Autoimmune pancreatitis is a form of chronic pancreatitis that frequently causes acute episodes with clinical symptoms parallel to those of acute pancreatitis. Corticosteroids are effective in the treatment of 90% of autoimmune pancreatitis cases, but for the remaining 10%, options are limited. Due to their significant immunomodulatory capabilities, mesenchymal stromal cells (MSCs) have been proposed as a novel treatment strategy for various immune and inflammatory pathologies including those with autoimmune origins. Here, we not only highlight the most recent MSC live-cell experiments to address acute pancreatitis, but also discuss the opportunities afforded by the emergence of the newly identified field of MSC necrobiology. We conclude that the putative employment of MSC derivatives provides a newer and simpler therapeutic approach that could have significant advantages over the use of cells themselves.
because MSCs clearly would not be an ideal therapeutic strategy for gallstones or alcohol-induced pancreatitis which already possesses successful treatment regimens. Here, we provide updates on new approaches reported in the field, and also discuss the use of MSC derivatives in the treatment of autoimmune pancreatitis.

Mesenchymal stromal cells were once thought to mitigate various pathologies solely through anti-inflammatory and tissue regenerative pathways. Autologous MSC therapy gained its first regulatory approval, for the treatment of acute myocardial infarction, in 2011 [5] although not without creating some continuing controversy [6]. In fact, MSCs have been shown to exhibit an immunomodulatory phenotype through four distinct mechanisms [7] (Fig. 1). The latter include modulating the proliferation and differentiation of dendritic, B, and T cells and mediating the polarization of monocytes from an inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. In addition, MSCs can reduce the production of reactive oxygen species such as superoxide anions, which inhibit the apoptosis of neutrophils. Finally, MSCs can diminish endothelial cell responses to pro-inflammatory cytokines such as TNF-α, IL-1, and IFN-γ [7].

MSCs for the treatment of immune pathologies

Due to their significant immunomodulatory capabilities, MSCs have been proposed as a novel treatment strategy for various pathologies wherein the immune system is either compromised or dysfunctional, including those with autoimmune origins (Fig. 2). Indeed, MSCs have shown success in the treatment of systemic lupus erythematosus [8], rheumatoid arthritis [9], type 1 diabetes mellitus [10], multiple sclerosis [11], liver failure associated with hepatitis B virus [12], ulcerative colitis [13], dacryoadenitis [14], Sjögren’s syndrome [15], and systemic scleroderma [15]. A very recent example is the co-administration of MSCs with pancreatic islets in immunocompetent type 1 diabetic wild-type mice. Glycemic control was restored, using human mesenchymal cells, and a clear demonstration provided evidence of the suppression of T-cell activation without the need for prior ex vivo licensing (stimulation) with the inflammatory cytokines interferon-Y (IFN-Y), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) [16]. The first approval, with government reimbursement, for the treatment of an immune condition with MSCs was that in Japan in 2016, for the treatment of both pediatric disease and adult acute graft-versus-host disease (aGVHD) [17]. Thus, the acute inflammatory episodes of autoimmune pancreatitis may represent an appropriate therapeutic target for MSCs in cases refractory to the use of corticosteroids.

Recent cellular approaches

One recent approach has pretreated (licensed) umbilical-derived mesenchymal stromal cells with angiotensin II before employing them in the treatment of severe acute pancreatitis in Sprague-Dawley rats [18]. The rationale was to maximize the constitutive angiogenic properties of UCMSCs. The pretreated cells demonstrated an enhanced ability to abrogate pancreatitis compared with cells that had not been licensed. This conclusion was established through the histological assessment of pancreatic sections using measures of necrosis, edema, vacuolization, and inflammation as well as through the observation of myeloperoxidase and serum amylase levels. The treated cells were also shown to increase the paracrine release of vascular endothelial growth factor (VEGF) which has been proven to be an important factor in pancreatic tissue healing [18].

In another study, human adipose tissue-derived mesenchymal stromal cells were transfected with siRNA targeting tumor necrosis factor-α (TNF-α) and compared with their untransduced, control counterparts in the treatment of caerulein and lipopolysaccharide-induced severe acute pancreatitis in C57BL/6 mice. Pancreas-to-body weight ratio, tissue edema, necrosis of acinar cells, and inflammatory cell infiltration were all improved in the control group, demonstrating the role played by TSG-6 in ameliorating the disease. Specifically, the pro-inflammatory cytokines, TNF-α, IL-1β, IL-6, and markers of endoplasmic reticulum stress, Grp78, CHOP, and caspase-12, were decreased, while anti-inflammatory cytokine, IL-10, was increased in the control group [19].

