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Review Paper

Amniotic Fluid as a Potential Source of Extracellular Vesicles With Anti-inflammatory and Regenerative Properties

Kamyab Hassanpour[1], Amir Hossein Norooznezhad[2*]

1. School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.
2. Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran.

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ABSTRACT

Cell therapy, especially with mesenchymal stem cells (MSCs), is a potent treatment for many diseases or disorders. Meanwhile, MSCs-based cell-free products, such as extracellular vesicles (EVs) have been suggested as an alternative to MSCs. These MSC-EVs have been used in different trials to treat various inflammatory-dependent disorders. MSCs, according to their isolated tissue source, could present different therapeutic features and their derived EVs. One of the new sources for MSC isolation is amniotic fluid (AF). In addition, other than MSCs, new studies have used AF as an acceptable source for EV isolation. These isolated EVs from AF (AF-EVs) or AF-derived MSCs EVs (AF-MSC-EVs) have been used in different in-vitro and animal studies to treat a wide variety of inflammatory-dependent pathological conditions due to their confirmed anti-inflammatory potentials (through suppressing different pro-inflammatory cytokines). Meanwhile, in other conditions requiring repairing properties (e.g. wound healing or myocardial infarction), considering their regenerative and angiogenic potentials, these EVs have shown proper therapeutic results. Furthermore, other than the in-vitro and animal studies, AF-EVs containing treatment have successfully been used in some clinical trials and showed no adverse events among the patients and expressed potent anti-inflammatory properties through suppression of two very important pro-inflammatory cytokines, namely interleukin 6 and tumor necrosis factor α. Accordingly, AF-EVs and AF-MSC-EVs could be suitable choices for treatment due to their anti-inflammatory and regenerative properties. However, further clinical studies are needed.

*** Corresponding Author:**
Amir Hossein Norooznezhad, MD.
Address: *Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran.*
Phone: *+98 (918) 8564304*
E-mail: *norooznezhad@gmail.com*

Introduction

Cell therapy has been stated as a new therapeutic approach using major cell categories, including stem, progenitor, or primary cells. Stem cell therapy, as a pioneer treatment option, has been tested in different pathological settings, such as autoimmune, neurological, cardiovascular, liver, renal, ophthalmologic, and skeletal diseases/disorders [1]. The therapeutic potentials of stem cells in clinics have been suggested due to their paracrine secretions which could induce hematopoiesis, angiogenesis, and tissue reconstruction through the released growth factors, cytokines, chemokines, and trophic factors [2-4]. Extracellular vesicles (EVs) are a group of lipid bilayer-surrounded vesicles derived from different types of cells [5] and could be categorized into apoptotic bodies, micro-vesicles, and exosomes [6]. EVs have important roles in physiological and pathological conditions through cell communications [7] and have been used as disease biomarkers, therapeutic agents, and vehicles for drug delivery [8]. These communicating agents carry a wide variety of biomolecules, such as messenger ribonucleic acid, micro ribonucleic acid, DNA, active lipids, cytokines, and growth factors inside them which vary depending on the secreting origin [9]. The most studied EVs are from cells, including cancer-associated fibroblasts, tumor-associated macrophages, immunocytes, and mesenchymal stem cells (MSCs) [5]. Accordingly, this study reviews the therapeutic potentials of amniotic fluid (AF) MSCs (AF-MSCs) as well as their derived EVs in three settings, namely in-vitro, animal, and human studies.

MSCs

Among cells secreting EVs with therapeutic properties, MSCs have been studied more than others. These cells are known for their ability to self-renew [10], potential for inflammatory response regulation [11], and regenerative properties [12]. MSCs have been used in different clinical trials for inflammatory-dependent diseases or disorders, such as rheumatoid arthritis [13], osteoarthritis [14], liver cirrhosis [15], heart failure [16], COVID-19 [17], psoriasis [18], amyotrophic lateral sclerosis [19], and severe sepsis [20]. Regarding the safety of this treatment, a recent systematic review and meta-analysis has investigated 55 randomized controlled clinical trials (RCTs) and stated that the MSCs therapy is a favorable safe treatment [21].

MSCs-derived EVs

Following acceptable results from randomized controlled trials performed on therapeutic applications of MSCs in different inflammatory-dependent pathological conditions, investigations on MSC-derived EVs became a field of interest [22]. MSC-derived EVs have been used in clinics on different pathological conditions, such as COVID-19 [23], sensitive skin [24], stages III and IV chronic kidney disease [25], and chronic graft-versus-host disease and dry eye disease [26]. Also, we have great experiences regarding the treatment of COVID-19 [27], chronic cutaneous graft-versus-host disease [28], systemic sclerosis [29], and chemotherapy-induced hair loss [30] with MSC-derived EVs. MSC-EVs, as cell-free products, have been suggested as a potent treatment option instead of MSCs with at least similar therapeutic potential.

Sources of MSCs and their derived EVs

MSCs can be found in a wide variety of tissues, especially in niches of perivascular areas. The main sources of these cells are two main groups, including adult (bone marrow, adipose tissue, peripheral blood, and menses blood) and neonatal birth-associated tissues (cord blood, umbilical cord, and placenta) [10, 12, 31]. Although MSCs might have similar expressions of surface antigens and phenotypes, they certainly have different potentials [32]. The difference in the function of MSCs by the origin also could be implied by the immunomodulatory functions of their derived EVs. According to Shin et al., the secretomes of fetal-derived MSCs (e.g. placenta and Wharton's jelly) compositionally are more diverse in comparison to adult-derived MSCs (adipose and bone marrow). They hypothesized that the stronger therapeutic potential of fetal-derived MSCs might be due to this difference [33]. Another similar study by Jeon et al. investigated characteristics of MSCs with different origins (adipose tissue, placenta, and bone marrow). According to their results, placental-derived MSCs seemed to be more effective for clinical applications compared to other sources [32].

AF and MSCs potentials

Human AF harvested (stem) cells (AFSCs) have been used in different in-vitro studies, such as heart valve leaflets [34, 35], fetal tracheal reconstruction [36], and bone grafts [37, 38]. In the in-vivo setting, kidney acute tubular necrosis [39], ischemic heart disease [40], and hyperoxic lung injury [41] are among the other successfully studied pathologies treated by AFSCs. In the early

2000s, after the evaluation of the second trimester's AF, this fluid was introduced as a new source of human MSCs [42-44]. The AF-MSCs have been isolated mostly during the amniocentesis which is performed at weeks 16-28 of gestation [45, 46]. However, other studies isolated these cells before [47] and after [48] this period. AF has some advantages compared to other sources of MSCs among them being a less invasive method of harvesting has attracted attention [49]. In 2012, Moorefield et al. hypothesized that AFSCs might have similar immune-modulatory effects compared to MSCs due to their high similarity in terms of differentiation potential and surface marker expression. After a series of experiments, they found the ability of inflammatory response suppression in these cells [50]. In an in-vivo study, Dionig et al. investigated the therapeutic potential of in-utero treatment of AF-MSCs for spina bifida. According to their results, these stem cells maintained partial to complete coverage in the treated animals [51]. Moreover, AF-MSCs have been used in an in-vivo model of peripheral nerve regeneration which showed an increase in myelination and improvement of motor function [52]. Soler et al. evaluated the potential of AFSCs in a rat model of bladder dysfunction of Parkinson's disease. They showed that cell therapy with AFSCs could ameliorate bladder dysfunction in their studied model [53]. Also, another study on the effects of AFSCs on an animal model of Parkinson disease showed behavioral improvement after the treatment [54]. An in-vivo study by Zani et al. evaluated the therapeutic potentials of AFSCs in a model of necrotizing enterocolitis. Their results showed that AFSCs could improve clinical condition, survival rate, and gut function in an animal model of necrotizing enterocolitis [55]. These cells have been studied for possible applications in regenerative medicine and immune system-dependent diseases due to their angiogenic and anti-inflammatory potentials.

