运动干预诱导缺血性脑卒中后神经再生的机制

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摘要 缺血性脑卒中(IS)具有高发病率、高致残率以及高病死率的特点,是当前脑血管疾病防治的难点,也是全球范围内重点关注的健康卫生问题。IS发生后,为了应对缺血、缺氧刺激诱发的脑梗死区神经元的输入丢失,机体会自发地启动自我修复机制,重组脑内神经元功能连接和神经通路。然而,神经功能的完全恢复仅仅依靠机体所具备的这种自我修复和功能重建是远远不够的,仍然需要通过有效的临床治疗手段最大化激发和强化这种能力。因此,探索一种能够有效促进神经元重塑、再生,改善神经元损伤诱导的功能障碍的治疗方法是防治IS的核心问题和首要研究方向。目前,运动干预作为临床应用可行性高、患者接受度高的康复治疗技术,已纳入到多种疾病的康复治疗计划中,是有效防治脑血管疾病的补充和替代疗法。本研究综述运动干预对IS后神经再生的调控机制,以期为运动防治IS提供理论基础。运动干预是以中枢神经系统可塑性为基础,可通过多层次、多途径、多靶向发挥脑神经保护作用,包括调控突触芽生、连接和传递效率,改善再生轴突和靶细胞间的功能联系,促进血管生成,保护神经血管单元完整性,调控相关抑制神经再生因素和诱导多种神经再生相关的神经生长因子表达,促进神经干细胞增殖等,参与调控中枢神经再生环境,改善缺血后受损的神经功能。

关键词 缺血性脑卒中;运动干预;神经再生;轴突再生;神经血管单元

缺血性脑卒中(ischemic stroke,IS)约占脑卒中的87%,是全球发病率和致残率较高的疾病之一[1]。随着社会的发展,IS不再只是影响老年人的疾病,其发病年龄逐步呈现年轻化。IS发病后30 d病死率为16%~32%,严重影响人类的生活质量[2]。IS患者生命体征稳定后即可介入康复治疗(如运动疗法、作业疗法等)。IS诱发的各种功能障碍的恢复程度与中枢神经系统(central nervous system,CNS)神经元再生密切相关[3-4]。运动干预以CNS可塑性为基础,通过促进受损区和周围相关区神经元的生长发育,激活处于静止状态的内源性神经干细胞(neural stem cells,NSCs),促进突触芽生和轴突再生等机制,诱导神经再生,修复机体功能障碍[5]。本研究旨在综述运动干预对IS后神经再生的调控机制,以期为运动防治IS提供理论基础。

1 神经再生与脑缺血

IS是由栓子或血栓导致血管狭窄或闭塞引起的,使存活的脑组织缺血缺氧和葡萄糖损失、神经元三磷酸腺苷(adenosine triphosphate,ATP)产生变少,进而引发一系列复杂的病理生理变化,是一种高度复杂和异质的疾病[6-7]。脑缺血发生后,脑细胞主要经历细胞损伤/死亡、细胞恢复/轴突再生和神经胶质增殖/瘢痕形成3个病理过程[8]。脑缺血中

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心区神经细胞坏死和再灌注导致的神经细胞死亡是引起神经功能缺损的根本原因。此外，有研究证实神经元的存活影响脑功能的稳定性和完整性，IS后造成的各种功能障碍与神经再生有着密切联系[3-4]。

2 运动干预与缺血性脑卒中

运动干预可从多层次、多途径、多靶向对IS发挥脑保护作用，诱导内环境与神经再生相关的多种神经生长因子的表达，参与中枢神经再生环境的调节[9]。但其治疗效果与干预方式、时间和强度等有重要的关系。

目前动物实验采用的运动康复干预方式主要包括强制性运动疗法、高强度间歇训练、中等强度持续训练、跑台和跑笼训练等。

2.1 强制性运动疗法

强制性运动疗法是以CNS可塑性及脑功能重组理论为基础的新型神经康复技术。其治疗重点在于通过限制健侧肢体的运动，改善和克服IS急性期、亚急性期所形成的习得性废用状况，并对患肢集中进行大量、重复地强化练习，以帮助其更好地恢复功能[10]。