Ongoing challenges

While the above studies demonstrate convincing evidence that mesenchymal stromal cells could, in the future, be used as a novel treatment strategy for the acute episodes of autoimmune pancreatitis, it is important to acknowledge some limitations in the current scientific literature. Firstly, as we have previously discussed, to be clinically relevant, an animal model needs to be designed to specifically reflect the cause of the pancreatitis, such as autoimmune pancreatitis. Also, studies need to be conducted on the use of MSCs in large animal models whose gastroenterological
anatomies are more similar to that of humans. Finally, as the cells are being proposed as a novel clinical therapy it is important to recognize barriers that could prove to be problematic as discussed below.

Mesenchymal stromal cells can be isolated from a plethora of human sources including adipose, brain, endometrial, placental, and umbilical cord tissue as well as bone marrow, cord blood, amniotic fluid, various regions of Wharton’s jelly, and dental pulp [20,21]. However, it is becoming increasingly clear that the functional phenotype of a particular population of MSCs varies with both the tissue source employed and the conditions under which the cells are culture-expanded [22]. Despite these disparate origins, the overall abundance of MSCs in the human body is still relatively low, for example, only 0.001–0.01% of cells in the bone marrow are MSCs [20]. MSC therapy usually requires hundreds of millions of MSCs; in the aforementioned studies, 1 million cells were used in the study conducted on mice and 10 million cells were used on the rats [18–19]. In an ongoing Phase III, human clinical trial being conducted for chronic graft-versus-host disease, a dose of 2 million cells per kilogram was injected six times intravenously [23]. Clearly, due to the scarce number of MSCs in the human body and the large number needed for putative therapy, a barrier might exist wherein the demand for cells needed for therapy cannot be met. In vitro cell expansion is the only way to yield such a high volume of cells, but this can take up to 10 weeks [24]. In addition, as described in the aforementioned studies, transfected or pretreated (licensed) cells have been proposed, which are more complicated and costly to produce.

Fig. 1. The immunomodulatory effects of MSCs all have demonstrated proven efficacy in models of chronic inflammatory and autoimmune diseases. Included with permission from Munir and McGettrick [7].
Live cells, dead cells, and derivatives

Therapy with live MSCs has a singular advantage over the use of their derivatives: The cells can differentiate to provide the connective tissue stroma of the recipient organ [25]. However, although MSCs have been proposed to assist with the significant stromal tissue damage that occurs in pancreatitis, the cell implantation time is too short for differentiation to occur. The two most common methods of MSC delivery for acute pancreatitis are intravenous and intraperitoneal. Less than 1% of MSCs survive for over a week after intravenous administration [26,27], while when injected intraperitoneally, after 20 min MSCs fail to be detected in peritoneal lavage fluid and begin to form large aggregates [28]. This evidence suggests that the main therapeutic benefit of mesenchymal stromal cells is in their immunomodulatory capacity. Thus, the therapeutic advantage of live MSCs over derivatives does not extend to the cells’ immunoregulatory properties.

Recent literature describes the new and exciting field of ‘MSC necrobiology’, which proposes a novel solution to some of the aforementioned barriers. Necrobiology provides four mechanisms by which derivatives of mesenchymal stromal cells can maintain significant clinical efficacy: apoptosis, autophagy, mitochondrial transfer, and extracellular vesicles [29]. MSC products derived from these pathways have been proven to ameliorate a plethora of pathologies (Table 1). Indeed, MSC derivatives (Fig. 2) have, in some cases, been shown to be as therapeutically beneficial as living MSCs [30–33], but have the advantage of being able to pass easily through the circulatory system.

Mesenchymal stromal cells that have undergone apoptosis have been shown to reduce inflammatory endpoints in mouse models of allergic airway inflammation induced by ovalbumin (OVA) causing noncytotoxic T helper-type cell inflammation [34]. Apoptotic rat adipose-derived MSCs have also been proven superior in ameliorating the condition of cecal ligation and puncture-induced sepsis in rat models in comparison with living MSCs [35–37]. Autophagic mesenchymal stromal cells have also been proven to have therapeutic benefits. MSCs derived from human bone marrow that have undergone autophagy have been proven to regulate CD4+ T helper cells via TGF-β1 signaling [38]. Similarly, when MSCs underwent autophagy as a result of the administration of rapamycin, their ability to suppress CD4+ T helper cell proliferation was improved [38]. MSCs subjected to mitochondrial transfer also seem to be effective in mitigating the symptoms of asthma [39], chronic obstructive pulmonary disorder [40], cardiomyopathy [41], acute respiratory distress syndrome, and sepsis [42]. There is also evidence that extracellular vesicles derived from MSCs hold clinical efficacy in pathologies of the kidney [43], heart [44], lung [45], and skin [46].