Angiogenesis

Angiogenesis has been defined as new micro-capillary formation from pre-existing structures. This phenomenon could be seen in pathological (e.g. tumor growth and metastasis, psoriasis, corneal neovascularization, and hemophilic arthropathy) conditions [56-60] as well as physiological (female reproductive cycle, wound healing, and revascularize in ischemic heart tissues) situations [61-63]. This phenomenon consists of different steps among the most important of which are degradation of the basement membrane, endothelial cell activation, migration, proliferation, and tube formation [64]. The main trigger of angiogenesis seems to be hypoxia and lack of nutrients which cells start to release different factors among the most important of them is hypoxia-inducible factor 1α (HIF-1α). HIF-1 has synergistic correlations with crucial angiogenic factors, such as vascular endothelial growth factor and placental growth factor [65].

Inflammation

Inflammation is a nonspecific defensive state in tissues against infectious or noninfectious (toxic compounds, damaged cells, endogenous antigens, and irradiation) situations [66, 67] which depending on the onset, divides into acute [68] and chronic [66]. Although acute inflammation has been considered a defense mechanism [69] and is a required step in some physiological events, such as wound repair [70], it could cause severe life-threatening conditions, such as pancreatitis [71] and acute respiratory distress syndrome [72]. Chronic inflammation, on the other hand, has been a destructive phenomenon leading to or involving in pathologies [66], such as psoriasis [73], rheumatoid arthritis [74], ulcerative colitis, Crohn's disease [75], endometriosis [76], and increased risk of infections and malignancies [77]. Among the most important mediators of inflammation, some interleukins (IL; for instance IL-1β and IL-6), tumor necrosis factor α (TNF-α), and some chemokines (e.g. CXCL8) [78, 79] are critical.

Angiogenic and anti-inflammatory potentials of amniotic fluid-derived MSCs

Thus far, some studies have investigated the angiogenic and anti-inflammatory potentials of AF-derived MSCs (AF-MSCs). Mirabella et al. have evaluated the angiogenic potential of AF-MSCs in in-vivo and in-vitro models. The endothelial cells treated with AF-MSC condition media (ACM), containing their secretomes showed to have cytoprotective effects on endothelial cells. Also, in the migration assay, endothelial cells treated with ACM showed better results compared to condition media of human umbilical cord-derived fibroblasts. To assess the tube formation, endothelial cells in Matrigel were treated with ACM and serum-free medium which showed a significant increase in formed tubes in favor of ACM. In the in-vivo angiogenesis assay (hind-limb ischemic mouse), higher neoarteriogenesis was observed following ACM treatment [80]. In another study, investigations showed over-expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) in AF-MSCs. These adhesion molecules are role players in angiogenesis and cell migration [81, 82]. AF-MSCs and ACM could modulate immune activation by blocking lymphocyte activation [50]. In a study on an animal

model of acute hepatic failure, the therapeutic potential of AF-MSCs was drawn through the increased levels of transforming growth factor β (TGF-β) and VEGF [83]. Another in-vivo study on fulminant hepatic failure used AF-MSCs overexpressing IL-1 receptor antagonist (IL-1Ra) as a possible treatment. According to their results, the treatment decreased mortality and increased survival rates as well as prevention of liver failure. Treatment with these cells led to a significant decrease in the serum IL-6 and TNF-α [84]. In a mice model of colitis, Legaki et al. showed that conditioned media of spindle-shaped AF-MSCs could decrease TNF-α and increase TGF-β at protein levels. Also, at the expression levels, TNF-α and IL-1β experienced a decrease in expression. On the other hand, an increasing pattern of expression was observed for TGF-β and IL-10 [85] as potent anti-inflammatory agents [86]. Another suggested pathway for the anti-inflammatory potential of AF-MSCs is through decreasing IL-6. As it has been shown in a hyperoxia-induced pulmonary alveolar injury animal model, IL-6 levels followed a decreasing pattern in the lung tissue after AF-MSC treatment [87].

Amniotic fluid-MSCs-derived EVs

As mentioned previously, MSCs-derived EVs of cells isolated from different sources, such as placenta [27-30], umbilical cord [88, 89], bone marrow [90, 91], and adipose tissue [92, 93] have been used as a possible treatment for different pathological conditions. In pregnant women, the levels of microparticles in AF were 41-fold higher than in their plasma [94] which was a clue for future investigations. Thus far, some studies have investigated the possible therapeutic potentials of AF-MSC-EVs. In an in-vivo model of bronchopulmonary dysplasia, Bellio et al. demonstrated favorable results following the treatment of animals with AF-MSC-EVs which among the proved mechanisms of action were inhibition of IL-1β expression. Also, they showed the EVs derived from AF-MSCs have a network of free radical scavenging [95]. Also, Del Rivero et al. showed that AF-MSC-EVs could affect human T-cells and induce strong immunomodulatory effects in an in-vitro model [96]. AF-MSCs have been used to treat necrotizing enterocolitis in vivo [55]. Another study has used the cell-free product of AF-MSCs, EVs, in the same condition. This specific treatment decreased necrotizing enterocolitis occurrence, intestinal injury, and gut inflammation. This study found a significant decrease in IL-6 and TNF-α as possible pathways for the obtained results [97]. Another study investigated the therapeutic potentials of spindle-shaped AF-MSCs-derived secretomes and exosomes in a model to assess inflammatory bowel disease. This treatment led to a decrease in LPS-induced inflammation through suppression of IL-1β, IL-6, and TNF-α expression in subepithelial myofibroblasts. Also, the expression of IL-10, an anti-inflammatory cytokine significantly increased after the treatment [98]. Among the regenerative studies, AF-MSC-EVs have been used for improving the clinical status in a rodent model of fetal lung underdevelopment [99]. As Li et al. demonstrated, AF-derived EVs (AF-EVs) were able to induce tube formation and migration in human umbilical endothelial cells in in-vitro models following oxygen and glucose deprivation. Moreover, they found higher expression of HIF-1α and VEGF in the cerebral cortex of neonatal rodents [100]. Other than the mentioned pathological conditions, AF-MSC-EVs/AF-SC-EVs/AF-EVs have also been used for the treatment of different pathological conditions, such as fetal hypoplastic lungs [101], pulmonary hypoplasia [102], ischemia/reperfusion condition [103], Alzheimer's disease [104], myocardial infarction [105], wound healing and skin regeneration [106, 107], chemotherapy-induced ovarian failure [108, 109], osteoarthritis [110], osteoporosis [111], Alport syndrome [112], and azoospermia [113].

