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成体神经发生损伤与调控在神经退行性疾病中的新进展

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摘　要：成体神经发生在哺乳动物大脑中持续存在，新生神经元能够整合到已有神经网络并参与调节神经网络兴奋性。在增龄性相关的神经退行性疾病发生发展过程中，成体神经发生易受局部微环境的影响，成体神经发生异常与神经退行性疾病患者的焦虑、抑郁和认知障碍密切相关。本文系统性总结神经退行性疾病 (阿尔茨海默病、帕金森病和亨廷顿病) 患者和动物模型的成体神经发生异常的病理机制，探讨靶向调控成体神经发生在衰老相关的神经退行性疾病中的应用效果，为预防和治疗神经退行性疾病提供新的思路和方法。

关键词：神经发生；阿尔茨海默病；帕金森病；亨廷顿病
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Progress in the study of the dysfunction and regulation of adult neurogenesis in neurodegenerative diseases

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Abstract: Adult neurogenesis (ANG) exists in almost all mammalian brains, and newborn neurons can integrate into the existing neural network and participate in regulating the excitability of the neural network. ANG is vulnerable to the pathologic microenvironment in the development of age-related neurodegenerative diseases. Aberrant ANG correlates with depression, anxiety and cognition decline in patients with neurodegenerative diseases. In this review, we summarize the study on the mechanism underlying aberrant ANG and the effects of modulating ANG on neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease), thus providing new insights into or therapy targets for neurodegenerative diseases.

Key words: neurogenesis; Alzheimer's disease; Parkinson's disease; Huntington's disease

在人口老龄化大背景下，增龄性相关的神经退行性疾病已成为危害老年人群生命健康的主要疾病，成体神经发生异常是阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD) 和亨廷顿病 (Huntington's disease, HD) 等共有的病理特征 [1]。在生理条件下，神经发生在大多数哺乳动物包括人类海马中持续存在且在动物胚胎期最为活跃[2-3]。哺乳动物在成年后，齿状回颗粒下层 (subgranular zone, SGZ) 和侧脑室室管膜下层 (subventricular zone, SVZ) 仍保有神经干细胞 (neural stem cells, NSCs) 增殖生成新生神经元的能力 [4]，其中 80% 的 NSCs (Nestin$^+$) 先分化成为未成熟神经元 (doublecortin, DCX$^+$)，并最终发育成为成熟颗粒神经元 (NeuN$^+$) 或球旁神经元，剩余 20% NSCs 通过对称性分裂回补神经干细胞库 [5]。既往研究表明，SVZ 区成体神

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经发生参与动物对气味的识别和记忆过程[6]，SGZ区成体神经发生参与调控动物遗忘、记忆和情绪功能[7-9]。

成体神经发生受年龄、生活方式和炎症等多种因素影响，其中年龄是影响成体神经发生的最主要因素之一[10]。在人体发育过程中，大脑新生神经元数量随着个体年龄增加而逐渐减少，在病理条件下，脑内有毒物质如淀粉样蛋白(amyloid beta, Aβ)、α突触核蛋白(α-synuclein, α-Syn)和亨廷顿蛋白(Huntingtin, HTT)等聚集体可抑制NSCs增殖、分化和成熟，并导致神经元死亡，加速神经退行性疾病的发生发展[1, 10-11]。鉴于AD、PD和HD病理学特征均包括特异性神经元死亡，可能与成体神经发生损伤存在联系[12]。基于此，本文主要以AD、PD和HD为例，总结领域内最新研究进展，并针对成体神经发生在神经退行性疾病患者和动物模型中的病理变化及调控成体神经发生对神经退行性疾病的作用展开综述。

1　成体神经发生与AD

AD是最常见的神经系统退行性疾病，异质性强，占老年期痴呆50%~70%。目前世界上有5 500万AD患者，其中1 100万在中国[13]。全基因组相关性分析(genome-wide associated sequence, GWAS)揭示与AD相关的风险基因已有100余个，这些基因与AD发生发展密切相关[14]。AD患者脑萎缩可能与成体神经发生损伤密切相关[10]。

