

## · 综述 ·

## 间充质干细胞外泌体改善急性肺损伤机制的研究进展

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**【摘要】** 急性肺损伤(ALI)/急性呼吸窘迫综合征(ARDS)是一种高病死率的临床危重综合征。目前尚无有效的治疗策略,大多数患者预后较差。研究发现,间充质干细胞来源的外泌体(MSC-Exos)具有抑制肺部过度炎症反应、抑制肺泡细胞凋亡、促进上皮细胞再生等作用。因此,有必要通过综述 MSC-Exos 改善 ALI/ARDS 的潜在机制,为 ALI/ARDS 提供新的治疗思路。

**【关键词】** 间充质干细胞; 外泌体; 急性肺损伤

**Research progress on the mechanism of mesenchymal stem cell-derived exosomes on improving acute lung injury** Zhang Xiaobo<sup>1</sup>, Ba Te<sup>2</sup>, Huang Ruijuan<sup>2</sup>, Wang Hongyu<sup>2</sup>. <sup>1</sup> Third Clinical College of Inner Mongolia Medical University, Baotou 014010, China; <sup>2</sup> Department of Burn Surgery, Inner Mongolia Burn Research Institute, Inner Mongolia Baogang Hospital, Baotou 014010, China  
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**【Abstract】** Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a clinically critical syndrome with a high mortality rate. At present, there is no effective treatment strategy, and the prognosis of most patients is poor. At present, research has found that mesenchymal stem cell-derived exosomes (MSC-Exos) have functions, such as inhibiting excessive lung inflammation, suppressing alveolar cell apoptosis, promoting epithelial cell regeneration and alleviating mitochondrial damage. This article reviews the possible mechanisms about how MSC-Exos improves ALI/ARDS, providing new therapeutic approaches for ALI/ARDS.

**【Key words】** Mesenchymal stem cells; Exosomes; Acute lung injury

间充质干细胞(mesenchymal stem cell, MSCs)是一种具有免疫调节功能的成体干细胞亚型,具有修复受损肺组织和减轻急性肺损伤(acute lung injury, ALI)/急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)的潜力<sup>[1]</sup>。最近,越来越多的研究表明 MSCs 发挥治疗作用是通过旁分泌作用实现的。间充质干细胞来源的外泌体(MSC-derived exosomes, MSC-Exos)作为其主要的旁分泌组分,是发挥生物学功效的关键<sup>[2]</sup>。外泌体是由细胞分泌的纳米级、球形细胞外囊泡,直径通常在 30~150 nm,由脂质双分子层包裹,能够携带多种生物活性分子,包括蛋白质、核酸(mRNA, miRNA)、脂质和线粒体成分<sup>[3]</sup>。外泌体可以由包括间充质干细胞在内的所有细胞分泌,其形成过程包括内吞作用、内体的成熟和细胞外释放。外泌体不仅能够作为细胞间的信使,还可以通过膜融合、旁分泌信号、吞噬或受体介导的内吞作用,将其携带的生物活性分子转运至受体细胞,从而发挥生物学效应,包括减轻炎症、抑制肺泡上皮及内皮细胞凋亡、促进肺泡上皮及内皮细胞再生、减轻线粒体损伤<sup>[4-6]</sup>。因而,可通过综述 MSC-

