综　述

间充质干细胞和神经细胞共培养技术及其应用研究进展

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[摘要]　体外细胞共培养是一项研究特定生物学问题的重要技术，近年来被广泛应用于神经系统疾病的研究中。神经系统疾病具有多样性、常见性、难治性等特点，一直是科研人员致力攻克的医学难题。间充质干细胞(MSCs)和神经细胞共培养技术为治疗神经系统疾病带来了希望。该技术实现了在一个系统设计和控制的共培养环境中，探索神经细胞在生理、病理或毒性条件下的形态和功能，以及细胞间相互作用的分子事件。MSCs指导的神经发生和神经再生将对神经系统疾病未来的治疗策略产生重大影响。本文系统性回顾MSCs与神经细胞共培养技术的进展，阐述共培养模型的应用前景，旨在为神经系统疾病的治疗提供新思路。

[关键词]　间充质干细胞；神经元；共同培养技术；神经胶质；神经系统疾病

Research progress on co-culture and application of mesenchymal stem cells and nerve cells

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[Abstract]　Co-culture is an important technique to study specific biological problems, and has been widely applied recent years in the field of nervous system diseases which are characterized by diversity, commonality and intractability, and have always been a medical problem that researchers are committed to overcoming. The co-culture of mesenchymal stem cells (MSCs) and nerve cells provides hope for treatment of nervous system diseases. As a systemically designed and controlled environment, co-culture technology can be used to explore the morphology and function of nerve cells under physiological, pathological or toxic conditions, as well as the molecular events of intercellular interaction. Neurogenesis and nerve regeneration directed by MSCs will have a significant impact on therapeutic strategies for neurological diseases in the future. The research progress in co-culture of MSCs and nerve cells has been systematically reviewed in present paper, and described the application prospect of co-culture model, so as to provide ideas for the treatment of nervous system diseases.

[Key words]　mesenchymal stem cells; neurons; co-culture techniques; neuroglia; nervous system diseases

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细胞培养是目前体外实验中最基本也是最常用的方法之一。随着新兴理念的不断提出和相关技术的不断改进，细胞培养在方式和过程上均发生了质的飞跃，而共培养技术便是其中之一。共培养技术是将不同种细胞置于同一体系中进行培养，可相对真实地模拟细胞在体内的生长环境并还原细胞在体内的性状，从而达到普通生物化学培养难以企及的效果[1]。目前，细胞共培养技术已深入应用于调控细胞增殖、诱导细胞分化、维持细胞功能等方面，也被用于体外生理及病理模型、药物作用机制及部位、组织工程等研究热点。神经系统疾病是一类严重影响人类生活质量的疾病，因神经再生能力有限，传统治疗往往存在局限性且疗效欠佳。间充质干细胞(mesenchymal stem cells，MSCs)是一群具有自我更新、多向分化潜能的成体干细胞群，与神经细胞共存时，可通过形式多样的信号进行调控[2]。近年来大量研究证实，在神经受损的修复过程中，MSCs对神经细胞发挥了减少细胞凋亡、促进细胞修复等积极作用[1-2]。此外，在成熟神经细胞或神经支持细胞的诱导下，MSCs能够分化为多种细胞，从而发挥引导轴突再生、调节免疫、促进再生的作用[3-4]。共培养技术为研究MSCs和神经细胞之间的相互作用和转化关系提供了细胞学的支撑。本文对MSCs与神经细胞共培养的种类及应用进展进行综述，旨在为神经系统疾病的治疗提供新思路。

1　MSCs与神经细胞共培养体系的种类

共培养体系中的细胞主要包括MSCs、神经细胞和神经支持细胞。MSCs来源广泛，一般可通过原代培养获得[5]。在各种来源的MSCs中，骨髓间充质干细胞(bone marrow mesenchymal stem cells，BMSCs)最为常用，脂肪、脐带、胎盘、胚胎、扁桃体来源的MSCs也有所涉及，亦有使用牙髓干细胞(dental pulp stem cells，DPSCs)的报道[6-7]。这几种干细胞的提取部位虽然存在差异，但在促进神经恢复方面却展示了相似的能力。用于共培养的神经细胞主要包括大脑海马神经元、脊髓背根节神经元(dorsal root ganglia，DRG)、视网膜神经节细胞等中枢神经细胞，以及螺旋韧带成纤维细胞等外周神经细胞。研究涉及的神经支持细胞则包括小胶质细胞、施万细胞(Schwann cells，SCs)、少突胶质细胞、嗅鞘细胞(olfactory ensheathing cells，OECs)等，可通过动物解剖提取、酶解离、稀释培养获得[8-9]。