AF-EVs have been used in clinical investigations as well. A study demonstrated the use of AF-derived nanoparticles containing not only EVs and exosomes but also cytokines and growth factors under the manufacturer name of Zofin™ (Organicell Regenerative Medicine, Inc. in Miami, FL, USA). No serious adverse events were observed among the patients caused by this treatment. Following the treatment with Zofin™, COVID-19-associated symptoms resolved or at least not progressed. Also, pro-inflammatory factors including C-reactive protein, IL-6, and TNF-α improved after the treatment [114]. This time, another study investigated the therapeutic potentials of Zofin™ on three patients diagnosed with severe COVID-19 who were hospitalized in the intensive care unit. No adverse event related to the treatment was observed among the patients and intensive care unit clinical status and improvement in their respiratory system were observed [115]. Moreover, Zofin™ was tested on a patient with long COVID-19 presented with respiratory impairment and shortness of breath which evaluation of clinical status and imaging modalities showed improvement in the symptoms [116]. A summary of all the mentioned studies is shown in Table 1.

Future studies and concerns

The EVs derived from AF, AFSCs, and AF-MSCs could be potent research avenues for future studies on inflammatory-dependent diseases/disorders as well as

Table 1. Sample of important studies on amniotic fluid-derived stem cells, MSCs, and MSCs-derived EVs

Cell Type	Author(s) (Year)	Target of Assessing Therapeutic Potential	Used Model
Amniotic fluid-derived stem cells	Weber et al. (2012) [35]	Fetal heart valve pathologies	Animal (sheep)
	Peister et al. (2009) [38]	Mineral deposition (bone formation)	Animal (rat)
	Perin et al. (2010) [39]	Acute tubular necrosis	Animal (mice)
	Bollini et al. (2011) [40]	Ischemic heart disease	Animal (rat)
	Chang et al. (2013) [54]	Parkinson disease (behavioral improvement)	Animal (rat)
	Zani et al. (2014) [55]	Necrotizing enterocolitis	Animal (rat)
	Carraro et al. (2008) [41]	Hyperoxic lung injury	Animal (mice)
Amniotic fluid-derived MSCs	Kunisaki et al. (2006) [36]	Fetal tracheal reconstruction	Animal (sheep)
	Steigman et al. (2009) [37]	Bone grafting	Animal (rabbit)
	Pan et al. (2009) [52]	Peripheral nerve regeneration	Animal (rat)
	Soler et al. (2012) [53]	Bladder dysfunction of Parkinson's disease	Animal (rat)
	Dionigi et al. (2015) [51]	Spina bifida	Animal (rat)
Amniotic fluid MSCs-derived EVs	Bellio et al. (2021) [95]	Bronchopulmonary dysplasia	Animal (rat)
	O'Connell et al. (2021) [97]	Necrotizing enterocolitis	Animal (mice)
	Antounians et al. (2021) [99]	Fetal lung underdevelopment	Animal (rat)
	Li et al. (2022) [100]	Hypoxic encephalopathy	Animal (mice)
Amniotic fluid stem cell-derived EVs	Xiao et al. (2016) [108]	Chemotherapy-induced ovarian failure	Animal (mice)
	Sedrakyan et al. (2017) [112]	Alport syndrome	Animal (mice)
	Khalaj et al. (2022) [101]	Fetal Hypoplastic Lung	Animal (rat)
	Khalaj et al. (2022) [102]	Pulmonary hypoplasia	Animal (rat)
	Gatti et al. (2020) [104]	Oxidative stress in Alzheimer's disease	Animal (mice)
	Zavatti et al. (2020) [110]	Osteoarthritis	Animal (rat)
	Costa et al. (2022) [105]	Myocardial infarction	Animal (mice)
	Zhang et al. (2021) [106]	Wound healing and skin regeneration	Animal (rat)
	Wgealla et al. (2022) [107]	Wound healing and skin regeneration	Animal (mice)
Amniotic fluid MSCs-derived EVs	Geng et al. (2022) [109]	Premature ovarian failure	Animal (mice)
Amniotic fluid-derived EVs	Mobarak et al. (2021) [113]	Azoospermia	Animal (rat)
	Bellio et al. (2021) [114]	Mild-to-moderate acute COVID-19	Human
	Mitrani et al. (2021) [115]	Severe COVID-19	Human
	Mitrani et al. (2021) [116]	Long COVID-19	Human

regenerative medicine. As mentioned previously, this source (AF) has some advantages, such as easy access and being less invasive. However, there could be some concerns about them. They have been studied less than the other similar cells and EVs. Also, AF is the first human body fluid that their derived EVs have been used in clinical trials and data regarding them is not comparable with EVs derived from isolated cells cultured under good manufacturing practice. However, considering the already discussed advantages and growing evidence on this topic, the answers to these questions and concerns will be found soon.

Conclusion

Cell therapy (e.g. MSCs) has been introduced as a new treatment approach for many diseases/disorders. Despite many successes in this field, cell-based cell-free therapeutic agents (EVs) have been bolded recently due to their potency and safety. MSC-EVs could be obtained from different sources the most popular one is culturing the cells and then collecting EVs from their conditioned media. Other than MSCs, recently, AF has been used for the isolation of EVs. The EVs obtained from AF or AF-derived cultured cells (MSCs/SCs) have been tested in many in-vitro, animal, and human studies for treating different pathological conditions through their anti-inflammatory and angiogenic potentials. AF could be an acceptable source of both MSCs and EVs for cell-based and cell-free treatments; however, further clinical trials are still needed.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and supervision: Amir Hossein Norooznezhad; Investigation and writing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Buzhor E, Leshansky L, Blumenthal J, Barash H, Warshawsky D, Mazor Y, et al. Cell-based therapy approaches: The hope for incurable diseases. Regenerative Medicine. 2014; 9(5):649-72. [DOI:10.2217/rme.14.35] [PMID]

[2] Joerger-Messerli MS, Marx C, Oppliger B, Mueller M, Surbek DV, Schoeberlein A. Mesenchymal stem cells from wharton's jelly and amniotic fluid. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2016; 31:30-44. [DOI:10.1016/j.bpobgyn.2015.07.006] [PMID]