Exos 改善 ALI/ARDS 的潜在机制,为 ALI/ARDS 提供新的治疗思路。

#### 一、MSC-Exos 通过抑制肺部过度炎症反应改善 ALI

急性肺损伤的显著特征是炎症反应的过度激活。炎症风暴的发生通常是由于内因或外因的刺激,导致肺部组织损伤,进而引发大量免疫细胞的募集和细胞因子的释放。这种反应不仅损害了肺上皮细胞的完整性,还增加了肺微血管内皮细胞的通透性。同时,肺泡腔中的液体渗出,产生肺水肿,进一步发展为 ARDS<sup>[7-9]</sup>。核因子  $\kappa$ B (nuclear factor kappa-B, NF- $\kappa$ B) 信号通路涉及一系列参与免疫调节和炎症反应的关键转录因子,在维持宿主正常生理活动中起着至关重要的作用,如感染和促炎细胞因子的存在可激活 NF- $\kappa$ B 信号通路。NF- $\kappa$ B 通过磷酸化被激活,会诱导多种炎症细胞因子的产生,包括肿瘤坏死因子- $\alpha$  (tumor necrosis factor, TNF- $\alpha$ )、白细胞介素  $1\beta$  (interleukin  $1\beta$ , IL- $1\beta$ ) 和 IL-6<sup>[10]</sup>。在大肠杆菌内毒素诱导的 ALI 模型中, NF- $\kappa$ B 通路的激活可促进肺部炎症反应,并且 NF- $\kappa$ B 的持续激活与肺损伤的严重程度相关<sup>[11]</sup>。Xu 等<sup>[12]</sup>发现, MSC-Exos 可减弱 NF- $\kappa$ B 通路的激活,降低促炎细胞因子的表达,从而抑制炎症反应; NF- $\kappa$ B 可作为 MSC-Exos 保护肺因烟雾吸入引起的急性损伤的潜在靶点。Zhang 等<sup>[13]</sup>的研究提出,外泌体可以通过影响 NF- $\kappa$ B 信号通路中 p65 和蛋白激酶 B (protein kinase B, Akt)/核因子 E2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)/血红素氧化酶-1 (hemoxygenase-1, HO-1) 信号通路减

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轻炎症来减少心肺分流术后相关的ALI。Toll样受体4(toll-like receptor 4,TLR4)是一种重要的模式识别受体,可识别细胞外刺激,启动下游信号通路,通过髓样分化蛋白88(myeloid differentiation factor 88, Myd88)非依赖通路和Myd88依赖通路激活NF- $\kappa$ B信号通路,上调炎症因子的表达<sup>[14]</sup>。MSC-Exos在严重烧伤诱导的ALI中具有显著的抗炎作用,并可降低TLR4/NF- $\kappa$ B通路相关蛋白的表达。当外泌体中的miR-451表达受到抑制时,这些影响被逆转<sup>[15]</sup>。此外,因肠缺血再灌注引起的ALI动物模型中,注射MSC-Exos可减少肺泡和间质水肿、肺出血和炎症细胞浸润,同时下调TLR4和NF- $\kappa$ B的表达<sup>[16]</sup>。在一项体外研究中,MSC-Exos可抑制TNF- $\alpha$ 和IL-1 $\beta$ 的分泌,促进抗炎因子TGF- $\beta$ 的分泌,抑制T细胞分化为Th17细胞,并增加调节性T细胞的水平<sup>[17]</sup>。

此外,外泌体还可以上调CD206和精氨酸酶1等M2巨噬细胞标志物的表达,进而促进巨噬细胞分泌IL-10。MSC-Exos可以抑制T细胞向Th17细胞的分化,增加Treg细胞的水平,减少中性粒细胞的聚集<sup>[18-19]</sup>。Heo等<sup>[20]</sup>发现,MSC-Exos可以通过增加M2巨噬细胞标志物的表达来调节巨噬细胞极化。Wang等<sup>[21]</sup>发现,MSC-Exos可以抑制肺巨噬细胞的聚集,抑制IL-27的合成和释放,降低IL-6、TNF- $\alpha$ 和IL-1 $\beta$ 的含量,减轻脓毒症诱导的肺损伤,注射重组IL-27可逆转外泌体对脓毒症诱导肺损伤的保护作用。动物实验表明,MSC-Exos能够有效转移线粒体成分,保持巨噬细胞线粒体完整性和氧化磷酸化水平,恢复气道巨噬细胞的代谢和免疫稳态,缓解肺部炎症<sup>[22]</sup>。此外,研究表明来自MSC-Exos的miRNA,如miR-125a-3p,可以提高调节性T细胞的存活率,并阻止T细胞向效应细胞分化<sup>[23]</sup>。