此外，在进行某些病理相关的研究时，需要使用病理状态的神经细胞。这些细胞一般不是直接从神经病理组织中提取，而是先通过解剖纯化或购买获得正常细胞，再使用化学物质进行病理损害。有研究发现，利用吗啡处理细胞，可在体外模拟阿片类药物的依赖作用[10]；另有研究为模拟心搏骤停后的脑损伤，在体外使用氯化钴处理神经元，成功建立了缺氧诱导的细胞损伤模型[11]。根据实验目的不同，可采用以下多种方式建立细胞共培养体系。

1.1　直接接触共培养　直接接触共培养是将两种细胞接种于同一载体上，不同种类的细胞间可直接接触[12]。这种方法能够观察两个相邻细胞之间的直接相互作用，如细胞间黏附和缝隙连接等。

1.2　间接接触共培养　间接接触共培养是两种细胞处于同一培养环境，但不直接互相接触，通过培养基质内营养物质的交流来实现细胞间的交流。这种方法能够观察两种细胞通过旁分泌进行的相互作用，其中Transwell小室共培养技术是较为成熟且应用较多的实验方法[13]。

1.3　微流控装置共培养　微流控装置是根据神经细胞轴突长、树突分支多的特点设计出的一个可控且隔离的共培养系统，是目前体外研究突触传导和接触功能的最佳模型。在微流控装置中，神经细胞接种于微管一侧的腔室，轴突可沿着微管的方向伸出，从而达到另一侧的腔室，充分模拟体内神经纤维末端的生长情况；微管两侧的腔室相对分离，可灵活地研究多种微环境的作用[14]。

1.4　类器官共培养　类器官培养(即组合体外培养系统)保存了体内原始组织的解剖和功能特征，能够再现原始系统的细胞结构和细胞间接触，因此在系统特异性体外研究中具有显著优势[15]。目前，已有研究将MSCs与中脑皮质类器官脑片、海马类器官脑片、视网膜类器官外植体和内耳类器官培养物进行共培养，这些研究揭示了干细胞介导的神经组织再生和保护作用，有助于加速基础研究向临床应用的转化[16]。

1.5　生物材料共培养　生物材料可在体外调节细胞行为，常用于评估细胞反应过程中微观结构的变化及其与生理功能的关系，在神经组织工程研究中占有重要地位。在不同材料上研究神经细胞与MSCs的共培养，可能是提高神经再生效率的潜在途径[17]。常见的体外培养材料可分为刚性材料和弹性材料，刚性材料包括不同硬度和微管尺寸的壳聚糖基质，弹性材料包括有机高分子纤维支架和蛋白质凝胶，这些生物材料已在共培养体系中展现了促进神经生长的能力[17-18]。共培养研究为体外开发性能更好的生物材料提供了实验基础，也为临床神经组织工程应用提供了更有效的解决方案。

2　MSCs与神经细胞共培养体系的应用进展

2.1　在神经损伤修复研究中的应用　MSCs是一

类具有神经营养潜能的多能干细胞，可通过旁分泌等途径对受损部位的神经系统细胞进行调控。MSCs产生的神经营养因子和其他生物活性物质在神经损伤的治疗方面具有巨大潜力，是治疗神经系统疾病的理想工具[19]。在共培养系统中，MSCs分泌Ⅰ型胶原、脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)、胶质细胞系源性神经营养因子(glial cell line-derived neurotrophic factor，GDNF)、神经营养素-3(neurotrophin-3，NT-3)和神经生长因子(nerve growth factor，NGF)等物质，通过促进神经元突起生长、促进髓鞘再生两种策略推动神经损伤的修复[20]。