[3] Hsieh JY, Wang HW, Chang SJ, Liao KH, Lee IH, Lin WS, et al. Mesenchymal stem cells from human umbilical cord express preferentially secreted factors related to neuroprotection, neurogenesis, and angiogenesis. PloS One. 2013; 8(8):e72604. [DOI:10.1371/journal.pone.0072604] [PMID]

[4] Gao LR, Zhang NK, Ding QA, Chen HY, Hu X, Jiang S, et al. Common expression of stemness molecular markers and early cardiac transcription factors in human Wharton's jelly-derived mesenchymal stem cells and embryonic stem cells. Cell Transplantation. 2013; 22(10):1883-900. [DOI:10.3727/096368912X662444] [PMID]

[5] Sheta M, Taha EA, Lu Y, Eguchi T. Extracellular vesicles: New classification and tumor immunosuppression. Biology. 2023; 12(1):110. [DOI:10.3390/biology12010110] [PMID]

[6] Ginini L, Billan S, Fridman E, Gil Z. Insight into extracellular vesicle-cell communication: From cell recognition to intracellular fate. Cells. 2022; 11(9):1375. [DOI:10.3390/cells11091375] [PMID]

[7] Beetler DJ, Di Florio DN, Bruno KA, Ikezu T, March KL, Cooper LT Jr, et al. Extracellular vesicles as personalized medicine. Molecular Aspects of Medicine 2023; 91:101155. [DOI:10.1016/j.mam.2022.101155] [PMID]

[8] van Niel G, Carter DRF, Clayton A, Lambert DW, Raposo G, Vader P. Challenges and directions in studying cell-cell communication by extracellular vesicles. Nature Reviews. Molecular Cell Biology. 2022; 23(5):369-82. [DOI:10.1038/s41580-022-00460-3] [PMID]

[9] Norooznezhad AH, Nabavian SM. Mesenchymal stromal cell extracellular vesicles: A possible strategy for prevention of preterm birth. Medical Hypotheses. 2023; 172:111032. [DOI:10.1016/j.mehy.2023.111032]

[10] Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. Cell Transplantation. 2011; 20(1):5-14. [DOI:10.3727/096368910X] [PMID]

[11] Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases.Nature Reviews. Nephrology 2018; 14(8):493-507. [DOI:10.1038/s41581-018-0023-5] [PMID]

[12] Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. Cell Communication and Signaling. 2011; 9:12. [DOI:10.1186/1478-811X-9-12] [PMID]

[13] Ghoryani M, Shariati-Sarabi Z, Tavakkol-Afshari J, Ghasemi A, Poursamimi J, Mohammadi M. Amelioration of clinical symptoms of patients with refractory rheumatoid arthritis following treatment with autologous bone marrow-derived mesenchymal stem cells: A successful clinical trial in Iran. Biomedicine & Pharmacotherapy. 2019; 109:1834-40. [DOI:10.1016/j.biopha.2018.11.056] [PMID]

[14] Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-Articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase iib, randomized, placebo-controlled clinical trial. Stem Cells Translational Medicine. 2019; 8(6):504-11. [DOI:10.1002/sctm.18-0122] [PMID]

[15] Shi M, Li YY, Xu RN, Meng FP, Yu SJ, Fu JL, et al. Mesenchymal stem cell therapy in decompensated liver cirrhosis: a long-term follow-up analysis of the randomized controlled clinical trial. Hepatology International. 2021; 15(6):1431-41. [DOI:10.1007/s12072-021-10199-2] [PMID]

[16] Bartolucci J, Verdugo FJ, González PL, Larrea RE, Abarzua E, Goset C, et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: A phase 1/2 randomized controlled trial (rimecard trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy]). Circulation Research. 2017; 121(10):1192-204. [DOI:10.1161/CIRCRESAHA.117.310712] [PMID]

[17] Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, et al. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. Stem Cells Translational Medicine. 2021; 10(5):660-73. [DOI:10.1002/sctm.20-0472] [PMID]

[18] Cheng L, Wang S, Peng C, Zou X, Yang C, Mei H, et al. Human umbilical cord mesenchymal stem cells for psoriasis: A phase 1/2a, single-arm study. Signal Transduction and Targeted Therapy. 2022; 7(1):263. [DOI:10.1038/s41392-022-01059-y] [PMID]

[19] Petrou P, Kassis I, Yaghmour NE, Ginzberg A, Karussis D. A phase II clinical trial with repeated intrathecal injections of autologous mesenchymal stem cells in patients with amyotrophic lateral sclerosis. Frontiers in Bioscience. 2021; 26(10):693-706. [DOI:10.52586/4980] [PMID]

[20] He X, Ai S, Guo W, Yang Y, Wang Z, Jiang D, et al. Umbilical cord-derived mesenchymal stem (stromal) cells for treatment of severe sepsis: Aphase 1 clinical trial. Translational Research. 2018; 199:52-61. [DOI:10.1016/j.trsl.2018.04.006] [PMID]

[21] Thompson M, Mei SHJ, Wolfe D, Champagne J, Fergusson D, Stewart DJ, et al. Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: An updated systematic review and meta-analysis. EClinicalMedicine. 2020; 19:100249. [DOI:10.1016/j.eclinm.2019.100249] [PMID]

[22] Harrell CR, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Mesenchymal stem cell-derived exosomes and other extracellular vesicles as new remedies in the therapy of inflammatory diseases. Cells. 2019; 8(12):1605. [DOI:10.3390/cells8121605] [PMID]

[23] Zarrabi M, Shahrbaf MA, Nouri M, Shekari F, Hosseini SE, Hashemian SR, et al. Allogenic mesenchymal stromal cells and their extracellular vesicles in COVID-19 induced ARDS: A randomized controlled trial. Stem Cell Research & Therapy. 2023; 14(1):169. [DOI:10.1186/s13287-023-03402-8] [PMID]

[24] Ye C, Zhang Y, Su Z, Wu S, Li Y, Yi J, et al. hMSC exosomes as a novel treatment for female sensitive skin: An in vivo study. Frontiers in Bioengineering and Biotechnology. 2022; 10:1053679. [DOI:10.3389/fbioe.2022.1053679] [PMID]

[25] Nassar W, El-Ansary M, Sabry D, Mostafa MA, Fayad T, Kotb E, et al. Umbilical cord mesenchymal stem cells derived from extracellular vesicles can safely ameliorate the progression of chronic kidney diseases. Biomaterials Research. 2016; 20:21. [DOI:10.1186/s40824-016-0068-0] [PMID]

[26] Zhou T, He C, Lai P, Yang Z, Liu Y, Xu H, et al. miR-204-containing exosomes ameliorate GVHD-associated dry eye disease. Science Advances. 2022; 8(2):eabj9617. [DOI:10.1126/sciadv.abj9617] [PMID]

[27] Zamanian MH, Norooznezhad AH, Hosseinkhani Z, Hassaninia D, Mansouri F, Vaziri S, et al. Human placental mesenchymal stromal cell-derived small extracellular vesicles as a treatment for severe COVID-19: A double-blind randomized controlled clinical trial. Journal of Extracellular Vesicles. 2024; 13(7):e12492. [DOI:10.1002/jev2.12492] [PMID]