肺泡巨噬细胞是肺的第一道防线。不同形式的肺泡巨噬细胞死亡,如焦亡、自噬和坏死,可共同诱导肺部炎症<sup>[24]</sup>。在这3种死亡形式中,焦亡可诱导IL-1 $\beta$ 、IL-18等大量促炎细胞因子的分泌,是一种在炎症反应中起关键作用的细胞死亡形式<sup>[25]</sup>。焦亡是典型的caspase-1或非典型的caspase-11/4/5介导的炎症细胞死亡,其发生取决于Gasdermin蛋白家族的激活,病原体相关的分子或损伤相关的分子通过激活炎性小体使caspase-1激活<sup>[26]</sup>。激活的caspase-1引起消皮素的N末端域形成孔道,导致细胞肿胀和细胞膜穿孔。此外,激活的caspase-1诱导IL-1 $\beta$ 和IL-18分别裂解为成熟形式的IL-1 $\beta$ 和IL-18,随后通过细胞膜上的孔释放<sup>[27]</sup>。该过程促进肺中中性粒细胞的积累,增加肺泡灌洗液中细胞因子IL-6、IL-1 $\beta$ 和TNF- $\alpha$ 的水平,加重ALI<sup>[28]</sup>。因此,肺泡巨噬细胞焦亡可能是治疗ALI的新靶点。Zhang等<sup>[29]</sup>发现应用MSC-Exos可显著改善体外循环术后大鼠的巨噬细胞浸润和氧化应激,下调肺组织和肺泡巨噬细胞中caspase-1等热降解相关蛋白的表达,降低支气管肺泡灌洗液中IL-18和IL-1 $\beta$ 的分泌。MSC-Exos通过激活Yes-相关蛋白(Yes associated protein, YAP)/ $\beta$ -catenin轴抑制体外循环诱导的细胞焦亡。Liu等<sup>[30]</sup>的研究则表明,MSCs-Exos显著改善了ALI小鼠的肺部炎症反应,降低了肺泡毛细血管膜通透性。其机制可能是MSCs-Exos通过靶向caspase-1介导的miRNA和具有免疫调节功能的蛋白抑制肺泡巨噬细胞焦亡。

上述研究表明,MSC-Exos可通过减弱NF- $\kappa$ B活化、抑制促炎因子分泌、减少中性粒细胞聚集、调节巨噬细胞向M2型极化、抑制肺泡巨噬细胞焦亡等途径减轻肺部炎症反应从而改善ALI。