1.1　AD与成体神经发生损伤

AD患者虽保有成体海马神经发生(adult hippocampal neurogenesis, AHN)[15]，但与同龄老人相比，其AHN衰减的更快[16]。AHN受海马局部微环境调控，在AD病理条件下，Aβ/Tau寡聚体蛋白和胶质细胞增生均可抑制AHN。当NSCs暴露在Aβ寡聚体环境下时，NSCs增殖和分化被显著抑制[17]。通过转基因技术在小鼠基因组中敲入或者过表达人源突变型淀粉样前体蛋白(amyloid precursor protein, APP)以模拟AD患者脑内淀粉样斑块沉积，既往研究表明不同品系APP转基因小鼠AHN在淀粉样斑块沉积前后有所差异。例如，PDGF-$APP_{Sw,Ind}$小鼠SGZ和SVZ区增殖期神经干细胞数量在淀粉样斑块沉积前后均显著高于同龄对照组小鼠[18]。Yu等[19]利用免疫组化检测发现，3月龄APP/PS1小鼠海马区增殖性NSCs数量无显著变化，而12月龄APP/PS1小鼠增殖性NSCs数量却显著增加。有趣的是，虽然PDGF (platelet-derived growth factor-β)-$APP_{Sw,Ind}$和APP/PS1小鼠增殖性NSCs数量增加，但上述AD小鼠海马齿状回成熟神经元数量并无明显变化，提示多数NSCs在分化为神经元过程中趋于凋亡[18-19]。Pan等[20]研究表明Aβ并不是损伤AD小鼠AHN最危险的因素，过表达hAPP对AHN的抑制作用显著高于Aβ。此外，PS1突变基因不影响海马NSCs的增殖和分化[21]，但如果同时敲入APP和PS1基因，如APP/PS1和5×FAD (familial Alzheimer's disease)小鼠，那么双转基因小鼠AHN就会被显著抑制[21-22]。Aβ不仅抑制AHN，同时还影响新生神经元形态结构和电生理功能，2~3月龄hAPP-J20小鼠海马新生神经元在发育早期(第14~21天)，其树突长度、树突棘数量、诱发兴奋性和抑制性突触后电流幅度均显著高于同龄对照组小鼠，而在发育后期(第28~122天)，hAPP-J20小鼠海马新生神经元树突长度、树突分支和树突棘数量均显著减少，提示Aβ可能通过增加抑制性神经元突触传递或者打破兴奋-抑制平衡进而损伤AD小鼠AHN[23]。AD小鼠海马新生神经元数量及兴奋性增加可能与AD早期癫痫样电活动相关，Fu等[24]研究表明hAPP-J20小鼠青春期癫痫样电活动加速海马NSCs增殖，但同时也加速海马神经干细胞池衰竭，这可能是hAPP-J20小鼠AHN在青年期增加而在中老年期减少的原因。综上，AD小鼠成体神经发生损伤不仅与Aβ沉积有关，还与hAPP过表达相关，Aβ对新生神经元的数量、形态结构和电生理功能均有显著影响。

Tau蛋白是一类微管结合蛋白，根据其10号外显子剪切位点不同可生成3个或者4个微管结合蛋白。无论是3R还是4RTau蛋白均可辅助轴突转运和细胞骨架结构稳定，其中3RTau蛋白微管亲和力较低且在未成熟神经元高表达，表达量随年龄增加而逐渐减少[25]。此外，Tau蛋白是新生神经元发育成熟所必需的，敲除内源性Tau蛋白的原代神经元成熟期推迟[26]，敲除Tau蛋白的小鼠SGZ和SVZ区AHN增加，且Tau-KO小鼠SGZ区AHN在应激环境下未受到损伤[27]。另一方面，Tau蛋白磷酸化水平增加是AD典型的病理特征之一，针对hTau模型小鼠的研究表明，在磷酸化Tau蛋白聚集体形成之前，hTau小鼠海马区AHN已显著下降，其机制与海马增殖性NSCs数目减少有关，与凋亡水平增加无关[28]。磷酸化Tau蛋白亦可在AD患者和模型小鼠海马齿状回GABA能神经元大量聚集，在海马抑制性神经元中过表达hTau通过去抑制神

经通路加速 AHN 衰减以及星型胶质细胞增生 [29]。Tau 蛋白聚集体也在 AD 患者海马齿状回星型胶质细胞内被发现，在海马区星型胶质细胞内过表达 3RTau 蛋白通过改变线粒体代谢抑制 AHN，进而损伤小鼠空间记忆功能 [30]。综上，AD 患者和模型小鼠海马新生神经元数量均呈年龄依赖性下调，提示 AD 海马成体神经发生损伤 (表 1)。

