

小胶质细胞在神经发育和神经退行性疾病中的吞噬作用与调节机制

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【摘要】 小胶质细胞是神经胶质细胞的一种, 具有吞噬、清除、抗原提呈、促进损伤修复和分泌细胞外信号分子等多种功能。其中, 吞噬功能在神经发育、脑组织维持、突触重塑、神经退行性疾病发生发展及淀粉样 β 蛋白的清除等方面都发挥着重要作用。本文就小胶质细胞在神经发育及神经退行性疾病中的吞噬功能及其调节机制作一简要综述, 以期对神经退行性疾病的治疗提供新思路。

【关键词】 小胶质细胞; 吞噬; 神经发育; 淀粉样 β 蛋白; 神经退行性疾病

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Phagocytic function of microglia and underlying regulatory mechanism in neurodevelopment and neurodegenerative diseases

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【Abstract】 Microglia, a type of neuroglia, has a variety of functions such as phagocytosis, clearance, antigen presentation, promotion of repairment of injury and secretion of extracellular signaling molecules, in which phagocytosis of microglia plays a crucial role in maintaining brain tissue, remodeling synapses, clearance of several aberrant proteins such as amyloid β in neurodegenerative diseases, and in neurodevelopment. This review briefly summarizes the phagocytic function of microglia with underlying regulatory mechanism in neurodevelopment and neurodegenerative diseases, aiming to provide a new thought for the therapy of neurodegenerative diseases.

【Key words】 microglia; phagocytosis; neurodevelopment; A β ; neurodegenerative diseases

小胶质细胞(microglia)是神经胶质细胞的一种, 约占大脑中神经胶质细胞的10%~15%, 相当于定居在脑和脊髓中的巨噬细胞。近年来的研究发

现, 与其他组织巨噬细胞的起源不同, 小胶质细胞起源于卵黄囊, 并在胚胎发育早期进入脑组织, 特化为小胶质细胞^[1-2]。这提示小胶质细胞具有其特

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定的功能。目前已知的小胶质细胞功能包括清除功能、吞噬功能、抗原提呈功能、突触剥离作用、促进损伤修复和分泌细胞外信号等,在神经发育、脑组织维持、突触重塑、神经炎症、脑部感染、细胞毒性以及神经退行性病变等生理和病理过程中发挥着重要作用。

小胶质细胞的吞噬作用(phagocytosis)指受体介导的吞噬和清理脑组织中的“废物”,维持脑组织稳态的过程。病理状态下小胶质细胞被激活,活化的小胶质细胞可以吞噬凋亡细胞碎片、痴呆症患者脑组织中的淀粉样 β 蛋白(amyloid- β protein, A β)、髓鞘碎片、脑组织内感染病原等多种物质,从而起到清理有害物质、抗炎等作用。在生理状态下,未经活化的小胶质细胞同样可以清理大脑发育过程中产生的凋亡细胞以及一些多余的突触等^[3-4],在脑组织发育、形态发生、突触重塑等过程中发挥着重要作用。

1 小胶质细胞的吞噬是多步骤的生理病理过程

小胶质细胞的吞噬作用不仅是脑组织内凋亡细胞碎片、髓鞘碎片、感染病原以及痴呆症患者脑内 A β 淀粉样蛋白等无用或有害物质清除的主要机制,也是记忆形成时的突触剥离(synaptic stripping)过程的重要步骤^[4-7]。小胶质细胞的吞噬过程十分复杂,涉及到多种分子的参与,至今尚未完全研究清楚。目前被大家广泛接受的小胶质细胞吞噬模型是类似于巨噬细胞吞噬的三步模型,即吞噬靶标的发现(find me)、吞噬(eat me)和消化(digest me)^[8]。

1.1 吞噬靶标的发现

脑组织内的凋亡细胞会释放 ATP 和 UTP 到细胞外,而在细胞外基质中,ATP 和 UTP 会被外核苷酸酶降解为 ADP 和 UDP^[9]。胶质细胞的表面存在有多种嘌呤能受体,其中,ATP 及其代谢产物可以激活受体 P2Y1-14、P2X1-7、P2Y12 等 P2 家族成员,UDP 及其代谢产物可以激活 P2Y6;激活的受体可以进一步活化细胞内一系列信号途径,如 PI3K/AKT,进而促使胶质细胞向吞噬靶标运动,或伸出伪足将吞噬靶标包围^[7, 10-13]。