## 二、MSC-Exos通过抑制肺泡上皮和内皮细胞凋亡改善ALI

肺上皮细胞在维持肺泡稳定性中起着关键作用,多种刺激[如芥子气、高氧、脂多糖(lipopolysaccharide, LPS)等]诱导细胞凋亡可导致上皮屏障功能障碍,发展为ALI<sup>[31]</sup>。研究发现,MSC-Exos可保护肺上皮细胞免受ALI的伤害。Mao等<sup>[32]</sup>通过在小鼠的内侧和背部表面注射芥子气诱导ALI模型,发现骨髓来源的MSC-Exos通过上调G蛋白偶联受体家族C组5型A(G protein-coupled receptor class C group 5 member A, GPRC5A),促进上皮型粘附素、紧密连接蛋白-1、闭合蛋白、闭锁连接蛋白1等连接蛋白的表达和重新定位,抑制上皮细胞凋亡,促进上皮屏障功能的恢复。Li等<sup>[33]</sup>证明,MSC-Exos内的微小RNA-21-5p(miR-21-5p)具有抗凋亡特性,气管内给予MSC-Exos可抑制肺上皮细胞的内在和外在凋亡途径。用miR-21-5p拮抗剂预处理的间充质干细胞完全消除了MSC-Exos介导的对半胱氨酸天冬氨酸蛋白酶3(cysteinyl aspartate specific proteinase 3, caspase-3)、8和9的抑制,降低了MSC-Exos对肺上皮细胞的保护作用。此外,MSC-Exos对长链非编码RNA(lncRNAs)的转移也可以在抑制肺上皮细胞凋亡中发挥重要作用。外泌体转染lncRNA-p21可通过下调miR-181和上调沉默信息调节因子相关酶1表达来抑制上皮细胞凋亡并预防ALI<sup>[31]</sup>。MSC-Exos能够降低某些内源性细胞因子的水平,抑制肺上皮细胞凋亡,也能够过表达有益分子以提高其抗凋亡作用,如过表达miR-30b-3p的MSC-Exos能够抑制LPS诱导的肺泡上皮细胞凋亡,促进LPS处理的小鼠肺上皮细胞的增殖<sup>[34]</sup>。磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)-Akt是一条重要的细胞内信号通路,参与细胞增殖和存活、细胞凋亡、血管生成、蛋白质合成和脂质代谢等生物学过程<sup>[35]</sup>。PI3K-Akt信号通路参与许多疾病的病理生理过程,包括ALI/ARDS<sup>[36]</sup>。脂肪源性MSC-Exos的miR-126可以通过激活PI3K-Akt信号通路,减弱组蛋白诱导的内皮细胞凋亡,降低肺血管通透性。相反,Akt抑制剂会增加组蛋白诱导的血管渗漏<sup>[37]</sup>。MSC-Exos还可以通过将miR-425转移到上皮细胞,激活PI3K-Akt信号通路,从而减轻高氧诱导的ALI,提高细胞活力,防止细胞凋亡<sup>[37]</sup>。

ALI进展的特征之一是氧化应激反应<sup>[38]</sup>。过量促炎细胞因子的积累可导致肺组织发生氧化应激,进而导致ALI的发生。Gong等<sup>[39]</sup>研究发现人脐带间充质干细胞衍生的外泌体中的miR-199a-5p在人支气管上皮细胞和小鼠模型中可通过减少活性氧、脂质过氧化产物和增加抗氧化酶的活性,减少肺细胞氧化应激和凋亡。MSC-Exos携带的miR-21-5p是一种促癌miRNA,能有效抵抗细胞凋亡。Li等<sup>[33]</sup>分别用缺氧或miR-21-5p拮抗剂处理小鼠骨髓源性间充质干细胞,可升高或降低MSC-Exos中miR-21-5p的浓度。研究发现,MSC-Exos以miR-21-5p依赖的方式减弱小鼠肺缺血-再灌注损伤,有效减少氧化应激诱导的细胞凋亡。



上述研究表明, MSC-Exos 可通过对 lncRNAs 的转移、降低内源性细胞因子水平、上调 G 蛋白偶联受体家族中连接蛋白的表达、激活 PI3K-Akt 信号通路等作用抑制肺泡上皮细胞和内皮细胞的凋亡从而改善 ALI。

三、MSC-Exos 通过促进肺泡上皮和内皮细胞再生改善 ALI

ALI/ARDS 的病理特征是弥漫性肺泡损伤,包括肺内皮和上皮细胞的损伤。修复屏障功能降低肺泡上皮-内皮细胞膜通透性是 ALI 的治疗策略<sup>[8]</sup>。MSC 能够进入受损组织,调节免疫系统,促进肺泡上皮细胞和内皮细胞的再生,在肺损伤中发挥重要的保护作用。据报道, MSC-Exos 能够诱导 II 型肺泡细胞的再生,从而促进内皮细胞的修复与再生<sup>[40-41]</sup>。