[28] Norooznezhad AH, Yarani R, Payandeh M, Hoseinkhani Z, Kiani S, Taghizadeh E, et al. Human placental mesenchymal stromal cell-derived exosome-enriched extracellular vesicles for chronic cutaneous graft-versus-host disease: A case report. Journal of Cellular and Molecular Medicine. 2022; 26(2):588-92. [DOI:10.1111/jcmm.17114] [PMID]

[29] Assar S, Mohammadzadeh D, Norooznezhad AH, Payandeh M, Hassaninia D, Pournazari M, et al. Improvement in the clinical manifestations of interstitial lung disease following treatment with placental mesenchymal stromal cell extracellular vesicles in a patient with systemic sclerosis: A case report. Respiratory Medicine Case Reports. 2023; 46:101923. [DOI:10.1016/j.rmcr.2023.101923] [PMID]

[30] Norooznezhad AH, Yarani R, Payandeh M, Hoseinkhani Z, Mahmoudi H, Kiani S, et al. Treatment of persistent chemotherapy-induced hair loss (Alopecia) with human mesenchymal stromal cells exosome enriched extracellular vesicles: A case report. Heliyon 2023; 9(4):e15165. [DOI:10.1016/j.heliyon.2023.e15165] [PMID]

[31] Berebichez-Fridman R, Montero-Olvera PR. Sources and clinical applications of mesenchymal stem cells: State-of-the-art review. Sultan Qaboos University Medical Journal. 2018; 18(3):e264-77. [DOI:10.18295/squmj.2018.18.03.002] [PMID]

[32] Jeon YJ, Kim J, Cho JH, Chung HM, Chae JI. Comparative analysis of human mesenchymal stem cells derived from bone marrow, placenta, and adipose tissue as sources of cell therapy. Journal of Cellular Biochemistry. 2016; 117(5):1112-25. [DOI:10.1002/jcb.25395] [PMID]

[33] Shin S, Lee J, Kwon Y, Park KS, Jeong JH, Choi SJ, et al. Comparative proteomic analysis of the mesenchymal stem cells secretome from adipose, bone marrow, placenta and wharton's jelly. International Journal of Molecular Sciences. 2021; 22(2):845. [DOI:10.3390/ijms22020845] [PMID]

[34] Schmidt D, Achermann J, Odermatt B, Breymann C, Mol A, Genoni M, et al. Prenatally fabricated autologous human living heart valves based on amniotic fluid derived progenitor cells as single cell source. Circulation. 2007; 116(11 Suppl):I64-70. [DOI:10.1161/CIRCULATIONAHA.106.681494] [PMID]

[35] Weber B, Emmert MY, Behr L, Schoenauer R, Brokopp C, Drögemüller C, et al. Prenatally engineered autologous amniotic fluid stem cell-based heart valves in the fetal circulation. Biomaterials. 2012; 33(16):4031-43. [DOI:10.1016/j.biomaterials.2011.11.087] [PMID]

[36] Kunisaki SM, Freedman DA, Fauza DO. Fetal tracheal reconstruction with cartilaginous grafts engineered from mesenchymal amniocytes. Journal of Pediatric Surgery. 2006; 41(4):675-82; discussion 675-82. [DOI:10.1016/j.jpedsurg.2005.12.008] [PMID]

[37] Steigman SA, Ahmed A, Shanti RM, Tuan RS, Valim C, Fauza DO. Sternal repair with bone grafts engineered from amniotic mesenchymal stem cells. Journal of Pediatric Surgery. 2009; 44(6):1120-6; discussion 1126. [DOI:10.1016/j.jpedsurg.2009.02.038] [PMID]

[38] Peister A, Deutsch ER, Kolambkar Y, Hutmacher DW, Guldberg RE. Amniotic fluid stem cells produce robust mineral deposits on biodegradable scaffolds. Tissue Engineering. Part A. 2009; 15(10):3129-38. [DOI:10.1089/ten.tea.2008.0536] [PMID]

[39] Perin L, Sedrakyan S, Giuliani S, Da Sacco S, Carraro G, Shiri L, et al. Protective effect of human amniotic fluid stem cells in an immunodeficient mouse model of acute tubular necrosis. Plos One. 2010; 5(2):e9357. [DOI:10.1371/journal.pone.0009357] [PMID]

[40] Bollini S, Pozzobon M, Nobles M, Riegler J, Dong X, Piccoli M, et al. In vitro and in vivo cardiomyogenic differentiation of amniotic fluid stem cells. Stem Cell Reviews and Reports. 2011; 7(2):364-80. [DOI:10.1007/s12015-010-9200-z] [PMID]

[41] Carraro G, Perin L, Sedrakyan S, Giuliani S, Tiozzo C, Lee J, et al. Human amniotic fluid stem cells can integrate and differentiate into epithelial lung lineages. Stem Cell. 2008;; 26(11):2902-11. [DOI:10.1634/stemcells.2008-0090] [PMID]

[42] In 't Anker PS, Scherjon SA, Kleijburg-van der Keur C, Noort WA, Claas FH, Willemze R, et al. Amniotic fluid as a novel source of mesenchymal stem cells for therapeutic transplantation. Blood. 2003; 102(4):1548-9. [DOI:10.1182/blood-2003-04-1291] [PMID]

[43] Prusa AR, Marton E, Rosner M, Bernaschek G, Hengstschläger M. Oct-4-expressing cells in human amniotic fluid: A new source for stem cell research? Human Reproduction. 2003; 18(7):1489-93. [DOI:10.1093/humrep/deg279] [PMID]

[44] Kaviani A, Guleserian K, Perry TE, Jennings RW, Ziegler MM, Fauza DO. Fetal tissue engineering from amniotic fluid. Journal of the American College of Surgeons. 2003; 196(4):592-7. [DOI:10.1016/S1072-7515(02)01834-3] [PMID]

[45] Moschidou D, Mukherjee S, Blundell MP, Jones GN, Atala AJ, Thrasher AJ, et al. Human mid-trimester amniotic fluid stem cells cultured under embryonic stem cell conditions with valproic acid acquire pluripotent characteristics. Stem Cells and Development. 2013; 22(3):444-58. [DOI:10.1089/scd.2012.0267] [PMID]

[46] Zhang L, Zhang XH, Liang MY, Ren MH. Prenatal cytogenetic diagnosis study of 2782 cases of high-risk pregnant women. Chinese Medical Journal. 2010; 123(4):423-30. [PMID]

[47] Moschidou D, Mukherjee S, Blundell MP, Drews K, Jones GN, Abdulrazzak H, et al. Valproic acid confers functional pluripotency to human amniotic fluid stem cells in a transgene-free approach. Molecular Therapy. 2012; 20(10):1953-67. [DOI:10.1038/mt.2012.117] [PMID]