此外,趋化因子、细胞因子、生长因子等也具有增强小胶质细胞清除细胞碎片的作用,如分形趋化因子(CX3CL1)、白介素 34(IL-34)、纤维母细胞生长因子(FGF2)等^[14-15]。

1.2 吞噬

吞噬过程即受体介导的识别与吞噬过程,小胶质细胞表面的很多受体都参与了这一过程,其中一部分受体介导小胶质细胞与靶标的识别和桥接,另一部分受体激发内在化过程^[16]。

根据功能的不同,可将小胶质细胞表面受体简单地分为两类。第一类是病原侦测相关分子(detection of pathogen-associated molecular patterns, PAMPS),主要由清除剂受体(scavenger receptor)与 Toll 样受体、免疫球蛋白超家族成员协同作用,对脑部的细菌、真菌等病原进行侦测、桥接吞噬。这类受体包括 CD36、CD68、COX-1、MARCO、SR-1、SR-2、TLR2、TLR4、DECTIN-1、MR 等^[4, 17-21]。第二类是凋亡细胞侦测相关分子(detection of apoptotic cell-associated molecular patterns, ACAMPs),细胞凋亡时,细胞膜内侧的磷脂酰丝氨酸(phosphatidylserine, PS)暴露于细胞膜表面,可以与 ACAMPs 中最主要的一类受体(PS 受体)结合。这类 PS 受体主要介导小胶质细胞与凋亡细胞的识别,包括 BAI-1、MER、PSR、STABILIN-2、TIM-1、TIM-4 等^[4, 22];另一类分子可以介导小胶质细胞与凋亡细胞桥接,如乳脂球表皮生长因子(milk fat globule-epidermal growth factor, MFG-E8)等^[23]。

此外,还有一些分子可以激发内在化过程,包括整合素家族成员和 IgG 超家族成员,参与小胶质细胞与靶标的桥接和内在化的激发^[24-25]。其中, IgG 超家族成员中的 TREM2,可以激活 SRC/SYK/RAC1 等细胞运动相关信号通路,激发内在化过程;同时可以通过抑制 RAS/ERK 减少炎症因子分泌^[26]。

1.3 消化

脑组织内的凋亡细胞碎片、感染病原、髓鞘碎片、A β 淀粉样蛋白等在受体的介导下,形成吞噬体,进一步与早期或晚期胞内体融合,形成吞噬溶酶体。吞噬溶酶体内存在多种水解酶和组织蛋白酶,可以对吞噬的物质进行降解^[27]。

2 小胶质细胞的吞噬作用与神经发育

哺乳动物的中枢神经来源于外胚层。人类胚胎发育的第三周左右,在胚胎背侧,神经外胚层发育形成神经板,是神经元和胶质细胞的来源。神经板随后卷曲发育成为神经管。神经管最初由一层增生能力极强的神经上皮构成,不同的部分可分别

发育为大脑、小脑、延脑和脊髓等,共同组成构筑精巧、功能精细复杂的神经系统^[28]。

神经细胞和胶质细胞的增生、迁移与凋亡,是神经发育和形态发生的关键。细胞生长与凋亡之间的平衡失调将会导致各种神经发育畸形和疾病。凋亡神经细胞的清除对于神经的正常发育至关重要,而小胶质细胞吞噬正是神经组织内凋亡细胞清除的主要途径。小胶质细胞在变形状态下可以在脑组织中迁移,并在凋亡细胞周围聚集^[29]。有体外培养实验证实,活化的小胶质细胞可以吞噬死亡的浦肯野细胞和海马神经元^[30-31]。