Hippo/YAP 信号通路可调节细胞增殖和器官再生,促进肺血管屏障修复,以及肺泡上皮细胞损伤后肺部炎症缓解和肺泡再生<sup>[42]</sup>。研究表明,骨髓源性 MSC-Exos 通过激活 Hippo 信号通路可促进肺上皮屏障修复,从而对芥子气肺损伤产生保护作用<sup>[42]</sup>。角质细胞生长因子(keratinocyte growth factor, KGF)是人间充质干细胞分泌的有丝分裂原,在促进肺泡上皮细胞增殖和 DNA 修复、改善氧化诱导的上皮细胞通透性等方面发挥关键作用。研究表明, MSC-Exos 通过将 KGF 的 mRNA 转移到受体细胞,发挥增强肺泡液清除、降低肺蛋白通透性和抑制受损肺泡中细菌增殖的作用<sup>[43]</sup>。另有研究表明,异恶唑-9(Isoxazole 9, ISX-9)能够上调 MSCs 分泌 KGF 以加速上皮细胞的再生并逆转肺纤维化<sup>[44]</sup>。Zhu 等<sup>[45]</sup>发现 MSC-Exos 能够缓解大肠杆菌内毒素诱导的 ALI,其携带的 KGF 发挥了关键作用。

上述研究表明 MSC-Exos 能通过激活 Hippo/YAP 信号通路及分泌 KGF 促进肺泡上皮和内皮细胞再生从而改善 ALI。

四、MSC-Exos 通过减轻肺泡上皮细胞线粒体损伤改善 ALI

在 ALI 的发生、发展过程中,线粒体产生的活性氧能够导致线粒体 DNA 转录缺陷和线粒体功能障碍,受损的线粒体能够进一步驱动肺部的不良反应<sup>[46]</sup>。Sun 等<sup>[47]</sup>的研究表明, MSC-Exos 能够抑制活性氧的产生和改善线粒体 DNA 损伤,从而减少肺泡上皮细胞的凋亡;其是通过包裹在 MSC-Exos 中的 MiRNA-Let-7 调节凝集素样氧化低密度脂蛋白受体-1 (lectin-like Ox-LDL receptor-1, LOX-1) 来发挥作用。Dutra 等<sup>[48]</sup>证实, LPS 刺激会破坏线粒体膜电位,增加线粒体活性氧的产生,抑制线粒体呼吸。而 MSC-Exos 介导的线粒体转移恢复了正常的线粒体自噬和线粒体生物发生,减轻了 LPS 对线粒体呼吸的抑制,缓解了线粒体功能障碍,恢复了肺泡上皮细胞的屏障完整性<sup>[49]</sup>。另有研究表明, LPS 诱导的 ALI 小鼠受损的肺泡上皮细胞在吞噬骨髓的 MSCs 释放携带线粒体的外泌体后,肺泡上皮细胞的生物能量学得到改善,存活率提高;同时,发现如果 MSC-Exos 中含有功能失调的线粒体或缺乏缝隙连接蛋白 43,则会降低小鼠的存活率<sup>[50]</sup>。近期证据表明,功能失调的线粒体会扰乱肺泡上皮细胞和巨噬细胞的代谢适应性,导致 ARDS 等多种肺部疾病<sup>[51]</sup>。Morrison 等<sup>[52]</sup>的研究发现 MSC-Exos 能够将线粒体转移到肺泡巨噬细胞,促进巨噬细胞的氧化磷酸化,从而诱导巨噬细胞极化至抗炎表型,增强巨噬细胞的吞噬作用,改善 LPS 诱导的体内肺损伤。

## 五、局限性与展望

尽管现有研究表明 MSC-Exos 可通过多种途径改善 ALI,但具体的分子机制仍不够明确。MSC-Exos 中携带的多种生物活性分子(如 miRNA、蛋白质等)如何相互作用、共同发挥作用,以及在不同细胞类型中的具体作用机制尚需深入研究。此外, MSC-Exos 的功能可能因来源细胞的不同、培养条件的变化以及分离纯化方法的不同而存在显著差异。这种异质性使得在不同实验条件下,外泌体的生物学效应可能会有所不同。

综上所述, MSC-Exos 可通过抗炎、抑制细胞凋亡、促进细胞再生、减轻线粒体损伤等途径改善由多种原因引起的 ALI,其中外泌体携带的 miRNA、线粒体、蛋白质等物质是改善 ALI 的关键。然而,当前研究使用的 MSC-Exos 携带多种 miRNA、蛋白质等,在加入相应拮抗剂后治疗效果虽有降低,但无法证实外泌体携带多种物质对 ALI 是单一还是联合作用,因此体外预处理 MSC,诱导其产生特定 RNA 或蛋白质是探明机制的一个方向。