MSCs共培养可促进神经元突起的生长，有望应用于多种神经退行性或损伤性疾病的治疗[21]。首先，在对阿尔兹海默症的研究中，MSCs常与海马神经元进行共培养。大脑海马区的主要功能是参与近期记忆、情绪控制及内脏功能调节，是阿尔兹海默症等疾病的主要病变部位之一[22]。海马神经元与人脐带来源的MSCs间接接触共培养后，初级树突数量增多、长度增加，同时突触标记物表达水平增高，提示在人脐带来源的MSCs存在时海马细胞可形成更多突触[23]。此外，在对脊髓损伤的治疗方面，脊髓神经元与MSCs共培养也具有巨大潜力[1]。有研究指出，与对照培养组或成纤维细胞共培养组相比，与BMSCs共培养的脊髓神经元突起生长更明显[24]。此外，在视觉相关疾病的研究中，已有共培养促进视觉神经修复的报道，该研究发现，在Transwell系统中，与大鼠DPSCs、BMSCs两种干细胞共培养可促进视网膜神经节细胞的存活和轴突生成，为视网膜神经修复的细胞疗法提供了支持[7]。

通过神经支持细胞促进髓鞘再生是神经修复的另一重要策略。在中枢神经系统中，神经纤维的髓鞘由少突胶质细胞形成，在外周神经系统则由SCs形成，而共培养系统的诱导作用可推动少突胶质细胞和SCs的生长，从而促进髓鞘的形成和神经修复[25-27]。已有研究发现，MSCs可促进少突胶质细胞的分化成熟，如胎盘来源的间充质干细胞(placental mesenchymal stem cells，PMSCs)、外胚层间充质干细胞(ecto-mesenchymal stem cells，EMSCs)与少突胶质细胞前体细胞共培养时，可通过旁分泌诱导少突胶质细胞前体细胞分化为成熟的髓鞘少突胶质细胞，进而促进髓鞘再生[25-26]。另有研究发现，这种促成熟作用与Notch信号通路和丝裂原活化蛋白激酶/细胞外调节蛋白激酶(mitogen-activated protein kinase/extracellular regulated protein kinases，MAPK/ERK)信号通路被抑制有关[27]。此外，MSCs还可促进SCs的生长。在共培养系统中，MSCs可通过旁分泌细胞外基质蛋白-5(fibulin 5，FBLN5)促进SCs的增殖及髓鞘形成[28]。总之，共培养体系中的MSCs可促进神经元突起的生长，还可促进少突胶质细胞和SCs的生长，从而促进髓鞘的再生，在神经修复领域拥有广阔的应用前景。

2.2 在神经免疫调节研究中的应用 神经炎症几乎存在于所有类型的神经系统疾病中[29]。体外实验常利用MSCs分泌神经营养因子、免疫调节因子和抗凋亡因子，调节神经系统的免疫功能，进而保护神经系统[30-31]。中枢神经系统损伤后，小胶质细胞迅速激活并聚集，在损伤部位引发炎症反应。活化的小胶质细胞可分为具有促炎、损伤作用的M1型和具有抗炎、修复作用的M2型。大量研究发现，MSCs可通过诱导M2型小胶质细胞极化发挥神经保护作用[32-34]。脂肪干细胞(adipose-derived stem cells，ADSCs)可分泌GDNF，通过上调磷脂酰肌醇3激酶/蛋白激酶B(phosphatidylinositol 3-kinase/protein kinase B，PI3K/Akt)通路抑制小胶质细胞M1型转化而促进M2型形成[35]。有研究将人MSCs与大鼠视网膜组织块进行间接接触共培养，结果发现MSCs来源的旁分泌信号使小胶质细胞的数量减少，并抑制小胶质细胞的M1型转化，从而起到保护视网膜神经节细胞的作用[36]。此外，M2型小胶质细胞营造的抗炎环境对神经细胞可产生积极影响，最终起到防止脱髓鞘、促进神经修复的作用。因此，通过共培养进行免疫调节也是治疗神经炎性疾病的一种合适策略[33]。