小胶质细胞的吞噬作用在突触重塑和环路形成中同样发挥着关键作用^[32]。神经发育过程中,不仅有大量的神经元凋亡,同时也伴随着突触的重塑过程。哺乳动物出生后,在丘脑、小脑、嗅球、海马等突触重塑活跃的脑区都有反应性小胶质细胞的存在,并与未成熟突触紧密接触;研究发现小胶质细胞中含有被吞噬的突触蛋白,证实小胶质细胞可以通过吞噬作用对突触进行修剪^[33-34]。而在成体脑组织中,小胶质细胞也可以通过对突触的修剪作用影响突触可塑性。神经元通过突触网络通信是认知活动的基础;而随着年龄增加,神经元树突密度降低和突触可塑性丧失是认知障碍发生的细胞基础^[35-36]。研究表明,小胶质细胞参与突触的成熟和修剪;抑制小胶质细胞的活性可改变相关神经元的树突重塑和长时程增强 (long-term potentiation, LTP)^[37-39]。

突触的修剪与上述细胞凋亡碎片的吞噬过程类似,退化的突触被小胶质细胞识别后,激活 P2X 和 P2Y 等嘌呤受体,进而激活一系列运动相关的胞内信号,促使细胞形成伪足,包裹退化的突触,形成吞噬溶酶体,在细胞内完成分解过程^[40-41]。

3 小胶质细胞的吞噬作用与常见神经退行性疾病

3.1 阿尔兹海默病 (Alzheimer's disease, AD)

AD 是最常见的神经退行性疾病之一。A β 沉积是 AD 的主要病理特征,可以引起进行性的神经认知功能下降。脑组织中 A β 肽段的堆积与斑块的形成主要是由于 A β 蛋白产生与清除之间的不平衡所致,因此促进大脑中 A β 的清除对于减缓 AD 的发展具有积极作用^[42-44]。

小胶质细胞的吞噬作用是脑中 A β 清除的主要途径之一。通过全基因组关联分析 (genome wide

association studies, GWAS), 最新研究揭示了许多 AD 风险基因与小胶质细胞的吞噬功能密切相关^[45-47]。其中, ABCA7、TREM2、CR1、APOE 可以激活小胶质细胞的吞噬功能^[48-50]; 而 CD33、INPP5D (SHIP-1) 则对吞噬功能有抑制作用^[51-52]。研究发现,疾病发展的不同阶段小胶质细胞可能扮演着不同的角色^[53-54]。在疾病发生的早期阶段,正常的小胶质细胞可以通过吞噬、水解作用清除 A β ^[55]。而随着疾病进展, A β 也通过毒性作用影响着小胶质细胞的吞噬功能^[56]。在 AD 疾病发生后,病理状态下的小胶质细胞的吞噬作用使树突功能障碍进一步恶化,吞噬濒危的神经元^[57-58], 同时通过分泌促炎细胞因子加速疾病的发展^[59]。

A β 的吞噬过程受到小胶质细胞多种膜受体的调节。有文献报道目前已知的 7 个在小胶质细胞表达的受体, BECLIN-1 在 AD 中表达下调, Fc γ RIIb、SCARA-1、CD36、RAGE、TREM2 和 CD33 在 AD 中表达上调^[60]。其中 Beclin-1 缺失降低小胶质细胞对 A β 的摄取^[61-62]; Fc γ RIIb 介导促进 A β 斑块的清除^[63-64]; SCARA-1 可以提高小胶质细胞结合并吞噬 A β 的能力^[65-66]; CD36 通过 PPAR γ 信号提高 A β 吞噬^[67]; RAGE 通过结合 A β 引起炎症反应并促进淀粉样变性^[68]; TREM2 作用于 DAPI2 可在不引起炎症反应的情况下激活小胶质细胞吞噬功能^[26]; CD33 与 A β 肽段内在化的降低有关^[69]。这些线索提示我们,或许可以通过寻找节点基因,抑制小胶质细胞分泌促炎因子,激发吞噬功能清除 A β , 减缓 AD 病理进程。

3.2 帕金森病 (Parkinson's disease, PD)

PD 的主要病理特征包括黑质中多巴胺能神经元变性和路易小体形成。作为路易小体的主要成分、PD 的风险基因, α -突触核蛋白 (α -synuclein, α -syn) 在 PD 发生发展中扮演重要角色^[70-71]。了解 α -syn 在胞外清除和降解的机制对于改善 PD 疾病进程至关重要。