## 参 考 文 献

- [1] Hu Q, Zhang S, Yang Y, et al. Extracellular vesicles in the pathogenesis and treatment of acute lung injury [J]. Mil Med Res, 2022,9(1): 61.
- [2] Tang Y, Zhou Y, Li HJ. Advances in mesenchymal stem cell exosomes: a review[J]. Stem Cell Res Ther, 2021,12(1): 71.
- [3] Lotfy A, AboQuella NM, Wang H. Mesenchymal stromal/stem cell (MSC)-derived exosomes in clinical trials [J]. Stem Cell Res Ther, 2023,14(1): 66.
- [4] Pathan M, Fonseka P, Chitti SV, et al. Vesiclepedia 2019; a compendium of RNA, proteins, lipids and metabolites in extracellular vesicles [J]. Nucleic Acids Res, 2019,47(D1): D516-D519.
- [5] Alexander M, Hu R, Runtsch MC, et al. Exosome-delivered microRNAs modulate the inflammatory response to endotoxin [J]. Nat Commun, 2015,6: 7321.
- [6] Khalaj K, Figueira RL, Antounians L, et al. Systematic review of extracellular vesicle-based treatments for lung injury: are EVs a potential therapy for COVID-19? [J]. J Extracell Vesicles, 2020,9(1): 1795365.
- [7] Chen W, Huang Y, Han J, et al. Immunomodulatory effects of mesenchymal stromal cells-derived exosome [J]. Immunol Res, 2016,64(4): 831-840.
- [8] Butt Y, Kurdowska A, Allen TC. Acute lung injury: a clinical and molecular review [J]. Arch Pathol Lab Med, 2016, 140(4): 345-350.
- [9] Mokrá D. Acute lung injury -from pathophysiology to treatment [J]. Physiol Res, 2020,69(Suppl 3): S353-S366.
- [10] Sun SC. The non-canonical NF- $\kappa$ B pathway in immunity and inflammation [J]. Nat Rev Immunol, 2017,17(9): 545-558.
- [11] Everhart MB, Han W, Sherrill TP, et al. Duration and intensity of NF-kappaB activity determine the severity of endotoxin-induced acute lung injury [J]. J Immunol, 2006,176(8): 4995-5005.
- [12] Xu B, Gan CX, Chen SS, et al. BMSC-derived exosomes alleviate smoke inhalation lung injury through blockade of the HMGB1/

