性研究, 指出hsa-miR-107, hsa-miR-26b等10个miRNA与AD密切相关, 甚至在症状出现前20年就可发生改变, 用于诊断AD的敏感性为0.75~0.95, 特异性为0.77~0.95. Karaglani等人[59]则利用自动机器学习方法分析公开的数据库, 找到3个miRNA可预测AD, AUC达0.975. 此外, miR-455-3p区分AD和正常对照的AUC为0.7953, miR-127-3p可区分AD和FTD[60]. miR-206和miR-132区分MCI和正常对照的AUC为0.981, Xie等人[61]发现, 血清中的miRNA-206, miRNA-132, miRNA-193b, miRNA-130b, miRNA-20a, miRNA-296, miRNA-329与AD相关, MCI患者外周血中miRNA-206和miRNA-132水平明显升高, 联合使用诊断AD相关的MCI特异性高达98.5%. 机制上, miRNA-206和miRNA-132可调控编码脑源性神经生长因子(brain-derived neurotrophic factor, BDNF)的*BDNF*

和编码去乙酰化酶1(SIRT1)的*SIRT1*，miRNA-206和miRNA-132水平升高，BDNF和SIRT1水平会降低[61]. BDNF可调控神经元的生长、可塑性及凋亡，外周血中高水平的BDNF与AD发病风险低有关[62]. Siedlecki-Wullich等人[63]检测了一组与突触蛋白相关的miRNAs血浆水平，发现MCI和AD患者的血浆中miR-92a-3p, miR-181c-5p和miR-210-3p显著上调，FTD患者未见变化.

miRNA作为AD的潜在生物标志物被广泛研究，目前，已发现有137种miRNAs在AD血液中发生改变. 由于缺乏方法学标准化和所报道的数据之间的高度变异性，最有希望的miRNA生物标志物候选还未被挑选出来[64]. 因此，miRNA是否能成为AD的诊断标准，还需要进一步研究.

1.4　细胞外囊泡

细胞外囊泡(extracellular vesicle, EV)是由细胞释放的各种具有膜结构的囊泡结构的统称，包括外泌体、微粒、凋亡小体，其携带细胞来源的多种蛋白质、DNA、mRNA、miRNA等物质[65]. 已被广泛接受的是, EV可为各种疾病的诊断或预测提供良好的生物标志物来源，如癌症[66~68]、代谢性疾病[69]、心血管疾病[70]和神经退行性疾病[71]. 在中枢神经系统中，已有许多研究证实神经源性EV中的AD相关致病蛋白(包括tau和Aβ)在AD的发病机制中发挥重要作用[72~75]. 血浆和脑脊液均可发现EV[65]，且外周血神经源性EV因为携带Aβ, P-tau等, 成为具有诊断AD潜能的敏感生物标志物.

最近, 外泌体中的神经源性蛋白被认为是AD的血浆生物标志物. 首都医科大学宣武医院贾建平教授团队[76]的研究显示，在外周血神经源性外泌体中，Aβ42, T-tau和P-tau水平与其在脑脊液中的水平高度相关，能够清楚区分MCI、AD患者和健康对照者，AUC为0.73~0.93，而且与脑脊液的诊断能力相当. Ellegaard Nielsen等人[77]使用邻近延伸分析测定AD、MCI患者及健康对照者血浆EV中182个蛋白的含量，确定了蛋白质图谱，从而可以区分三者. Eren等人[78]发现，外周血EV中的P-tau231, P-tau181等联合标志物, 区分AD前期的AUC为0.94，敏感性和特异性分别为86.0%和86.7%. 然而这些研究的样本量均不大，需要更多的人群研究结果进一步验证.