2.2 高强度间歇训练

高强度间歇训练是将短时间相对高强度运动与低强度恢复运动相结合的一种运动方式，运动时间一般＜30 min。其运动参数可根据不同人群和训练目标的需要进行调整，能够以较少的时间投入达到总运动量最大化，进而提高心血管系统的运动耐受性[11]。

2.3 中等强度持续训练

中等强度持续训练时间一般≥30 min，运动项目包括跑步、骑自行车和游泳等。中等强度持续训练是预防和管理心脑血管疾病最有效的运动治疗策略之一，也是目前研究最多的运动策略[12]。

2.4 跑台和跑笼训练

跑台和跑笼训练可以通过对运动参数（时间、速度、电击限流等）的控制，准确地量化训练方案及监控实验动物的运动强度，并可以减小实验操作难度。

早期进行康复训练对于功能的恢复至关重要，但介入的时间点是一个值得注意的问题。研究表明，脑卒中后6 h进行运动训练可能会增加促凋亡蛋白Bax和Caspase-3表达，诱导神经元细胞凋亡数量增加、促进机体内活性氧（reactive oxygen species，ROS）和乳酸的产生[13]。在脑缺血事件发生后24 h内进行锻炼可能也是有害的，但脑卒中后24～72 h内进行运动干预可避免不利于功能恢复的有害因素的影响，是理想的治疗时间[14-15]。此外，研究发现，低强度或中强度的连续运动可对大脑产生神经保护作用，而高强度的连续运动可能会对机体产生负面影响[16]。有研究显示，脑缺血发生后，低强度运动在改善大鼠空间记忆能力和海马突触可塑性等方面具有更显著的优势，而高强度运动却未能发挥这种有益作用[17]。因此，在选择利用不同运动疗法治疗IS时，应将运动的方式、持续时间和强度标准化、规范化，寻找出治疗时间窗和运动强度的最佳组合，以能充分发挥出运动的治疗效应。

3 运动干预对神经再生的调控作用

3.1 运动干预可增强抗损伤能力，促进神经元存活

脑神经元的能量储备能力非常弱，仅依赖葡萄糖做底物，很容易受到脑缺血和缺氧刺激的影响[18]。脑缺血后神经元的死亡或功能障碍是激活炎症反应的关键刺激因素，其会释放所谓的“危险信号”，如尿苷三磷酸、ATP等。这些信号可激活小胶质细胞，促使其迁移至脑梗死区，并释放ROS、蛋白酶、NO和促炎细胞因子等炎症介质，反过来影响神经细胞的结构和功能，诱导神经元死亡[19]。运动训练能够通过激活抗凋亡活性、增强促生存通路以及抑制促凋亡通路，促神经细胞存活[20]。CAO等[21]发现，跑步机训练可以通过介导cAMP/PKA信号通路抑制IS后神经元凋亡，提高神经细胞存活率。WANG等[22]发现缺血前跑步机运动可显著增加新旧含有热激蛋白72（heat shock protein 72，HSP72）的神经元百分比，并降低胶质纤维酸性蛋白阳性细胞的密度及星形胶质细胞的形态复杂性，减轻脑卒中大鼠的神经元凋亡。

脑缺血再灌注后ROS的过量产生是脑卒中后氧化应激和继发性脑损伤的重要原因。ROS不仅可以通过细胞效应导致细胞成分破坏和细胞死亡，引发线粒体功能障碍和自噬，还会影响血管张力、血小板活性以及内皮细胞通透性，最终导致神经元功能障碍[23-24]。运动干预可通过降低脑组织ROS含量和促炎因子的表达，增加抗氧化酶表达，保护神经元[25]；也可以通过减少脑组织ROS含量及Caspase-3蛋白的表达量，调节Bcl-2/Bax比值，抑制内质网应激，减少脑组织损伤[26-27]。此外，还可以增加内皮型NO合酶表达量，抑制氧化应激和炎症反应，诱导缺血耐受[28]。