1.2 AD与成体神经发生调控

成体神经发生受 Aβ 和 Tau 蛋白寡聚体影响，AD 小鼠海马区新生神经元形态结构和功能均是异常的，如果通过药物和遗传方法抑制海马区 AHN，AD 小鼠 (APP/PS1 和 hAPP-J20) 突触和认知功能则可得到显著改善 [33]。此外，如果将 AD 小鼠饲养在丰富环境笼中，海马新生神经元形态结构和突触可塑性可得到恢复，在丰富环境条件下增加 AHN 亦可改善 AD 小鼠认知功能 [37]。另一方面，跑轮运动的 AD 小鼠脑源性神经生长因子表达量增加且认知功能损伤得到修复 [22]。在神经干细胞中过表达 NeuroD1 以加速新生神经元成熟和功能整合被证明可改善 APP/PS1 小鼠空间记忆能力 [38]；亦有研究通过敲除神经干细胞 Bax 凋亡基因以增加 AHN 同样可逆转 5×FAD 小鼠认知功能 [39]。近年来，抗抑郁药物 (选择性 5-HT 再吸收抑制剂如氟西汀和帕罗西汀) 不仅可减缓 MCI 患者向 AD 发生发展 [40]，亦可增加成体神经发生以改善 APP/PS1 和 hTau 小鼠认知功能 [41-42]。迄今为止，针对多种 AD 动物模型的研究表明，如果能在 AD 早期阶段阻断 Aβ 和 Tau 蛋白等有毒物质对 AHN 的损伤亦或靶向性修复损伤的 NSCs，则可改善 AD 动物的认知功能 [22, 33, 39]。

2 成体神经发生与PD

PD 是一种运动障碍类神经退行性疾病 [1]，PD 患者在临床上表现为运动功能障碍，如静止性震颤、肌强直、运动迟缓和步态异常等 [2]。PD 起病隐匿，大脑常见 α-Syn 异常聚集形成的路易氏小体及黑质多巴胺神经元死亡 [2]。PD 患者除了典型运动功能障碍外，还伴有非运动功能障碍如嗅觉障碍、睡眠失调和认知损伤等。

2.1 PD与成体神经发生损伤

针对多种 PD 动物模型的研究表明，PD 非运动功能障碍与神经发生损伤密切相关。利用 6-OHDA (6-hydroxydopamine) 选择性杀死黑质多巴胺能神经元，小鼠 SGZ 和 SVZ 区域 NSCs 增殖、分化和成熟均显著减少 [43]。Lazarini 等 [44] 向黑质核团注射 6-OHDA 以损毁黑质投射到纹状体的多巴胺神经通路，从 SVZ 区迁移到嗅球的 GABA 能和多巴胺能神经元数量显著减少。利用鱼藤酮诱导的 PD 模型动物海马 SGZ 区域成体新生神经元数目显著减少 [45]。

表1 AD患者和动物模型成体神经发生变化情况汇总

样本	修饰基因	年龄	脑区	神经干细胞标记因子或蛋白	文献
3×Tg小鼠	APP/PSEN2/MAPT	1月龄	SGZ	$Sox2^{+}S100\beta^{+}$↓、DCX↓	[31]
APP/PS1小鼠	APP/PSEN1	6月龄	SGZ	BrdU↑	[32]
		5月龄	SGZ	DCX↓	[33]
5×FAD小鼠	APP/PSEN1	5月龄	SGZ	DCX↓	[22]
$APP^{NL\text{-}G\text{-}F}$小鼠	APP	6月龄	SGZ	BrdU↑	[34]
PS1小鼠	PSEN1	3月龄	SGZ	BrdU↑	[35]
Tg2576小鼠	APP	1.5月龄	SVZ	BrdU↓、DCX↑	[36]
hAPP-I5小鼠	APP	1~2.5月龄	SGZ	BrdU↓、DCX↓	[20]
hAPP-J20小鼠	APP	1、2月龄	SGZ	$BrdU^{+}Nestin^{+}$↑、DCX↑	[24]
		3、7、14月龄	SGZ	$BrdU^{+}Nestin^{+}$↓、DCX↓	
Tau-KO小鼠	Tau	7~8月龄	SGZ	无差异	[27]
hTau小鼠	$MAPT^{-/-}$	2、6、12月龄	SGZ	DCX↓、BrdU↓	[28]
腺病毒过表达小鼠	hTau	3月龄	SGZ	DCX↓、BrdU↓、Ki67↓	[29]
慢病毒过表达小鼠	LV-1N3R-V5	7月龄	SGZ	DCX↓、BrdU不变	[30]
AD患者	/	52~97岁	SGZ	DCX↓	[16]
MCI患者	/	86~95岁	SGZ	$DCX^{+}PCNA^{+}$↓	[15]