1.5　其他新型血浆生物标志物

随着科学技术的发展及AD的研究日渐深入, 越来越多的新型血浆标志物(AD神经损伤、突触变性、神经炎症等相关因子)进入人们的视野. 2018年的一项研究对1583名患者进行连续11年的NfL检测，结果显示AD患者中NfL水平升高，且与认知受损呈正相关[79]. 最新的一项研究显示，血浆NfL在诊断AD和预测AD的临床进展方面优于血浆T-tau的检测[80]. 2014年青岛大学的一项研究测量AD患者外周血中的TREM2 mRNA和蛋白质，ROC曲线分析显示，对单核细胞上TREM2蛋白水平的诊断准确率为70%，敏感性为68%, 特异性为72%[81]. 这表明TREM2可能作为一种新的非侵入性AD诊断生物标志物. 其他神经损伤或神经炎症相关的标志物[82~84], 如VIPLIP-1, neurogranin, YKL-40, SNAP-25等, 已有研究证明其脑脊液检测有作为AD突触变性和神经炎症的独立标志物的潜力，但血液检测还在初步探索中. 关于这些新型血浆标志物的研究较少，需要更多的研究来证明它们的诊断准确性和临床应用价值.

2　肠道菌群生物标志物

2.1　肠道菌群的功能及其变化

肠道菌群是指寄居在人类以及动物肠道内的大量微生物群. 一个成年人肠道包含了至少1000种不同的微生物, 其总数目达10^{14}个, 被称为人体的另外一个器官[85]. GM在正常情况下处于动态平衡中, 和宿主保持一种互利共生关系[86]，细菌的种数受人体发育阶段、身体状态和食物等影响，在一定条件下会出现菌群紊乱[87]. 菌群紊乱和多种疾病相关，如胃肠疾病、代谢性疾病、肝病、癌症、慢性疲劳综合征、行为及精神性疾病(如孤独症和抑郁症)、帕金森病等[88~91]. 最近, GM对中枢神经系统的影响受到极大的关注，GM的改变与包括自闭症、多发性硬化症和帕金森病在内的神经系统疾病有关[92,93]. 越来越多的研究表明, GM和AD的发生有关[94~97].

2.2　GM与AD

胃肠道内微生物与大脑间建立的双向连接被称为“微生物-肠道-大脑(the microbiota-gut-brain, MGB)

轴"[98]. 肠道菌群主要通过神经递质活性产物, 自身形成淀粉样蛋白, 引起低水平的炎性反应, 激活小胶质细胞产生神经炎症, 最终导致神经细胞损伤, 认知能力降低, 从而参与AD的病理发展[99]. 对粪便中微生物进行分析发现, AD患者粪便菌群中具有抗炎作用的直肠真杆菌丰度减少, 而促炎作用的志贺菌丰度增加, 且与血液炎症因子水平、AD严重程度呈正相关[100]. 另一方面, GM中大肠杆菌、乳酸菌、酵母菌和芽孢杆菌等细菌可以合成γ-氨基丁酸(γ-aminobutyri cacid, GABA)、5-羟色胺、多巴胺、丁酸、组胺等多种活性成分, 在大脑活动方面起重要作用[101]. GM改变导致的GABA水平降低[102], 与AD、焦虑和抑郁等有关[103]. 此外, 有研究发现, AD患者肠道短链脂肪酸(short-chain fatty acids, SCFA)显著减少[104]. SCFA是GM降解膳食纤维的产物, 有利于调节GM平衡、提高免疫力、促进神经递释放以及抗衰老等[105], 并能经肠道进入血液循环, 依赖单羧酸转运体通过血脑屏障, 影响大脑功能[106]. 另外, GM中占绝大多数的革兰氏阴性菌细胞壁结构成分脂多糖可经受损肠黏膜屏障进入血液循环, 并可通过血脑屏障, 触发神经炎症反应, 激活Toll样受体致小胶质细胞过度活化, 发生细胞毒性作用, 导致不可逆性AD病理性改变和认知功能障碍[107]. 由于GM具有容易检测、可以被调控等特点, 将GM作为AD生物标志物乃至预防和治疗的途径是新兴的具有潜力的研究方向.