脑血流量减少后,细胞膜离子泵被破坏,造成钾离子外流,Ca^{2+}和Na^{+}大量内流,导致兴奋性谷氨酸(glutamic acid,Glu)和氨基酸大量释放,形成兴奋性毒性[29]。Glu介导的兴奋性毒性是导致缺血性神经元死亡的主要原因。Glu与细胞去极化相结合会过度激活代谢型和离子型Glu受体、N-甲基-D-天冬氨酸受体和α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionicacid receptor,AMPAR),并通过单离子通道作用,进一步破坏钙稳态,形成一个恶性循环,破坏神经功能[30]。此外,兴奋性毒性损伤也会导致神经元自噬,造成神经元损伤。SAKAKIMA[31]研究发现,运动预处理可减少脑组织内Glu、代谢性谷氨酸受体第5亚型(mGluR5)和谷氨酸受体2B抗体(N-Methyl-d-Asprtate receptor-2B,NR2B)的过度表达,抑制Glu兴奋毒性,提高机体抗氧化能力,减轻氧化损伤。脑卒中后的强制性运动疗法可调控同侧感觉运动皮层中Glu受体的表达,增加树突棘的密度及复杂性,影响海马体突触可塑性[32]。LUO等[33]研究发现,高强度间歇训练可通过调控脑组织内组织型纤溶酶原激活剂、谷氨酸受体2A抗体(N-Methyl-d-Asprtate receptor 2A,NR2A)、NR2B的表达,调节Glu的传递,减少凋亡细胞的数量。HU等[34]发现,约束诱导运动疗法通过调控感觉运动皮层中GluR2的功能性突触的数量以及AMPAR的表达,介导缺血半球突触传递,进而促进IS后运动功能的恢复。

3.2 运动干预可促轴突再生

受损神经元的神经突或轴突再生在缺血性脑损伤后不久就已经开始[35]。轴突再生是脑缺血后神经再生的重要环节,是神经可塑性变化的重要标志。脑源性神经营养因子(brain derived neurotrophic factor,BDNF)影响整个生命过程中神经元的发育、分化,调控海马突触连接与突触传递效率,维持神经元的生存及功能,是CNS突触可塑性的重要调节剂[36-37]。当脑组织因缺血再灌注而发生损伤时,全脑(尤其是损伤侧半脑)BDNF表达升高,这可以减轻缺血缺氧引起的神经元损害,促进NSCs分化和血管的新生[38]。有研究表明,脑缺血后恢复过程需要一定量的BDNF,只有当脑内BDNF含量到达一定阈值,损伤大脑才能够恢复[39]。ZHANG等[40]研究证实,运动可以增加BDNF、神经突触素(synaptophysin,SYN)、突触后密度蛋白-95和集聚蛋白的表达,促进缺血半影区的突触发生。ABBASIAN等[41]研究发现,高强度间歇训练可激活过氧化物酶体增殖物激活受体γ共激活因子-1α(peroxisome proliferator-activated receptor γ coactivator-1α,PGC-1α)/纤连蛋白Ⅲ型结构域包含蛋白5(fibronectin type Ⅲ domain-containing protein 5,FNDC5)/BDNF信号通路,上调脑组织内PGC-1α、FNDC5、雌激素相关受体α及BDNF的表达,增加树突棘数量,并增强神经发生。CHENG等[42]研究发现,重复经颅磁刺激联合运动可显著上调BDNF、磷酸化酪氨酸激酶B和磷酸化苏氨酸蛋白激酶(p-serine-threonine kinase,p-Akt)的蛋白表达量,增加运动诱发电位,调控机体的电生理变化。有研究发现,跑步机运动能够修复髓鞘,减轻神经元变形及脑组织损伤,与其激活机体缺血半影区Wnt/β-catenin信号通路及上调BDNF和髓磷脂碱性蛋白表达量有关[43]。

脑缺血发生后,神经生长相关蛋白-43(growth-associated protein-43,GAP-43)表达量的增多标志着轴突再生,对突触功能的维持及递质释放起着重要作用[44]。机体在正常状态下,大部分脑组织中GAP-43处于低水平表达状态。而当脑缺血发生时,会诱发缺血脑组织周围GAP-43表达,参与激活神经纤维发芽、突触重建等神经再生过程。LI等[45]研究发现,轻度和剧烈运动方案均可通过调控GAP-43、低氧诱导因子-1α(hypoxia inducible factor-1α,HIF-1α)、BDNF等相关蛋白的表达量,诱导突触可塑性。PAN等[46]研究发现,补阳还五汤与体育锻炼联合治疗可显著提高GAP-43、SYN和微管相关蛋白-2的表达量,维持突触超微结构的完整性,改善神经行为缺陷。运动训练通过上调动脉前区GAP-43和SYN及脑组织中HSP70和内原癌基因的表达,促进IS后大鼠运动功能恢复[47]。