↓代表数目减少，↑代表数目增加。3×Tg，transgene； APP，amyloid precursor protein；PSEN 1/2，Presenilin 1/2；MAPT，microtube-associated protein tau；5×FAD，familial Alzheimer's disease；hAPP-I5，human amyloid precursor protein I5；hAPP-J20，human amyloid precursor protein J20；Tau-KO，MAPT knock out；hTau，mouse MAPT knock out, human MAPT transgenic；LV，lentivirus；DCX，doublecortin；BrdU，bromodeoxyuridine；MCI，mild cognitive impairment

有趣的是，Peng 等[46] 利用 MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride) 特异性杀死黑质多巴胺能神经元，小鼠 SVZ 区新生神经元反而异常增加。综上，不同 PD 造模药物对成体神经发生的损伤结果并不一致，原因可能与药物种类、作用剂量和时间有关[47]。

GWAS 分析揭示与 PD 相关的致病基因已有 90 余种，其中一些基因在维持 NSCs 稳态和调控其增殖和分化中具有重要作用[47]。例如，在小鼠海马中过表达人源野生型 α-Syn 蛋白抑制了新生神经元存活和树突发育，而敲除小鼠内源性 α/β-Syn 蛋白则增加了 AHN[48]。在兴奋性神经元中特异性表达 A53T 或 A30P 突变型 α-Syn 蛋白，小鼠 SGZ 和 SVZ 区新生神经元增殖、分化和成熟的数量均显著减少[49-50]。此外，针对多种 PD 转基因模型小鼠 (LRRK2 G2019S、VPS35 D620N、PINK1$^{-/-}$) 的研究发现，PD 模型小鼠海马和嗅球新生神经元数目减少，新生神经元树突分支和树突棘数目减少，提示 PD 转基因模型小鼠 AHN 受损[51-54]。

α-Syn 寡聚体蛋白是路易体痴呆 (Lewy body dementia, LBD) 和 PD 的共同致病因子，虽然大多数 PD 患者最终会发展为 LBD，但没有明确的病理学和分子特征可以将二者区分开[55]。Terreros-Roncal 等[1] 研究发现 α-Syn 蛋白在 LBD 患者海马新生神经元内大量聚集且 SGZ 区新生神经元数量显著减少。Braak I 期 PD 患者嗅球新生神经元数量减少与其早期嗅觉障碍密切相关，但在 SGZ 区，PD 患者未成熟神经元数量显著增加且树突发育出现异常[56]。由于与 PD 患者 AHN 相关的研究报道极为有限，且受限于样本保存情况及 PD 患者病情不同，PD 患者 AHN 病理变化还有待深入研究。综上，PD 患者和模型小鼠成体神经发生均出现异常 (表 2)。

2.2　PD与成体神经发生调控

PD 黑质 - 纹状体多巴胺能神经通路进行性退变虽不可逆，但可通过调整生活方式、靶向性药物和干细胞重编程等技术重塑多巴胺神经通路以改善 PD 模式动物运动和非运动功能障碍。针对 MPTP 诱导的 PD 模型动物的实验表明，通过耐力运动可增加 PD 小鼠新生神经元的产生，减少黑质多巴胺能神经元丢失[66]。Crowley 等[67] 研究发现跑轮训练可保护过表达 α-Syn 对大鼠海马成体神经发生的损伤，并且也能改善大鼠认知功能。此外，采用抗抑郁药物如氟西汀可挽救 A53T 小鼠成体神经发生损伤[50]。干细胞重编程技术近十年发展迅速，在 PD 模型动物上的实验表明利用诱导多能干细胞或者将局部星形胶质细胞重编程为神经元以重建黑质多巴胺能神经元神经通路可显著改善 PD 小鼠运动功能障碍[68]。