[48] You Q, Cai L, Zheng J, Tong X, Zhang D, Zhang Y. Isolation of human mesenchymal stem cells from third-trimester amniotic fluid. International Journal of Gynaecology and Obstetrics. 2008; 103(2):149-52. [DOI:10.1016/j.ijgo.2008.06.012] [PMID]

[49] Zhou J, Wang D, Liang T, Guo Q, Zhang G. Amniotic fluid-derived mesenchymal stem cells: Characteristics and therapeutic applications. Archives of Gynecology and Obstetrics. 2014; 290(2):223-31. [DOI:10.1007/s00404-014-3231-7] [PMID]

[50] Moorefield EC, McKee EE, Solchaga L, Orlando G, Yoo JJ, Walker S, et al. Cloned, CD117 selected human amniotic fluid stem cells are capable of modulating the immune response. Plos One. 2011; 6(10):e26535. [DOI:10.1371/journal.pone.0026535] [PMID]

[51] Dionigi B, Ahmed A, Brazzo J 3rd, Connors JP, Zurakowski D, Fauza DO. Partial or complete coverage of experimental spina bifida by simple intra-amniotic injection of concentrated amniotic mesenchymal stem cells. Journal of Pediatric Surgery. 2015; 50(1):69-73. [DOI:10.1016/j.jpedsurg.2014.10.004] [PMID]

[52] Pan HC, Chen CJ, Cheng FC, Ho SP, Liu MJ, Hwang SM, et al. Combination of G-CSF administration and human amniotic fluid mesenchymal stem cell transplantation promotes peripheral nerve regeneration. Neurochemical Research. 2009; 34(3):518-27. [PMID]

[53] Soler R, Füllhase C, Hanson A, Campeau L, Santos C, Andersson KE. Stem cell therapy ameliorates bladder dysfunction in an animal model of Parkinson disease. The Journal of Urology. 2012; 187(4):1491-7. [DOI:10.1016/j.juro.2011.11.079] [PMID]

[54] Chang YJ, Ho TY, Wu ML, Hwang SM, Chiou TW, Tsai MS. Amniotic fluid stem cells with low γ-interferon response showed behavioral improvement in Parkinsonism rat model. PloS One. 2013; 8(9):e76118. [DOI:10.1371/journal.pone.0076118] [PMID]

[55] Zani A, Cananzi M, Fascetti-Leon F, Lauriti G, Smith VV, Bollini S, et al. Amniotic fluid stem cells improve survival and enhance repair of damaged intestine in necrotising enterocolitis via a COX-2 dependent mechanism. Gut. 2014; 63(2):300-9. [DOI:10.1136/gutjnl-2012-303735] [PMID]

[56] Norooznezhad F, Rodriguez-Merchan EC, Asadi S, Norooznezhad AH. Curcumin: Hopeful treatment of hemophilic arthropathy via inhibition of inflammation and angiogenesis. Expert Review of Hematology. 2020; 13(1):5-11. [DOI:10.1080/17474086.2020.1685867] [PMID]

[57] Norooznezhad AH, Norooznezhad F. Cannabinoids: Possible agents for treatment of psoriasis via suppression of angiogenesis and inflammation. Medical Hypotheses. 2017; 99:15-8. [DOI:10.1016/j.mehy.2016.12.003] [PMID]

[58] Norooznezhad AH, Norooznezhad F, Ahmadi K. Next target of tranilast: Inhibition of corneal neovascularization. Medical Hypotheses. 2014; 82(6):700-2. [DOI:10.1016/j.mehy.2014.03.007] [PMID]

[59] Keshavarz M, Norooznezhad AH, Mansouri K, Mostafaie A. Cannabinoid (JWH-133) therapy could be effective for treatment of corneal neovascularization. Journal of Medical Hypotheses and Ideas. 2010; 4:3. [Link]

[60] Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: Causes, consequences, challenges and opportunities. Cellular and Molecular Life Sciences. 2020; 77(9):1745-70. [DOI:10.1007/s00018-019-03351-7] [PMID]

[61] Johnson T, Zhao L, Manuel G, Taylor H, Liu D. Approaches to therapeutic angiogenesis for ischemic heart disease. Journal of Molecular Medicine (Berlin, Germany). 2019; 97(2):141-51. [DOI:10.1007/s00109-018-1729-3] [PMID]

[62] Jahani M, Rezazadeh D, Mohammadi P, Abdolmaleki A, Norooznezhad A, Mansouri K. Regenerative medicine and angiogenesis; challenges and opportunities. Advanced Pharmaceutical Bulletin. 2020; 10(4):490-501. [DOI:10.34172/apb.2020.061] [PMID]

[63] Reynolds LP, Grazul-Bilska AT, Redmer DA. Angiogenesis in the female reproductive organs: Pathological implications. International Journal of Experimental Pathology. 2002; 83(4):151-63. [DOI:10.1046/j.1365-2613.2002.00277.x] [PMID]

[64] Petrioli R, Miano ST, Martellucci I. Chapter 3 - Antiangiogenic agents in the treatment of colorectal, gastric, and gastroesophageal junction adenocarcinoma. In: Morbidelli L, editor. Antiangiogenic drugs as chemosensitizers in cancer therapy. Cambridge, Massachusetts, United States: Academic Press; 2022. [DOI:10.1016/B978-0-323-90190-1.00007-X]

[65] Zimna A, Kurpisz M. Hypoxia-Inducible Factor-1 in Physiological and Pathophysiological Angiogenesis: Applications and Therapies. BioMed Research International. 2015; 2015:549412. [DOI:10.1155/2015/549412] [PMID]

[66] Khansari N, Shakiba Y, Mahmoudi M. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. Recent Patents on Inflammation & Allergy Drug Discovery. 2009; 3(1):73-80. [DOI:10.2174/187221309787158371] [PMID]

[67] Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017; 9(6):7204-18. [DOI:10.18632/oncotarget.23208] [PMID]

[68] Zotova N, Zhuravleva Y, Chereshnev V, Gusev E. Acute and chronic systemic inflammation: features and differences in the pathogenesis, and integral criteria for verification and differentiation. International Journal of Molecular Sciences. 2023; 24(2):1144. [DOI:10.3390/ijms24021144] [PMID]

[69] Nathan C, Ding A. Nonresolving inflammation. Cell. 2010; 140(6):871-82. [DOI:10.1016/j.cell.2010.02.029] [PMID]

[70] Koh TJ, DiPietro LA. Inflammation and wound healing: The role of the macrophage. Expert Reviews in Molecular Medicine. 2011; 13:e23. [DOI:10.1017/S1462399411001943] [PMID]

[71] Ismail OZ, Bhayana V. Lipase or amylase for the diagnosis of acute pancreatitis? Clinical Biochemistry. 2017; 50(18):1275-80. [DOI:10.1016/j.clinbiochem.2017.07.003] [PMID]

