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间充质干细胞治疗新型冠状病毒肺炎的机制及研究进展

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[摘　要]　新型冠状病毒肺炎(COVID-19)感染性强,且重型及危重型患者病死率高,缺乏特异性治疗方法,急需寻找安全有效的治疗方法。间充质干细胞(MSCs)具有免疫调节、组织修复、再生、迁移和归巢、抗病毒和抗炎等生物学特性。目前应用MSCs治疗COVID-19的研究已逐步开展。本文就2019新型冠状病毒(2019-nCoV)的致病机制、MSCs治疗COVID-19的潜在机制及面临的挑战进行综述。

[关键词]　间充质干细胞;新型冠状病毒肺炎;临床试验

Mechanism and research progress of mesenchymal stem cells in treatment of COVID-19

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[**Abstract**]　Coronavirus disease 2019 (COVID-19) is highly infectious, severe and critically ill patients have high mortality and lack specific treatment, so it is urgent to find safe and effective treatment methods. Mesenchymal stem cells (MSCs) have biological properties such as immune regulation, tissue repair, regeneration, migration and homing, antiviral and anti-inflammatory. At present, studies on use of MSCs in treatment of COVID-19 have been gradually carried out. This paper reviews pathogenesis of 2019 novel coronavirus (2019-nCoV), potential regulatory mechanisms and challenges of MSCs in treatment of COVID-19.

[**Key words**]　Mesenchymal stem cells;COVID-19;Clinical trials

世界卫生组织(World Health Organization,WHO)将2019新型冠状病毒(2019 novel coronavirus,2019-nCoV)感染的肺炎命名为2019新型冠状病毒肺炎(coronavirus disease 2019,COVID-19)[1-2]。截至2021年10月7日,我国累计确诊超过124 932人,累计死亡超过5 693人,累计境外输入9 215人。我国疫情从暴发至稳定再到小范围集中出现,且随着境外输入及节假日人群活动密集加大,2019-nCoV会继续存在很长时间,严重威胁人类生命安全。

目前多数重型及危重型COVID-19患者病情迅速进展为急性呼吸窘迫综合征、脓毒血症及多器官衰竭等,在抗病毒、抗菌、中医药等治疗基础上需给予机械通气支持治疗、循环治疗、抗凝治疗、血液净化等治疗,效果仍不理想[3]。因此,世界各地研究机构和医疗机构仍在积极开展临床试验,寻找安全有效的治疗方法。间充质干细胞(mesenchymal stem cells,MSCs)由于其免疫调节、组织修复及再生、迁移和归巢、抗病毒和抗炎等生物学特性,可能成为COVID-19的有效治疗方法[4-7]。以下就2019-nCoV的致病机制、MSCs治疗COVID-19的潜在机制及面临的挑战进行综述。

1　2019-nCoV的致病机制

2019-nCoV属于单股正链病毒,其表面有一种三聚体糖蛋白,称为刺突蛋白(Spike protein),这种蛋白与宿主细胞受体血管紧张素转换酶2(angiotensin converting enzyme 2,ACE2)结合进入人体细胞进行复制、繁殖,在丝氨酸蛋白酶2(transmembrane protease serine protease 2,TMPRSS2)、组织蛋白酶L

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（cathepsin L，CTSL）、弗林蛋白酶（Furin）协同作用下被启动，引发疾病（图 1）[8-10]。由于人体存在 ACE2 受体，且 ACE2 受体广泛存在于人肺泡Ⅱ型细胞（alveolar type Ⅱ cells，AT2）和毛细血管内皮细胞，AT2 细胞高表达 TMPRSS2，病毒入侵人体时，病毒表面的刺突蛋白在肺部被启动，肺脏成为 2019-nCoV 攻击的主要靶器官[11-12]。2019-nCoV 与肺泡上皮细胞、血管内皮细胞 ACE2 受体结合，导致肺泡上皮细胞受损和肺血管内皮通透性升高，蛋白漏出肺泡腔和肺间质，影响肺泡与血液间气体交换，导致氧合障碍[13]。另一方面，病毒在体内不断大量复制，引起体内免疫系统过度激活，大量炎症细胞因子导致细胞因子风暴综合征（cytokine storm syndrome，CSS），减少细胞因子产生是治疗 COVID-19 的关键，免疫疗法可能用于治疗 COVID-19[14-16]。