星形胶质细胞是维持CNS所必需的管家细胞,参与调控大脑的病理生理功能[48]。脑缺血发生后,脑组织中星形胶质细胞能够通过分泌神经营养因子和神经保护物质等途径影响神经细胞生长和发育,调节神经元兴奋性和突触传递[49-50]。运动训练可通过调控信号转导和STAT3/GPC6信号通路,激活脑组织内星形胶质细胞转变为神经保护表型,达到促进突触增殖,改善神经和运动功能的目的[49]。预处理运动可增加星形胶质细胞中BDNF、HIF-1α和P2X7受体的表达量,进而增强机体的抗凋亡活性[51]。OTSUKA等[52]研究发现,脑缺血前的运动预处理训练可通过上调HIF-1α和14-3-3γ表达,诱导星形胶质细胞和神经元介导的脑缺血耐受。JIANG

等[53]研究发现，体育锻炼可有效调控星形胶质细胞极化，促进慢性脑缺血后灌注不足大鼠髓鞘碎片的清除和髓鞘再生。

3.3 运动干预可调控相关抑制神经再生因素

脑缺血后出现的各种抑制性因素是致使神经再生能力不足的另一重要因素，包括神经生长抑制因子、神经胶质瘢痕等。神经突生长抑制蛋白-A（neurite outgrowth inhibitor-A，Nogo-A）主要存在于CNS中，是髓鞘相关轴突生长抑制因子的主要来源。在生理情况下，神经元成熟时Nogo-A表达降低，而脑缺血发生时会刺激其表达扩散，并在几天后整体升高[54]。当其与Nogo受体1（Nogo receptor，NgR1）结合，会激活下游RhoA/ROCK等信号通路，破坏线粒体结构及功能，促进凋亡蛋白产生，导致生长锥塌陷，抑制轴突再生[55]。早期强制性运动疗法可显著降低脑组织中NgR mRNA的表达水平，维持神经生长环境的稳定[48]。SHAHIDI等[56]研究证明，运动可以下调脑组织中神经生长负性调控因子Nogo-A、NgR和ROCK蛋白表达，促进轴突发芽。WANG等[57]研究发现，电针联合运动训练可明显降低脑组织中Nogo-A表达，抵消内在的神经突生长抑制，刺激轴突生长和突触发生。

大脑受损时，损伤部位的神经胶质细胞开始分裂，生成的星形胶质细胞和其他细胞堆积为致密的细胞斑块，形成神经胶质瘢痕。这不但在空间上限制轴突生长的范围，还会为炎症细胞和感染因子形成保护屏障。当再生轴突遇到神经胶质瘢痕环境时，会形成营养不良性端球，无法延伸生长锥[58]。此外，其分泌的蛋白聚糖[如硫酸软骨素蛋白聚糖（chondroitin sulfate proteoglycans，CSPGs）和硫酸角质素蛋白聚糖等]在脑缺血区堆积也会抑制轴突生长锥和神经突延伸[59]。有研究显示，4周跑步运动可以显著减轻短暂性脑缺血引起的星形胶质细胞活化，抑制神经胶质增生以及其他炎症相关因子的表达[60]。WIERSMA等[61]研究发现，运动干预可分解组织中堆积的CSPGs，增强皮质脊髓束的结构可塑性，改善功能连接，提高训练效果。

3.4 运动干预可促内源性神经干细胞增殖

NSCs分布在整个发育的大脑中，具有分化为多种细胞谱系（如神经元、星形胶质细胞和少突胶质细胞）的能力，其增殖、迁移和分化是推动脑缺血后恢复进程的关键步骤[62]。脑缺血发生时，触发机体自身的保护机制，激活多部位处于静息状态的内源性NSCs向缺血区迁移、分化，发挥神经保护作用，参与修复受损脑功能。