2.3 肠菌生物标志物

罗本燕团队[108]研究发现, AD患者粪便微生物多样性低于遗忘型轻度认知障碍(amnestic mild cognitive impairment, aMCI)患者, 且微生物群丰度和AD患者的临床严重程度评分之间存在显著相关性, AD患者Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae增加. GM可区分AD、aMCI与正常人, AUC分别为0.890、0.940, 区分AD的aMCI的准确性也很高, AUC为0.925. 陈生弟团队[109]研究显示, AD患者粪便中*Dorea*, *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Blautia*, *Escherichia*等增加, *Alistipes*, *Bacteroides*, *Parabacteroides*, *Sutterella*, *Paraprevotella*则减少, GM区分MCI和AD患者的准确性达93%. 在另一项研究中, 与健康对照组或淀粉样阴性对照组相比, 认知受损的脑淀粉样变性患者的粪便中抗炎*Eubacterium rectale*的丰度降低, 促炎*Escherichia*/*Shigella*的丰度增加, 且脑淀粉样变性患者血清中促炎细胞因子(包括IL-6, CXCL2, 3NLRP3和IL-1b)水平升高, 而抗炎因子IL-10水平降低[100]. 本团队[110]检测了AD患者粪便GM来源的外膜囊泡中的代谢产物, 发现了18种明显差异的小分子物质, 诊断的AUC值达0.815~0.951. 多项研究均显示, AD患者粪便中*Blautia*, *Akkermansia muciniphila*, *Bifidobacterium*等抑炎菌、益生菌减少, 而*Bacteroides*, *Actinobacteria*, *Escherichia*等则增加[104,111,112]. 由于AD相关GM研究规模均较小, 考虑到GM组成受到饮食和年龄等各种因素的影响, 对这些数据的解释往往很困难, 尤其是还缺乏高质量的前瞻性队列研究. 所以, 未来还需要在人体上进行纵向研究和随机对照试验, 以找出以GM为靶点的AD早期诊断和治疗的新策略.

3 总结

综上所述, 外周生物标志物在AD和其他神经退行性疾病方面的研究取得了实质性进展. 与CSF相比, AD血浆生物标志物将为全球最常见的与年龄相关的神经退行性疾病提供一种快速、非侵入性和经济有效的早期检测和诊断方法. 此外, 静脉穿刺是一种常规的、安全的操作, 不会对患者造成任何伤害. 因此, 血浆生物标志物的检查是可以接受的, 并且很容易推广. 然而, 蛋白质本身的波动性及检测手段的局限性都影响着目前研究结果的可靠性, 这使得血浆生物标志物筛查疾病变得困难. 可以通过严格限制研究条件、统一检测方法来提高研究的一致性和准确性; 开发一种全新的特别适合检测血浆中低丰度蛋白的定性、定量检测技术, 将高通量、高灵敏度和定量集于一体, 是发现生物标志物的最适方法. 随着蛋白组学、代谢组学检测技术的推动, 外周生物标志物有望成为一种简便可靠、可大范围应用的早期筛查手段. 其中, 质谱法可以检测到蛋白质浓度的轻微变化, 免疫组织化学可以高精度地识别特定蛋白质. 这些方法显著提高了血浆生物标志物预测AD发生和发展趋势的准确性. 另外, 已有团队研制出更灵敏便捷的蛋白芯片和生物信息学分析等技术应用于生物标志物检测. 目前, 致力于完善生物标志物蛋白组学、代谢组学及早筛早诊检测技术的开发, 对早日实现AD外周生物标志物的早期诊断有重要作用. 本文从AD病理生理变化的角度对其

血浆生物标志物和GM研究进展进行总结，除已经纳入诊断标准的Aβ42，T-tau及P-tau外，miRNA、EV、炎症反应标志物及肠道菌群等新型生物标志物尚在研究之中. 对这些有潜力作为AD早期诊断的外周生物标志物进一步研究, 可以为AD早期诊断、药物研发提供新方向, 带来新契机.

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Recent advances in blood and gut microbiota biomarkers for Alzheimer's disease

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Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, with a high prevalence among the elderly. However, the mechanism of its occurrence is not clear, and there is a lack of convenient means of early diagnosis, which makes it difficult to intervene in and treat the disease in its early stage. In recent years, with the development of mass spectrometry, immunological methods and other new technologies, potential biomarkers for early diagnosis and disease monitoring of Alzheimer's disease have been identified, including peripheral blood Aβ, p-tau, exosomes, miRNA, and intestinal bacteria. In this article, we reviewed the current research status of AD peripheral blood biomarkers and AD-related intestinal microbiota biomarkers, in order to provide a reference for the early diagnosis and prediction of the disease progression.

Alzheimer's disease, plasma biomarkers, gut microbiota, diagnostics, biomarkers

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