3　成体神经发生与HD

HD 是一种常染色体显性基因突变引起的神经退行性疾病，HD 起始于亨廷顿蛋白 (Huntingtin, HTT) 基因 CAG 重复性扩增引起蛋白 N 末端聚谷氨酰胺过度延长，进而在细胞质和细胞核内错误折

表2　PD患者和动物模型成体神经发生变化情况汇总

样本	修饰基因	年龄	脑区	神经干细胞标记因子或蛋白	文献
SNCA转基因小鼠	SNCA-OE	3~4月龄	SVZ、OB、SGZ	DCX↓、BrdU↓	[57]
	SNCA-KO	1月龄	SGZ	BrdU↑、SOX2↑、PCNA↑	[48]
	SNCA-A30P	2~4月龄	OB、SGZ、SVZ	DCX↓、BrdU↓	[49, 58]
	SNCA-A53T	4~5月龄	OB	DCX↓	[59]
		15月龄	SGZ、SVZ	PCNA↓、BrdU↓	[50, 60]
LRRK2转基因小鼠	LRRK2-G2019S	4月龄	SVZ、SGZ	BrdU↓、NR2F1↓	[61-62]
	LRRK2-R144G	/	/	Ki67↓、DCX↓	[63]
VPS35转基因小鼠	VPS35-D620N	/	SGZ	SOX2↓、BrdU↓、Ki67↓、DCX↓	[52]
PINK1敲除斑马鱼	PINK1-KO	12月龄	PVO	$Th1^{+}EdU^{+}$↓	[64]
DJ-1转基因小鼠	DJ-1-OE	2.5月龄	SGZ、SVZ	BrdU↑	[65]
LBD患者	/	62~89岁	SGZ	$Nestin^{+}S100\beta^{-}$↑、$Sox2^{+}$↑	[1]
PD患者	/	73~82岁	SGZ	$Nestin^{+}S100\beta^{-}$↑、DCX↑	[1]

↓代表数目减少，↑代表数目增加；KO，knockout；OE，overexpress；SNCA，α-synuclein；LRRK2，leucine-rich repeat kinase 2；VPS35，vacuolar protein sorting-associated protein 35；PINK1，PTEN induced putative kinase 1 knockout；OB，olfactory bulb；PCNA，proliferating cell nuclear antigen；Th1，tyrosine hydroxylase-1；EdU，5-ethynyl-2’-deoxyuridine；PVO，paraventricular organ；LBD，Lewy body dementia

叠形成不可溶性聚集体，导致纹状体中棘神经元和皮层投射神经元大量死亡[69]。临床上HD患者表现为舞蹈样动作、共济失调、认知功能下降和精神行为异常。

3.1 HD与成体神经发生损伤

HTT蛋白是生物体早期胚胎发育所必需的，缺失HTT基因的胚胎在发育至8.5天即死亡[69]。HTT蛋白亦是神经元分裂增殖所必需，干扰或者敲除HTT蛋白影响NSC纺锤丝形成和皮层神经元分化，而敲入mHTT (mutant HTT)蛋白不影响海马NSC增殖，但抑制海马新生神经元和胚胎期纹状体中棘神经元成熟[70-71]。此外，Xiang等[72-73]研究表明，与HTT紧密互作的HAP1蛋白(Huntingtin-associated protein)缺失同样影响神经元分裂和增殖，在小鼠生命早期敲除HAP1蛋白导致下丘脑和海马新生神经元数量显著减少。在R6/1、R6/2和YAC128转基因小鼠中可通过增加HTT基因CAG拷贝数来模拟HD病理特征，但不同小鼠HTT基因CAG拷贝数有所差异。既往研究表明，R6/2小鼠齿状回$BrdU^+$神经元数量在运动功能出现障碍前已开始下降，至11.5周时，与对照组小鼠相比，R6/2小鼠海马SGZ区新生神经元数目减少了66%，但SVZ区NSCs数目无显著变化[74]。与R6/2小鼠相比，R6/1小鼠AHN受损时间稍晚一些，在第20周R6/1小鼠海马新生神经元开始显著减少[75]。与同龄对照组小鼠相比，YAC128小鼠SVZ区新生神经元数量无显著变化[76]，但在9月龄时其海马新生神经元数目开始减少，至18月龄时已减少了26%。针对这三种模型小鼠的研究结果提示，mHTT聚集体蛋白可抑制海马AHN，但对SVZ区AHN无显著影响(表3)。