但是，内源性NSCs自发再生的修复过程是不充分且短暂的，因为这些新生成的神经元大多数在功能未成熟之前就死亡了，只剩下少量的细胞可以整合到神经元网络中。研究表明，内源性NSCs可被脑组织中的多种因子激活，包括BDNF、神经生长因子、血管内皮生长因子（vascular endothelial growth factor，VEGF）、胰岛素样生长因子-1（insulin-like growth factor-1，IGF-1）等[62]。KIM等[63]利用微流控系统观察发现，在连续浓度梯度生长因子中培养的NSCs黏附良好，并且响应生长因子的浓度梯度而增殖和分化。跑步机运动能够通过介导caveolin-1/VEGF信号传导，增加脑梗死区BrdU/NeuN阳性细胞的数量，促进半影区脑室下区NSCs的增殖、迁移和分化，促进缺血半影区的血管生成[64]。运动可激活脑梗死周围区域的IGF-1/Akt信号通路，增加脑梗死周围区域新神经元和神经祖细胞数量，减少脑梗死面积[65]。

3.5 运动干预可促进血管生成，改善神经血管单元完整性

“神经血管单元”概念的提出充分阐释了神经再生与血管生成之间的动态联系，并强调了血管生成在神经修复中的关键作用[66]。脑缺血发生后，脑血管生成和重塑是内源性神经修复反应的重要环节之一，可增加受损区域的血流量和营养代谢物质，为轴突芽生、生长和延伸提供良好的微环境，为重构神经元提供重要的神经血管底物[67]。血脑屏障（blood brain barrier，BBB）是调控大脑CNS稳态的动态屏障，参与调控血管生成、神经元发育和突触活动[30]。BBB的完整性在IS后缺失，破坏了神经与血管间的动态联系，导致细胞旁通透性增加、各种炎症细胞迁移到缺血部位，促使血管源性水肿、出血性转化和病死率增加[68]。ZHAI和FENG[69]研究发现，强制性运动疗法能够增强脑缺血/再灌注损伤后的血管生成和神经发生，维持BBB完整性，发挥神经保护作用。

基质金属蛋白酶（matrix metalloproteinase，MMP）可能是破坏BBB的关键因素。脑缺血后，神经元、星形胶质细胞、小胶质细胞以及内皮细胞可迅速产生MMP，降解基质层黏蛋白、胶原纤维与细胞纤连蛋白，破坏星形胶质细胞末端和内皮细胞之间的连接，对BBB造成不可逆的损害[70]。MMP表达在脑缺血性损伤中迅速上调，并在24～48 h达到活动高峰，这种高活性会增加继发性出血的风险[30]。脑缺

血前运动可抑制MMP-9的激活,防止慢性脑缺血导致的微血管损伤,改善神经功能缺损状况[71]。ZHANG等[70]研究发现,运动可以通过抑制MMP-9过表达,上调MMP组织抑制剂,改善脑缺血后BBB功能和基底膜的完整性。

VEGF是刺激血管生成的主要调节因子,具有促进缺血脑区神经血管重塑、调控对侧皮质延髓可塑性和保护神经细胞的功能[72]。当VEGF与其受体VEGFR1或VEGFR2在血管内皮细胞表面结合时,可激活血管生成的多个下游信号通路[73]。而脑组织中VEGF表达降低会对血管生成产生负调控作用[74]。延迟运动训练可上调脑梗死灶周围和对侧运动皮层中血管生成相关蛋白VEGFR2和血小板衍生生长因子受体β表达,促进血管发生,改善脑组织血液循环[75]。有氧运动通过诱导PGC-1α或HIF-1α的转录活性增加VEGF和VEGFR2水平,改善血管密度[76]。研究发现,跑步机运动可通过调控caveolin-1/VEGF通路、并上调BDNF、SYN-1等蛋白表达,改善脑缺血半影区树突和突触形态[77]。LI等[78]发现,约束诱导运动疗法可通过调节VEGF、HIF-1α和FIH-1表达,参与介导脑缺血后神经发生和血管生成。