- NF- $\kappa$ B pathway[J]. Life Sci, 2020,257: 118042.
- [13] Zhang TY, Zhang H, Deng JY, et al. BMMSC-derived exosomes attenuate cardiopulmonary bypass-related acute lung injury by reducing inflammatory response and oxidative stress [J]. Curr Stem Cell Res Ther, 2023,18(5): 720-728.
- [14] Lim KH, Staudt LM. Toll-like receptor signaling[J]. Cold Spring Harb Perspect Biol, 2013,5(1): a11247.
- [15] Liu JS, Du J, Cheng X, et al. Exosomal miR-451 from human umbilical cord mesenchymal stem cells attenuates burn-induced acute lung injury[J]. J Chin Med Assoc, 2019,82(12): 895-901.
- [16] Liu J, Chen T, Lei P, et al. Exosomes released by bone marrow mesenchymal stem cells attenuate lung injury induced by intestinal ischemia reperfusion via the TLR4/NF- $\kappa$ B pathway [J]. Int J Med Sci, 2019,16(9): 1238-1244.
- [17] Chen W, Huang Y, Han J, et al. Immunomodulatory effects of mesenchymal stromal cells-derived exosome[J]. Immunol Res, 2016,64(4): 831-840.
- [18] Lotfy A, Aboquella NM, Wang H. Mesenchymal stromal/stem cell (MSC)-derived exosomes in clinical trials[J]. Stem Cell Res Ther, 2023,14(1): 66.
- [19] Liu Y, Zhang M, Liao Y, et al. Human umbilical cord mesenchymal stem cell-derived exosomes promote murine skin wound healing by neutrophil and macrophage modulations revealed by single-cell RNA sequencing [J]. Front Immunol, 2023, 14: 1142088.
- [20] Heo JS, Choi Y, Kim HO. Adipose-derived mesenchymal stem cells promote M2 macrophage phenotype through exosomes[J]. Stem Cells Int, 2019,2019: 7921760.
- [21] Wang X, Liu D, Zhang X, et al. Exosomes from adipose-derived mesenchymal stem cells alleviate sepsis-induced lung injury in mice by inhibiting the secretion of IL-27 in macrophages [J]. Cell Death Discov, 2022,8(1): 18.
- [22] Xia L, Zhang C, Lv N, et al. AdMSC-derived exosomes alleviate acute lung injury via transferring mitochondrial component to improve homeostasis of alveolar macrophages [J]. Theranostics, 2022,12(6): 2928-2947.
- [23] Fujii S, Miura Y, Fujishiro A, et al. Graft-versus-host disease amelioration by human bone marrow mesenchymal stromal/stem cell-derived extracellular vesicles is associated with peripheral preservation of naive t cell populations[J]. Stem Cells, 2018,36(3): 434-445.
- [24] Fan EKY, Fan J. Regulation of alveolar macrophage death in acute lung inflammation[J]. Respir Res, 2018,19(1): 50.
- [25] Fink SL, Cookson BT. Caspase-1-dependent pore formation during pyroptosis leads to osmotic lysis of infected host macrophages[J]. Cell Microbiol, 2006,8(11): 1812-1825.
- [26] Shi J, Zhao Y, Wang K, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death[J]. Nature, 2015, 526(7575): 660-665.
- [27] Pinkerton JW, Kim RY, Robertson AAB, et al. Inflammasomes in the lung[J]. Mol Immunol, 2017,86: 44-55.
- [28] He X, Qian Y, Li Z, et al. TLR4-upregulated IL-1 $\beta$  and IL-1RI promote alveolar macrophage pyroptosis and lung inflammation through an autocrine mechanism[J]. Sci Rep, 2016,6: 31663.
- [29] Zhang T, Lu L, Li M, et al. Exosome from BMMSC attenuates cardiopulmonary bypass-induced acute lung injury via YAP/ $\beta$ -Catenin pathway: downregulation of pyroptosis [J]. Stem Cells, 2022. 40(12):1122-1133.
- [30] Liu P, Yang S, Shao X, et al. Mesenchymal stem cells-derived exosomes alleviate acute lung injury by inhibiting alveolar macrophage pyroptosis [J]. Stem Cells Transl Med, 2024, 13(4): 371-386.
- [31] Sui X, Liu W, Liu Z. Exosomal lncRNA-p21 derived from mesenchymal stem cells protects epithelial cells during LPS-induced acute lung injury by sponging miR-181 [J]. Acta Biochim Biophys Sin (Shanghai), 2021,53(6): 748-757.
- [32] Mao GC, Gong CC, Wang Z, et al. BMSC-derived exosomes ameliorate sulfur mustard-induced acute lung injury by regulating the GPRC5A-YAP axis [J]. Acta Pharmacol Sin, 2021, 42(12): 2082-2093.
- [33] Li JW, Wei L, Han Z, et al. Mesenchymal stromal cells-derived exosomes alleviate ischemia/reperfusion injury in mouse lung by transporting anti-apoptotic miR-21-5p [J]. Eur J Pharmacol, 2019,852: 68-76.
- [34] Yi X, Wei X, Lv H, et al. Exosomes derived from microRNA-30b-3p-overexpressing mesenchymal stem cells protect against lipopolysaccharide-induced acute lung injury by inhibiting SAA3 [J]. Exp Cell Res, 2019,383(2): 111454.
- [35] Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism [J]. Nat Rev Genet, 2006,7(8): 606-619.
- [36] Zhang L, Ge S, He W, et al. Ghrelin protects against lipopolysaccharide-induced acute respiratory distress syndrome through the PI3K/AKT pathway [J]. J Biol Chem, 2021, 297(3): 101111.
- [37] Mizuta Y, Akahoshi T, Guo J, et al. Exosomes from adipose tissue-derived mesenchymal stem cells ameliorate histone-induced acute lung injury by activating the PI3K/Akt pathway in endothelial cells[J]. Stem Cell Res Ther, 2020,11(1): 508.
- [38] Chen J, Li C, Liang Z, et al. Human mesenchymal stromal cells small extracellular vesicles attenuate sepsis-induced acute lung injury in a mouse model: the role of oxidative stress and the mitogen-activated protein kinase/nuclear factor kappa B pathway [J]. Cytotherapy, 2021,23(10): 918-930.
- [39] Gong C, Gu Z, Zhang X, et al. HMSCs exosome-derived miR-199a-5p attenuates sulfur mustard-associated oxidative stress via the CAV1/NRF2 signalling pathway[J]. J Cell Mol Med, 2023, 27(15): 2165-2182.
- [40] Barreca MM, Cancemi P, Geraci F. Mesenchymal and induced pluripotent stem cells-derived extracellular vesicles: the new frontier for regenerative medicine? [J]. Cells, 2020,9(5): 1163.
- [41] Laffey JG, Matthay MA. Fifty years of research in ARDS. Cell-based therapy for acute respiratory distress syndrome. biology and potential therapeutic value [J]. Am J Respir Crit Care Med, 2017,196(3): 266-273.
- [42] Hu C, Sun J, Du J, et al. The Hippo-YAP pathway regulates the proliferation of alveolar epithelial progenitors after acute lung injury[J]. Cell Biol Int, 2019,43(10): 1174-1183.