3.2 HD与成体神经发生调控

到目前为止，临床上虽无可治愈HD的药物，但有研究提示基因编辑、干细胞重编程和干细胞移植等技术在改善HD模型动物运动功能障碍和认知功能障碍等方面有较好的疗效。Tabrizi等[79]总结了CRISPR/Cas9 (clustered regularly interspersed short palindromic repeats)、RNAi (RNA interference)、反义寡聚核苷酸和小分子剪切调节剂等在减少mHTT蛋白表达量上的应用效果。利用iPSCs (induced pluripotent stem cells)或者MSCs (mesenchymal stem cells)衍生分化的纹状体中棘神经元以替代损伤和死亡的中棘神经元可挽救R6/2小鼠运动功能损伤。其次，可利用CRISPR/Cas9将HD源性iPSCs的mHTT基因重编辑为正常的CAG重复性序列，该策略在治疗HD患者方面有广泛的应用前景[80]。

4 总结

综上所述，虽然AD、PD和HD的病理机制和临床特征各有不同，但针对疾病模式动物的研究结果表明，AD、PD和HD神经发生均受到损伤。神经发生在哺乳动物高度保守，新生神经元从出生到整合到神经网络过程中易受到外界环境影响并产生变异[10]，如Aβ、Tau、α-Syn和mHTT等毒性蛋白。AHN异常可归纳为两方面：(1) 新生神经元数量没有变化，但其形态结构和功能是异常的，异常新生神经元可破坏已有神经网络兴奋-抑制平衡，与AD空间记忆损伤密切相关[23, 33, 81-82]；(2) 新生神经元数量异常增加或者减少，这普遍存在于AD、PD和HD等神经退行性疾病患者中[1]。此外，调控成体神经发生可作为预防和治疗增龄性神经退行性疾病的策略之一[37, 83]，利用iPSCs衍生的神经元或者药理学方法补充和修复损伤的神经元可改善AD和PD模式动物认知和运动功能损伤[68, 84]。不容忽视的是，在不改变疾病动物局部微环境条件下，在此新生的神经元又是否是异常的[85]，如何靶向性修复损伤的神经干细胞，这些问题仍有待进一步研究。

表3 HD患者和动物模型成体神经发生变化情况汇总

样本	CAG重复序列	年龄	脑区	神经干细胞标记因子或蛋白	文献
R6/1小鼠	115	1.2月龄	SGZ	BrdU↓	[75]
R6/2小鼠	145	0.8月龄	SGZ	BrdU↓、Ki-67↓、PCNA↓	[74]
YAC128小鼠	128	3月龄	SGZ	BrdU↓、Ki-67↓	[76]
$N171^{82Q}$小鼠	82	3月龄	SVZ	BrdU↓	[77]
BACHD小鼠	97	3月龄	SGZ	DCX↓	[78]
Hdh^{Q111}小鼠	109	胚胎期13.5~15.5天	纹状体	BrdU↓	[70]
HD患者	/	47~72岁	SGZ	$Nestin^+S100\beta^-$↑、DCX↑	[1]

↓代表数目减少，↑代表数目增加；BACHD，bacterial artificial chromosome-mediated transgenic HD；Hdh，Huntington disease gene

哺乳动物成体神经发生是近期研究热点，虽然大量研究已解析啮齿类动物成体神经发生机制，但对于灵长类动物，尤其是人类成体神经发生的认识，业界还知之甚少，已有的研究结论也存在争论[16, 86-87]。不可否认的是，新生神经元通过功能整合到已有的神经网络，这对哺乳动物情感和认知高级功能的实现具有重要意义[9]。成体神经发生变化也是大脑对外界环境刺激 (如丰富环境和运动) 的内在反应，当大脑内部微环境改变时 (如炎症和寡聚体蛋白)，神经干细胞增殖、分化和成熟亦会受到影响，进而影响大脑神经网络功能整合[10]。综上所述，通过总结当前 AD、PD 和 HD 成体神经发生损伤及调控的研究进展，以期能为神经退行性疾病研究提供新的认识和思考。

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