2　MSCs 治疗 COVID-19 的潜在调控机制

MSCs 是一种多能干细胞，贴壁生长，可分化为成骨细胞、软骨细胞、脂肪细胞，且具有独特的自我更新及归巢能力，具有抗炎等免疫调节特性，在临床应用上备受关注[17-18]。研究证实 MSCs 的潜在调控机制对 COVID-19 有治疗效果，本文将从 MSCs 的免疫调节、组织修复、再生、迁移和归巢、抗病毒和抗炎等机制对其在 COVID-19 治疗中发挥的作用及应用进行阐述。

2.1　MSCs 的免疫调节作用及其在 COVID-19 中的应用　MSCs 的免疫调节机制已被广泛研究，与固有免疫系统和获得性免疫系统中的免疫细胞相互作用调节免疫应答[4]。研究表明 2019-nCoV 影响正常的免疫应答，导致患者免疫系统受损和炎症反应失控，出现淋巴细胞减少、IgG 反应增强、细胞因子水平升高等现象[9]。MSCs 恰好在免疫调节方面具有优势，主要通过细胞直接接触或旁分泌作用发挥免疫调节作用[19]。研究报道 MSCs 的免疫调节作用归因于 MSCs 外泌体、囊泡的免疫调节特性[20]。此外，

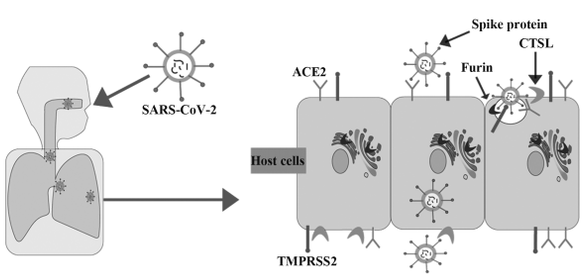

图 1　2019-nCoV 对人体细胞的致病机制

Fig. 1　Pathogenic mechanism of 2019-nCoV on human cells

MSCs 能够将巨噬细胞从促炎 M1 型向抗炎 M2 型转变，减轻炎症反应[21]。MSCs 还可抑制树突状细胞（dendritic cells，DCs）分化和成熟，减少 DCs 激活和炎症因子分泌[19]。同时，MSCs 能抑制 T 细胞过度增殖，并促进 T 细胞分泌 IL-10 和 IL-11 等抗炎细胞因子[22-23]。一项使用 MSCs 治疗 COVID-19 的试验中，研究者发现 MSCs 通过减少粒细胞-巨噬细胞集落刺激因子（granulocyte-macrophage colony stimulating factor，GM-CSF）使巨噬细胞从促炎 M1 型向抗炎 M2 型转变，从而发挥抗炎作用[24]。MSCs 的这些免疫调节作用使其被用于 COVID-19 治疗。

2.2　MSCs 的组织修复和再生作用及其在 COVID-19 中的应用　MSCs 可通过旁分泌途径发挥组织修复和再生作用，如分泌趋化因子、细胞因子和生长因子等[5]。动物试验中，MSCs 通过分泌血管内皮生长因子（vascular endothelial growth factor，VEGF）治疗脂多糖诱导的急性肺损伤大鼠，恢复其肺通透性，控制炎症，减轻肺损伤[25]。研究表明，MSCs 不仅可修复损伤的肺上皮细胞，还可促进 COVID-19 患者体内其他损伤组织修复，进一步证实 MSCs 在治疗 2019-nCoV 所致多器官损伤中的优势[26-27]。此外，研究再次证实 MSCs 在治疗 COVID-19 中的组织修复和再生作用，通过分泌血管生成素（angiopoietin 1，Ang-1）和角质形成细胞生长因子（keratinocyte growth factor，KGF）修复被 2019-nCoV 破坏的肺泡毛细血管屏障[28]。另一项研究也发现 MSCs 治疗的危重型 COVID-19 患者与未经 MSCs 治疗的对照组相比，TGF-β、VEGF、KGF、神经生长因子（nerve growth factor，NGF）等明显增加，表明 MSCs 的再生功能可修复 COVID-19 患者器官或组织损伤[29]。