[72] Bos LDJ, Ware LB. Acute respiratory distress syndrome: Causes, pathophysiology, and phenotypes. Lancet. 2022; 400(10358):1145-56. [DOI:10.1016/S0140-6736(22)01485-4] [PMID]

[73] Saalbach A, Kunz M. Impact of chronic inflammation in psoriasis on bone metabolism. Frontiers in Immunology. 2022; 13:925503. [DOI:10.3389/fimmu.2022.925503] [PMID]

[74] Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020; 9(4):880. [DOI:10.3390/cells9040880] [PMID]

[75] Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. Journal of Medicine and Life. 2019; 12(2):113-22. [DOI:10.25122/jml-2018-0075] [PMID]

[76] Jiang L, Yan Y, Liu Z, Wang Y. Inflammation and endometriosis. Frontiers in Bioscience. 2016; 21(5):941-8. [DOI:10.2741/4431] [PMID]

[77] Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nature Medicine. 2019; 25(12):1822-32. [DOI:10.1038/s41591-019-0675-0] [PMID]

[78] Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. The FEBS Journal. 2018; 285(16):2944-71. [DOI:10.1111/febs.14466] [PMID]

[79] Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. International Journal of Molecular Sciences. 2019; 20(23):6008. [DOI:10.3390/ijms20236008] [PMID]

[80] Mirabella T, Cilli M, Carlone S, Cancedda R, Gentili C. Amniotic liquid derived stem cells as reservoir of secreted angiogenic factors capable of stimulating neo-arteriogenesis in an ischemic model. Biomaterials. 2011; 32(15):3689-99. [DOI:10.1016/j.biomaterials.2011.01.071] [PMID]

[81] Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. Journal of Leukocyte Biology. 2020; 108(3):787-99. [DOI:10.1002/JLB.2MR0220-549R] [PMID]

[82] Kong DH, Kim YK, Kim MR, Jang JH, Lee S. Emerging Roles of Vascular Cell Adhesion Molecule-1 (VCAM-1) in immunological disorders and cancer. International Journal of Molecular Sciences. 2018; 19(4):1057. [DOI:10.3390/ijms19041057] [PMID]

[83] Zagoura DS, Roubelakis MG, Bitsika V, Trohatou O, Pappa KI, Kapelouzou A, et al. Therapeutic potential of a distinct population of human amniotic fluid mesenchymal stem cells and their secreted molecules in mice with acute hepatic failure. Gut. 2012; 61(6):894-906. [DOI:10.1136/gutjnl-2011-300908] [PMID]

[84] Zheng YB, Zhang XH, Huang ZL, Lin CS, Lai J, Gu YR, et al. Amniotic-fluid-derived mesenchymal stem cells overexpressing interleukin-1 receptor antagonist improve fulminant hepatic failure. Plos One. 2012; 7(7):e41392. [DOI:10.1371/journal.pone.0041392] [PMID]

[85] Legaki E, Roubelakis MG, Theodoropoulos GE, Lazaris A, Kollia A, Karamanolis G, et al. Therapeutic potential of secreted molecules derived from human amniotic fluid mesenchymal stem/stroma cells in a mice model of colitis. Stem Cell Reviews and Reports. 2016; 12(5):604-12. [DOI:10.1007/s12015-016-9677-1] [PMID]

[86] Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Critical Reviews in Immunology. 2012; 32(1):23-63. [DOI:10.1615/CritRevImmunol.v32.i1.30] [PMID]

[87] Solaiman A, Mehanna RA, Meheissen GA, Elatrebi S, Said R, Elsokkary NH. Potential effect of amniotic fluid-derived stem cells on hyperoxia-induced pulmonary alveolar injury. Stem Cell Research & Therapy. 2022; 13(1):145. [DOI:10.1186/s13287-022-02821-3] [PMID]

[88] Hashemian SR, Aliannejad R, Zarrabi M, Soleimani M, Vosough M, Hosseini SE, et al. Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: A case series. Stem cell research & therapy. 2021; 12(1):91. [DOI:10.1186/s13287-021-02165-4] [PMID]

[89] Chu M, Wang H, Bian L, Huang J, Wu D, Zhang R, et al. Nebulization therapy with umbilical cord mesenchymal stem cell-derived exosomes for covid-19 pneumonia. Stem Cell Reviews and Reports. 2022; 18(6):2152-63. [DOI:10.1007/s12015-022-10398-w] [PMID]

[90] Lightner AL, Sengupta V, Qian S, Ransom JT, Suzuki S, Park DJ, et al. Bone Marrow Mesenchymal Stem Cell-Derived Extracellular Vesicle Infusion for the Treatment of Respiratory Failure From COVID-19: A randomized, placebo-controlled dosing clinical trial. Chest. 2023; 164(6):1444-53. [DOI:10.1016/j.chest.2023.06.024] [PMID]

[91] Sengupta V, Sengupta S, Lazo A, Woods P, Nolan A, Bremer N. Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe covid-19. Stem Cells and Development. 2020; 29(12):747-54. [PMID]

[92] Zhu YG, Shi MM, Monsel A, Dai CX, Dong X, Shen H, et al. Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: A pilot study. Stem Cell Research & Therapy. 2022; 13(1):220. [DOI:10.1186/s13287-022-02900-5] [PMID]

[93] Shi MM, Yang QY, Monsel A, Yan JY, Dai CX, Zhao JY, et al. Preclinical efficacy and clinical safety of clinical-grade nebulized allogenic adipose mesenchymal stromal cells-derived extracellular vesicles. Journal of Extracellular Vesicles. 2021; 10(10):e12134. [DOI:10.1002/jev2.12134] [PMID]

[94] Uszyński W, Zekanowska E, Uszyński M, Zyliński A, Kuczyński J. New observations on procoagulant properties of amniotic fluid: microparticles (MPs) and tissue factor-bearing MPs (MPs-TF), comparison with maternal blood plasma. Thrombosis Research. 2013; 132(6):757-60. [DOI:10.1016/j.thromres.2013.10.001] [PMID]

[95] Bellio MA, Young KC, Milberg J, Santos I, Abdullah Z, Stewart D, et al. Amniotic fluid-derived extracellular vesicles: characterization and therapeutic efficacy in an experimental model of bronchopulmonary dysplasia. Cytotherapy. 2021; 23(12):1097-107. [DOI:10.1016/j.jcyt.2021.07.011] [PMID]

[96] Del Rivero T, Milberg J, Bennett C, Mitrani MI, Bellio MA. Human amniotic fluid derived extracellular vesicles attenuate T cell immune response. Frontiers in Immunology. 2022; 13:977809. [DOI:10.3389/fimmu.2022.977809] [PMID]

[97] O'Connell JS, Lee C, Farhat N, Antounians L, Zani A, Li B, et al. Administration of extracellular vesicles derived from human amniotic fluid stem cells: A new treatment for necrotizing enterocolitis. Pediatric Surgery International. 2021; 37(3):301-9. [DOI:10.1007/s00383-020-04826-6] [PMID]