小胶质细胞在清除 α -syn 方面具有重要作用,小胶质细胞的吞噬能力可能取决于特定的 α -syn 分子类型^[72-73]。研究发现,除了神经元可以释放 α -syn, 小胶质细胞中同样也有 α -syn 表达; 在小胶质细胞中,正常水平的 α -syn 可能参与脂质介导细胞信号,过量表达的 α -syn 则会使吞噬功能受损^[74-76]。在 PD 病人中, α -syn 异常聚集; 小胶质细胞快速增殖肥大, CD11b、CD68、MHC-I 和 MHC-II

等标记物增多;相对其他脑区,黑质中的小胶质细胞富集,同时小胶质细胞黑质定位诱发 PD 患者多巴胺神经元的免疫损伤^[77-79]。

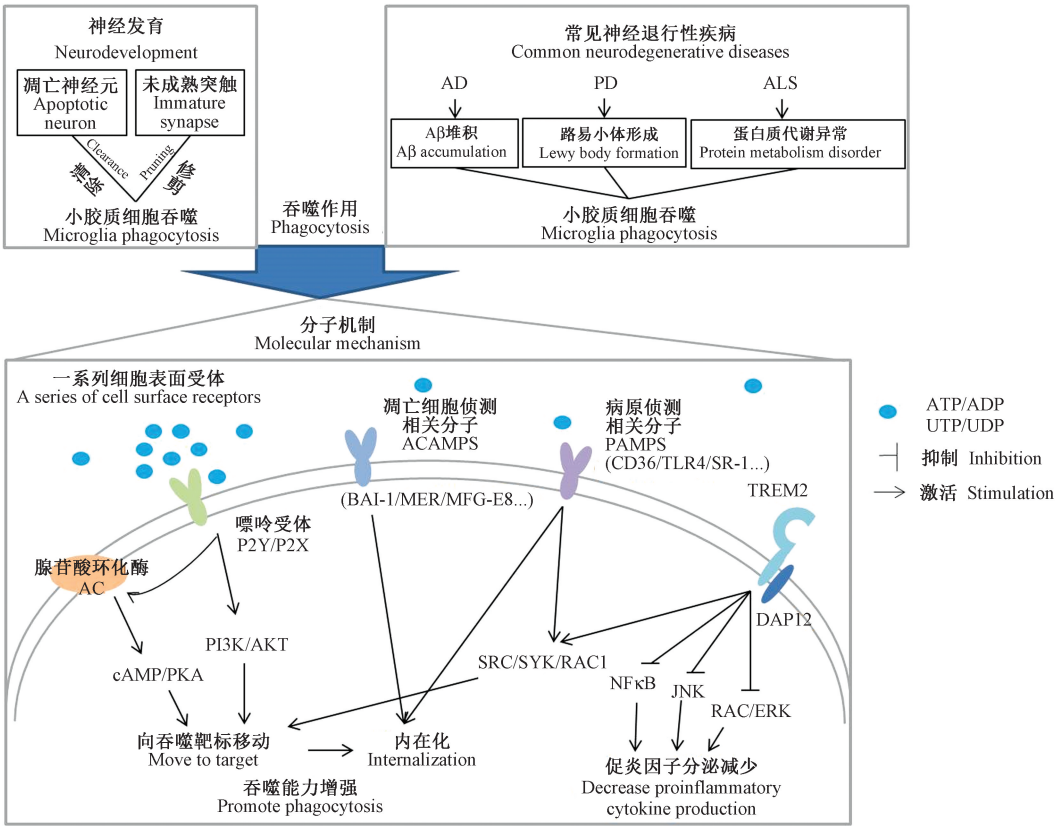
目前已知 α -syn 可以激活小胶质细胞上 TLR、CD36 等膜受体,并进一步激活 NF κ B、ERK1/2、p38MAPK 等胞内信号^[80-83],这些研究为我们寻找 PD 治疗靶点提供了新线索。

3.3 肌萎缩侧索硬化症 (amyotrophic lateral sclerosis, ALS)

ALS 是一种致命的神经退行性疾病,其病理特征为上运动神经元(大脑、脑干、脊髓)和下运动神经元(颅神经核、脊髓前角细胞)的进行性退变。目前已知 SOD1、C9ORF72 和 TARDBP/TDP - 43 是 ALS 的三大致病基因。损伤的运动神经元及星形胶