2.3　MSCs 的迁移和归巢作用及其在 COVID-19 中的应用　MSCs 迁移和归巢受化学因素（如趋化因子、细胞因子和生长因子）影响，具有趋化作用，可归巢至肺，进而分化为肺上皮细胞或分泌多种生长因子修复受损组织[30]。大量研究证实，组织损伤后基质细胞衍生因子 1（stromal cell derived factor-1，SDF-1）表达显著增加，表达趋化因子受体 4（chemokine receptor 4，CXCR4）的骨髓间充质干细胞（bone marrow stromal cells，BMSCs）沿着 SDF-1 浓度梯度完成迁移，到达组织损伤部位进行修复工作[31]。同时，MSCs 的迁移和归巢作用还受机械因素（如血液动力学）影响[5]。研究证实重型 COVID-19 患者被感染的上皮细胞 CXCL1、CXCL3、CXCL6、CXCL16 和 CXCL17 等趋化因子分泌明显增加，MSCs 可利用其

归巢作用随以上趋化因子迁移至肺，发挥修复及抗炎作用[32]。另有研究表明，静脉注射的BMSCs超过80%滞留于肺，其余部分迁移并归巢至其他组织，包括肝脏、脾脏和炎症损伤部位[33]。表明MSCs的迁移与归巢作用在治疗2019-nCoV所致多器官损伤中发挥重要作用。

2.4 MSCs的抗病毒和抗炎作用及其在COVID-19中的应用　MSCs可分泌抗菌肽（antimicrobial peptide，AMPs）、吲哚胺2，3-双加氧酶（indoleamine 2，3-dioxygenase，IDO）、IL-17和其他分子产生直接抗病毒作用[7]。研究表明，MSCs来源外泌体可减少流感病毒在猪肺内的复制，并显著减少流感病毒感染猪肺内病毒诱导的TH1类细胞因子产生[34]。此外，MSCs在治疗脂多糖诱导的急性肺损伤小鼠模型中，可引起受损肺中IL-1β下调和IL-10上调，通过抗炎作用改善肺功能[35]。MSCs还能通过转移其线粒体增强体内巨噬细胞和单核细胞吞噬活性，从而间接增强对细菌感染的固有免疫应答[36-37]。研究发现，COVID-19患者注射MSCs治疗后，血液中C-反应蛋白、TNF-α水平下降，外周血淋巴细胞、IL-10水平升高，说明MSCs可发挥抗炎作用[16]。此外，MSCs治疗的COVID-19患者中，炎症水平最高的个体IL-6下降程度最大，氧合指数改善幅度最大，证明MSCs具有下调炎症因子水平的作用[38]。周围炎症环境能够增强MSCs的免疫调节作用[39]。表明利用MSCs的抗炎及抗病毒特征治疗COVID-19具有可行性。

3　MSCs治疗COVID-19的临床试验

MSCs治疗COVID-19的相关临床试验在国内外正在进行。截至2021年10月，国际临床研究注册网站clinicaltrials. gov（搜索“COVID-19”“mesenchymal stem cell”）中有82个项目为MSCs治疗COVID-19的临床试验，我国占10项。综合相关临床试验观察到多数临床试验处于1/2期，入组患者主要为符合重型COVID-19诊断标准的研究对象（《新型冠状病毒肺炎诊疗方案》试行第八版），MSCs主要组织来源包括脐带组织（脐带、脐血、胎盘）、骨髓、脂肪、外囊泡（外泌体）、牙髓、嗅黏膜，脐带来源MSCs治疗COVID-19的临床试验最多，主要为静脉注射，剂量为0. 5×10^6~2. 0×10^6 cells/（kg·dose），少数为持续5~10 d的外泌体雾化吸入。表明MSCs治疗COVID-19的临床试验在国内外已成为研究热点（表1）。