[98] Katifelis H, Filidou E, Psaraki A, Yakoub F, Roubelakis MG, Tarapatzi G, et al. Amniotic fluid-derived mesenchymal stem/stromal cell-derived secretome and exosomes improve inflammation in human intestinal subepithelial myofibroblasts. Biomedicines. 2022; 10(10):2357. [DOI:10.3390/biomedicines10102357] [PMID]

[99] Antounians L, Catania VD, Montalva L, Liu BD, Hou H, Chan C, et al. Fetal lung underdevelopment is rescued by administration of amniotic fluid stem cell extracellular vesicles in rodents. Science Translational Medicine. 2021; 13(590):eaax5941. [DOI:10.1126/scitranslmed.aax5941] [PMID]

[100] Li P, Lu X, Hu J, Dai M, Yan J, Tan H, et al. Human amniotic fluid derived-exosomes alleviate hypoxic encephalopathy by enhancing angiogenesis in neonatal mice after hypoxia. Neuroscience Letters. 2022; 768:136361. [DOI:10.1016/j.neulet.2021.136361] [PMID]

[101] Khalaj K, Antounians L, Figueira RL, Post M, Zani A. Autophagy is impaired in fetal hypoplastic lungs and rescued by administration of amniotic fluid stem cell extracellular vesicles. American Journal of Respiratory and Critical Care Medicine. 2022; 206(4):476-87. [DOI:10.1164/rccm.202109-2168OC] [PMID]

[102] Khalaj K, Figueira RL, Antounians L, Gandhi S, Wales M, Montalva L, et al. Treatment with amniotic fluid stem cell extracellular vesicles promotes fetal lung branching and cell differentiation at canalicular and saccular stages in experimental pulmonary hypoplasia secondary to congenital diaphragmatic hernia. Stem Cells Translational Medicine. 2022; 11(10):1089-102. [DOI:10.1093/stcltm/szac063] [PMID]

[103] Castelli V, Antonucci I, d'Angelo M, Tessitore A, Zelli V, Benedetti E, et al. Neuroprotective effects of human amniotic fluid stem cells-derived secretome in an ischemia/reperfusion model. Stem Cells Translational Medicine. 2021; 10(2):251-66. [DOI:10.1002/sctm.20-0268] [PMID]

[104] Gatti M, Zavatti M, Beretti F, Giuliani D, Vandini E, Ottani A, et al. Oxidative stress in Alzheimer's Disease: In vitro therapeutic effect of amniotic fluid stem cells extracellular vesicles. Oxidative Medicine and Cellular Longevity. 2020; 2020:2785343. [DOI:10.1155/2020/2785343] [PMID]

[105] Costa A, Balbi C, Garbati P, Palamà MEF, Reverberi D, De Palma A, et al. Investigating the paracrine role of perinatal derivatives: human amniotic fluid stem cell-extracellular vesicles show promising transient potential for cardiomyocyte renewal. Frontiers in Bioengineering and Biotechnology. 2022; 10:902038. [DOI:10.3389/fbioe.2022.902038] [PMID]

[106] Zhang Y, Yan J, Liu Y, Chen Z, Li X, Tang L, et al. Human amniotic fluid stem cell-derived exosomes as a novel cell-free therapy for cutaneous regeneration. Frontiers in Cell and Developmental Biology. 2021; 9:685873. [DOI:10.3389/fcell.2021.685873] [PMID]

[107] Wgealla MMAMA, Liang H, Chen R, Xie Y, Li F, Qin M, et al. Amniotic fluid derived stem cells promote skin regeneration and alleviate scar formation through exosomal miRNA-146a-5p via targeting CXCR4. Journal of Cosmetic Dermatology. 2022; 21(10):5026-36. [DOI:10.1111/jocd.14956] [PMID]

[108] Xiao GY, Cheng CC, Chiang YS, Cheng WT, Liu IH, Wu SC. Exosomal miR-10a derived from amniotic fluid stem cells preserves ovarian follicles after chemotherapy. Scientific Reports. 2016; 6:23120. [DOI:10.1038/srep23120] [PMID]

[109] Geng Z, Chen H, Zou G, Yuan L, Liu P, Li B, et al. Human amniotic fluid mesenchymal stem cell-derived exosomes inhibit apoptosis in ovarian granulosa Cell via miR-369-3p/YAF2/PDCD5/p53 Pathway. Oxidative Medicine and Cellular Longevity. 2022; 2022:3695848. [DOI:10.1155/2022/3695848] [PMID]

[110] Zavatti M, Beretti F, Casciaro F, Bertucci E, Maraldi T. Comparison of the therapeutic effect of amniotic fluid stem cells and their exosomes on monoiodoacetate-induced animal model of osteoarthritis. Biofactors. 2020; 46(1):106-17. [DOI:10.1002/biof.1576] [PMID]

[111] Gatti M, Beretti F, Zavatti M, Bertucci E, Ribeiro Luz S, Palumbo C, et al. Amniotic fluid stem cell-derived extracellular vesicles counteract steroid-induced osteoporosis in vitro. International Journal of Molecular Sciences. 2020; 22(1):38. [DOI:10.3390/ijms22010038] [PMID]

[112] Sedrakyan S, Villani V, Da Sacco S, Tripuraneni N, Porta S, Achena A, et al. Amniotic fluid stem cell-derived vesicles protect from VEGF-induced endothelial damage. Scientific Reports. 2017; 7(1):16875. [DOI:10.1038/s41598-017-17061-2] [PMID]

[113] Mobarak H, Heidarpour M, Rahbarghazi R, Nouri M, Mahdipour M. Amniotic fluid-derived exosomes improved spermatogenesis in a rat model of azoospermia. Life Sciences.2021; 274:119336. [DOI:10.1016/j.lfs.2021.119336] [PMID]

[114] Bellio MA, Bennett C, Arango A, Khan A, Xu X, Barrera C, et al. Proof-of-concept trial of an amniotic fluid-derived extracellular vesicle biologic for treating high-risk patients with mild-to-moderate acute COVID-19 infection. Biomaterials and Biosystems. 2021;4:100031. [DOI:10.1016/j.bbiosy.2021.100031] [PMID]

[115] Mitrani MI, Bellio MA, Sagel A, Saylor M, Kapp W, VanOsdol K, et al. Case Report: Administration of amniotic fluid-derived nanoparticles in three severely Ill COVID-19 patients. Frontiers in Medicine. 2021; 8:583842. [DOI:10.3389/fmed.2021.583842] [PMID]

[116] Mitrani MI, Bellio MA, Meglin A, Khan A, Xu X, Haskell G, et al. Treatment of a COVID-19 long hauler with an amniotic fluid-derived extracellular vesicle biologic. Respiratory Medicine Case Reports. 2021; 34:101502. [DOI:10.1016/j.rmcr.2021.101502] [PMID]

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