质细胞释放错误折叠的 mSOD1 蛋白使其获得毒性作用,可以引起氧化性损伤;而其他 ALS 相关蛋白,如变异的 TDP-43,可能增加运动神经元中的氧化应激^[84-85]。

小胶质细胞一经激活诱发神经毒性或者神经保护作用,依赖于其激活状态及疾病发展阶段^[86]。在 ALS 早期,小胶质细胞 CD206、Ym1 表达升高,呈现为吞噬功能增强,能够促进修复及再生。随着疾病的发展,损伤的运动神经元释放危险信号,小胶质细胞呈现为 NOX2、ROS、TNF α 、IL1 和 IL6 等促炎因子分泌增加,产生神经毒性^[87-89]。mSOD1 可以激活小胶质细胞,通过 CD14、TLR2、TLR4 激活下游各种清除剂受体依赖的信号通路^[90-91]。死亡神经元和异常神经元在胞外释放 ATP 也可激活小胶质



注:在神经发育过程中,凋亡的神经元及未成熟的突触被小胶质细胞识别后,激活 P2X 和 P2Y 等嘌呤受体,进而激活一系列运动相关的胞内信号,如 PI3K、PKA、Src 等;活化的小胶质细胞通过变形虫样移动,包裹退化的突触,吞噬细胞碎片。在神经退行性疾病中,小胶质细胞通过利用多种受体,如 TREM2、TLR2、TLR4、TLR9、CD36 等,激活下游信号,直接或间接地促进 A β 、 α -syn 及其他错误折叠蛋白的吞噬。

图 1 小胶质细胞的吞噬功能在神经发育和神经退行性疾病中的作用和分子机制

Note. During neurodevelopment, apoptotic neurons and unmaturred synapses are recognized by multiple purinergic P2X/P2Y receptors in microglia cells, which trigger activation of a series of motion-related intracellular signaling, such as PI3K, PKA, and Src. Activated microglia move by amoeboid-like movements and gather around the lesion, clearing cellular debris by phagocytosis. In neurodegenerative diseases, microglia activate various receptors, including TREM2, TLR2, TLR4, TLR9 and CD36, which then activate downstream signaling, promoting phagocytosis of A β , α -syn and other misfolding proteins directly or indirectly.

Fig.1 Phagocytic function of microglia and underlying mechanism in neurodevelopment and neurodegenerative diseases

细胞,通过 P2X、P2Y 诱发一系列炎症反应^[89]。此外,C9ORF72 突变可以降低小胶质细胞清除聚合蛋白的能力,同时改变小胶质细胞的应答,引起神经炎症^[92]。

4 小结与展望

综上所述,小胶质细胞的功能是多方面的,主要包括神经组织的监视功能、吞噬作用以及细胞因子、炎症因子、趋化因子和生长因子的分泌等^[93-94]。关于小胶质细胞吞噬作用的分子机制,总结如图 1。在脑组织发育、功能维持中,小胶质细胞发挥其正常生理功能;而在神经退行性疾病发生发展等病理过程中,小胶质细胞则是调节神经炎症的主要细胞^[4, 95-96]。小胶质细胞就像一把双刃剑,一方面可以通过吞噬功能、生长因子分泌促进损伤的修复,另一方面也可以诱发神经炎症并加深免疫损伤。值得注意的是,小胶质细胞的吞噬和活化具有不同的调节机制。不论是活化的、终末的或是静息的小胶质细胞都具有吞噬功能,而活化的、终末的、静息的小胶质细胞对炎症因子和趋化因子等的分泌却并不相同的^[48, 94, 97-98]。尽管相关方向的研究较少,但这已经为解决小胶质细胞在神经疾病的发生发展过程中的“双刃剑”问题提供了线索。寻找小胶质细胞吞噬和活化调节过程的节点基因,加深对小胶质细胞不同状态调控的了解,通过干预使小胶质细胞向抑制疾病的方向发展,如加强吞噬作用、减弱炎症因子分泌等,可能将是神经退行性疾病治疗方法的发展方向之一。

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