2.3 在神经再生研究中的应用 中枢神经损伤很难实现自然再生，且听神经等外周神经损伤的恢复也相对困难。通过干预手段替换受损的神经细胞，可实现受损神经的再生。以BMSCs为代表的各种MSCs具有分化潜力，而功能成熟的神经系统细胞具有诱导MSCs分化的能力，在治疗神经系统病变方面前景广阔[2,37]。MSCs在功能成熟的神经细胞或神经支持细胞诱导下，以及外源或内源细胞因子的作用下，可分化为神经样细胞，并改善受损部位的神经功能[38]。功能成熟的DRG、OECs、SCs、星形胶质细胞等均为常见的发挥诱导作用的细胞[8-9]。

神经样细胞的最终产生和受损神经的功能改善已在大量研究中得到证实[39-41]。有学者在脊髓损伤相关研究中利用基因转染技术处理SCs和MSCs，发现可使SCs过量产生NT-3，以及MSCs过表达NT-3受体酪氨酸激酶C(tyrosine kinase，TrkC)，随后将处理过的SCs与MSCs进行共培养，在形态学和功能上证实了具有突触发生潜能的神经元样细胞的形成，并利用获取的细胞成功改善了脊髓横断大鼠的运动功能[42]。此外，在听觉相关研究中，MSCs与螺旋

韧带成纤维细胞共培养时，螺旋韧带成纤维细胞分泌的转化生长因子-β(transforming growth factor-β，TGF-β)具有促进MSCs向螺旋韧带成纤维细胞样细胞分化的能力，且MSCs移植后内耳受损大鼠的听觉明显改善[39]。共培养技术诱导产生的神经样细胞作为受损神经部位的细胞补充源，可促进神经再生，为受损神经的功能恢复提供了基础支持。

2.4 在神经肿瘤研究中的应用 中枢神经系统肿瘤常引起严重的临床症状，且治疗选择十分有限。MSCs对胶质细胞瘤具有趋向性和相互作用性，因此也代表了一种潜在的细胞治疗策略，且已有大量研究发现MSCs共培养可对肿瘤起到抑制作用[43-45]。在与胶质瘤共培养时，MSCs可通过释放抗血管生成因子抑制胶质瘤对内皮祖细胞(endothelial progenitor cells，EPCs)的募集和形成内皮管的能力，进而抑制肿瘤的血管生成，这可能是潜在的治疗方向[46]。然而，也有研究发现，MSCs对肿瘤细胞的抑制作用可能与时间相关[47]，该研究发现与胎儿BMSCs共培养的胶质瘤细胞在早期增殖活性增强，但3周后增殖明显受到抑制，这种双重作用提示我们必须全面观察在共培养不同时间点获得的数据[47]。

此外，神经毒性是许多化疗药物临床应用的主要限制因素，因此，研究干细胞对神经的保护作用在药物应用中具有重要意义。已有大量研究表明，干细胞共培养对中毒的神经细胞具有保护作用[48-49]。BMSCs通过直接接触共培养，可对顺铂诱导的DRG死亡产生神经保护作用，而AMSCs通过间接接触共培养可阻止谷氨酸诱导的神经细胞死亡[50-51]。另有研究将MSCs与感觉神经元间接共培养，结果发现其可明显逆转紫杉醇对感觉神经元的毒性作用[52]。总之，共培养的神经保护作用为化疗药物的中毒前预防和中毒后急救提供了全新的思路，在化疗药物的安全使用方面具有广阔的前景。

3 总结与展望

神经系统疾病的治疗与恢复仍是亟待解决的医学难题[53]。MSCs与神经细胞共培养技术的发展，将持续推动神经修复、神经免疫调节、神经再生、神经肿瘤等领域的基础与临床研究，为神经系统疾病的治疗提供更多策略，在临床应用方面前景广阔。未来，为了更大限度地利用MSCs与神经细胞共培养体系的治疗潜力，优化共培养前及共培养过程中的细胞处理策略至关重要，包括通过体外转染基因和使用定制的生物基质来调节细胞行为等[54-55]。此外，共培养体系中的调控机制也有待进一步深入研究[56-58]。

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