血管生成素(angiopoietin,ANG)是血管生成的分子参与机制,是其他血管生成调节剂(包括VEGF)作用所必需的因子;ANG与VEGF之间的密切联系在新血管生成中起关键作用[30]。HAFEZ等[79]研究发现,运动预处理通过增加VEGF和ANG mRNA的表达,增加微血管密度和完整性,减少缺血引起的内皮-基质-星形胶质细胞的超微结构改变。PIANTA等[80]发现,运动可显著升高缺血性纹状体中VEGF、VEGFR2和ANG-2表达水平,并降低脾脏中炎性因子CD45和TNF-α的表达,减轻神经血管损伤。临床研究证实,脑缺血前运动训练能够迅速增加缺血后同侧脑室下区中内源性ANG表达,并发现体外ANG治疗可以增加脑室下区衍生NSCs的数量,促进细胞增殖和迁移[81]。

内皮祖细胞(endothelial progenitor cells,EPCs)作为血管生成和重塑的关键介质,可以响应局部缺血移动到特定区域并分化为内皮细胞,并可能是脑卒中康复期间监测患者恢复状态的生物标志物。脑卒中后血液中ANG和EPCs水平在康复治疗期间增加,参与神经修复过程,是IS的潜在治疗靶点。MA等[82]研究发现,4周强度依赖性运动显著增加了EPC-EX和miR-126表达,并通过靶向SPRED1/VEGF通路调节EPC-EX对EC的保护作用。WANG等[83]研究发现,运动可增加脑组织和血浆中EPC-EX和miR-126水平,并提高N2a细胞的活性,恢复神经突长度。

4 小 结

神经再生与脑缺血的病理生理变化有着紧密联系,是临床上治疗脑血管疾病的重要靶点之一。本研究详细阐释了运动干预诱导脑缺血后神经再生的机制研究,证实了运动疗法可以调控神经元生存的内部及外部环境,诱导神经再生,重构脑神经元网络和修复受损的神经功能。但其所涉及的分子机制较为复杂,尚未完全阐明,仍需大量的临床试验或实验研究去补充和完善之前研究的空白和不足之处。在利用运动疗法治疗时,应从疾病整体把握,明确脑卒中并发症以及后遗症治疗间的潜在相互作用,确保康复治疗的有效性。在治疗方案选择时,可考虑采用联合策略进行治疗,充分发挥"1+1>2"的治疗效应,以最大限度地改善患者的功能障碍结局,提高其自我独立能力,重返家庭和社会。

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Mechanism of Nerve Regeneration after Ischemic Stroke Induced by Exercise Intervention

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ABSTRACT Ischemic stroke (IS) is characterized by high incidence, high disability rate and high mortality. It is a challenge in the prevention and treatment of cerebrovascular diseases, and it is also a major global health concern. Following the IS, in order to cope with the loss of input from neurons in the infarction area induced by ischemia and hypoxia stimulation, the body will spontaneously start the self-repair mechanism and reorganize the neuronal functional connections and neural pathways in the brain. However, the complete recovery of neurological function is far from enough when relying on the self-repair and functional reconstruction of the body alone, and it is still necessary to maximize and strengthen this ability through effective clinical treatment. Therefore, it is still the core issue and primary research direction to explore a treatment method that can effectively promote neuronal remodeling and regeneration, and improve neuronal injury-induced dysfunction for the prevention and treatment of IS. At present, exercise intervention, as a rehabilitation treatment technique with high clinical feasibility and high patient acceptance, has been included in the rehabilitation treatment plan for a variety of diseases, and is a complementary and alternative therapy for the effective prevention and treatment of cerebrovascular diseases. This study reviewed the regulatory mechanism of exercise intervention on nerve regeneration after IS, in order to provide a theoretical basis for the prevention and treatment of IS through exercise intervention. Based on the plasticity of the central nervous system, exercise intervention can play a neuroprotective role in the brain through multi-levels, multi-pathways and multi-targets, such as regulating synaptic budding, connection and transmission efficiency, improving the functional connection between regenerative axons and target cells, promoting angiogenesis and protecting the integrity of neurovascular units, regulating related inhibitory nerve regeneration factors, and inducing the expression of various nerve growth factors related to nerve regeneration and promoting the proliferation of neural stem cells, so as to participate in the regulation of central nervous regeneration environment, and improve the damaged nerve function after ischemia.
KEY WORDS ischemic stroke; exercise intervention; neuroregeneration; axon regeneration; neurovascular unit
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