- [43] Park J, Kim S, Lim H, et al. Therapeutic effects of human mesenchymal stem cell microvesicles in an ex vivo perfused human lung injured with severe *E. coli* pneumonia[J]. Thorax, 2019,74(1): 43-50.
- [44] Fujita Y, Kadota T, Kaneko R, et al. Mitigation of acute lung injury by human bronchial epithelial cell-derived extracellular vesicles via ANXA1-mediated FPR signaling[J]. Commun Biol, 2024,7(1): 514.
- [45] Zhu YG, Feng XM, Abbott J, et al. Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice[J]. Stem Cells, 2014,32(1): 116-125.
- [46] Supinski GS, Schroder EA, Callahan LA. Mitochondria and critical illness[J]. Chest, 2020,157(2): 310-322.
- [47] Sun L, Zhu M, Feng W, et al. Exosomal miRNA let-7 from menstrual blood-derived endometrial stem cells alleviates pulmonary fibrosis through regulating mitochondrial DNA damage[J]. Oxid Med Cell Longev, 2019,2019: 4506303.
- [48] Dutra SJ, Su Y, Calfee CS, et al. Mesenchymal stromal cell extracellular vesicles rescue mitochondrial dysfunction and improve barrier integrity in clinically relevant models of ARDS [J]. Eur Respir J, 2021,58(1):2002978.
- [49] Liu C, Xiao K, Xie L. Advances in the use of exosomes for the treatment of ALI/ARDS [J]. Front Immunol, 2022, 13: 971189.
- [50] Islam MN, Das SR, Emin MT, et al. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury[J]. Nat Med, 2012,18(5): 759-765.
- [51] Riou M, Alfatni A, Charles AL, et al. New insights into the implication of mitochondrial dysfunction in tissue, peripheral blood mononuclear cells, and platelets during lung diseases[J]. J Clin Med, 2020,9(5):1253.
- [52] Morrison TJ, Jackson MV, Cunningham EK, et al. Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer[J]. Am J Respir Crit Care Med, 2017,196(10): 1275-1286.
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