4　MSCs治疗COVID-19的前景及挑战

MSCs因具有强大的免疫调节及抗炎能力，对预防或减轻查尔格-施特劳斯综合征（Churg-Strauss syndrome，CSS）具有重要作用，治疗COVID-19时显示出良好前景，还可用于联合疗法，如联合康复者血浆。文献表明MSCs协同康复者血浆对重型COVID-19患者有较好疗效[41]。但MSCs治疗COVID-19也有局限性，目前临床试验大部分未进行双盲或随机对照试验，且输注后长期随访困难，不利于观察输注后不良反应及后遗症。不同来源MSCs选择无

表1　文中提及已发表的MSCs治疗COVID-19的临床试验

Tab. 1　Published clinical trials of MSCs in treatment of COVID-19 mentioned in this study

MSCs sources	Number of patients	Results	Conclusion	Reference
Unknown	7	↓ C-reactive protein ↓ TNF-α ↑ IL-10 ↑ Lymphocyte ↓ Overactivated cytokine-secreting cells ↓ Lung inflammation ↑ Clinical improvement	Intravenous transplantation of MSCs was safe and effective for treatment in patients with COVID-19 pneumonia, especially for patients in critically severe condition	[16]
UC-MSCs	12	↓ Inflammatory cytokine concentrations ↓ Time to recovery ↓ Serious adverse events ↓ Mortality	UC-MSC infusions in COVID-19 with ARDS are safe	[24]
Unknown	25	↑ Serum levels of lactate ↑ Cardiac troponin T ↑ Creatine kinase-MB ↓ Lung inflammation ↑ Clinical improvement	MSCs therapy might be a promising option for treatment of severe COVID-19, but should be used cautiously, especially in patients with metabolic acidosis or coronary heart disease	[28]

续表1

MSCs sources	Number of patients	Results	Conclusion	Reference
WJ-MSCs	10	↓ C-reactive protein ↓ Procalcitonin ↓ Proinflammatory cytokines ↑ Inflammatory cytokines ↑ Growth factors ↓ WBC and neutrophil count ↑ Lymphocyte ↓ Mortality ↓ ICU stay	It demonstrated positive systematic and cellular effects of MSCs application on critically ill COVID-19 patients in a versatile way. This effect plays an important role in curing and reducing mortality in critically ill patients	[29]
UC-MSCs	9	↓ C-reactive protein ↓ IL-6 ↑ PaO_2/FiO_2 ↓ Inflammatory cytokines ↓ Lung inflammation ↑ Clinical improvement	Intravenous UC-MSCs infusion in patients with moderate and severe COVID-19 is safe and well tolerated	[38]
UC-MSCs	16	↑ PaO_2/FiO_2 ↓ Lung inflammation ↑ $CD4^+$T cells ↑ $CD8^+$T cells ↑ NK cells	Intravenous transplantation of UC-MSCs was safe and feasible for treatment of patients with severe and critically severe COVID-19 pneumonia	[40]

Note: UC-MSCs. Umbilical cord derived mesenchymal stem cells; WJ-MSCs. Wharton's jelly-derived mesenchymal stem cells.

明确规定，且注射剂量、注射方式、给药时间、给药次数也不同。其次，MSCs培养过程中可能影响某些表面受体表达，影响归巢能力，进而影响治疗效果[42]。目前已发表的关于MSCs治疗COVID-19的临床试验中，虽无严重不良反应报道，但出现过轻症不良反应，包括一过性面色潮红、低蛋白血症、失眠、胃肠道疾病和阵发性心律失常等[38,40]。综上，MSCs在COVID-19临床应用方面仍面临挑战。

5　总结

MSCs具有修复再生、归巢、抗炎、抗病毒与免疫调节潜能，已在COVID-19治疗中发挥重要作用，尽管目前临床数据与统计结果尚少，但随着研究者不断探索与实践，MSCs将成为一种非常有前景的细胞免疫治疗方法。

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