In recent years, exosome therapy for certain inflammatory conditions has garnered significant interest. Almost all cells in the human body can produce exosomes: Extracellular vesicles produced by an
endosomal pathway are approximately 30–150 nm in size [47]. Exosomes were previously thought of as having the sole responsibility of clearing cellular debris; however, recent scientific literature points to their ability to modulate intracellular environmental conditions. It is believed that only certain exosomes are immunoregulatory. Thus, a subclass of exosomes has been described as ‘signalosomes’, which, when released from MSCs, have an exceptional capacity for immunoregulation [47].

Exosome therapy using ‘signalosomes’ has been investigated for a plethora of pathologies including diseases of the heart [48], lung [49], kidney [50], brain [51], liver [52], intestines [53], skin [54], and nervous system [55] as well as for sepsis [56] and various cancers [57,58]. In 2014, a clinical trial was conducted using exosome therapy for steroid-refractory graft-vs-host disease and showed positive results [59]. Another study that investigated the use of exosomes as a novel therapeutic strategy for neonatal chronic lung disease compared their efficacy to that of a whole MSC population [60]. The study indicated that exosomes themselves hold an equivalent and sometimes even superior ability to modulate the inflammatory response. The use of MSC derivatives for treatment holds several advantages over the use of a live MSC population. They can be less costly to produce and can last up to 6 months when stored at −20 °C [61]. Derivatives are also a safer treatment option compared with whole MSCs as there are no risks associated with mutagens.

**Table 1.** Details of published studies investigating the therapeutic efficacy of MSC derivatives originating from four distinct necrobiology pathways.

| Authors         | Mechanism/Pathway | Condition(s) of interest                                                                 | Results                                                                 |
|-----------------|-------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Galleu et al. [34] | Apoptosis         | Allergic airway inflammation and Graft-versus-host disease                             | ↓ Eosinophil infiltrate in bronchoalveolar lavage (BAL) and             |
| Chang et al. [35] | Apoptosis         | Sepsis syndrome induced by cecal puncture and ligation                                | ↓ Inflammatory endpoints                                               |
| Chen et al. [36]  | Apoptosis         | Kidney injury induced by sepsis                                                      | ↑ Immunomodulation                                                     |
| Sung et al. [37]  | Apoptosis         | Lung and kidney injury induced by sepsis syndrome                                      | ↓ Lung and kidney injury                                               |
| Gao et al. [38]   | Autophagy         | This study investigated generally if the activation of autophagy in MSCs ameliorates their immunosuppressive capacity | ↑ TGF-β1 secretion                                                     |
| Yao et al. [39]   | Mitochondrial transfer | Asthma                                                                                   | ↑ Immunomodulation                                                     |
| Li et al. [40]    | Mitochondrial transfer | Airway epithelial cell damage induced by cigarette smoke in chronic obstructive pulmonary disorder (COPD) | ↓ Asthma inflammation, IL-4, IL-5, IL-13                                |
| Zhang et al. [41] | Mitochondrial transfer | Cardiomyopathy                                                                          | Improved heart function                                               |
| Morrison et al. [42] | Mitochondrial transfer | Acute respiratory distress syndrome (ARDS)                                              | ↑ M2 macrophage expression                                             |
| Collino et al. [43] | Extracellular vesicle derivation | Acute kidney injury                                                                    | ↓ TNF-α                                                                |
| Lai et al. [44]   | Extracellular vesicle derivation | Myocardial ischemia/reperfusion injury                                                  | ↓ IL-8                                                                 |
| Li et al. [45]    | Extracellular vesicle derivation | Acute lung injury                                                                       | ↑ Renal tubular cell proliferation                                      |
| Wu et al. [46]    | Extracellular vesicle derivation | Cutaneous injury                                                                         | ↑ Wnt4                                                                 |

973
or oncogenicity. However, it should be pointed out that there is no documented technique to isolate ‘signalosomes’ from exosomes derived from other biogenic pathways, which may not possess the same immunomodulatory capacity [47].

Exosomes, in general, can be isolated by several methods. One of the most common methods is ultracentrifugation, although this requires costly apparatus (for industrial scale-up) and the technique can promote vesicle aggregation which is detrimental to the structural and metabolic integrity of the exosomes produced [62]. Milder techniques of isolation have been described, for example, gradient density isolation and size-exclusion chromatography. However, these techniques also have issues as density-based separation may lead to enrichment as opposed to true isolation which may result in the presence of unwanted particles [63,64]. Additionally, this technique does not allow for the large-scale bioprocessing of exosomes, therefore making it an unrealistic technique in the context of therapy [63,64].

Fortunately, there are other MSC-derived products that are disruptive since production technology is far simpler and less costly than producing exosomes. Studies have been conducted indicating that cellular lysates have a similar therapeutic benefit in the treatment of various pathologies as compared to exosomes and whole-cell MSCs themselves. Eleven published studies use cellular lysate derived from mesenchymal stromal cells from different origins to treat diverse conditions. The studies investigate the lysate’s effect on aging [65], erectile dysfunction [66], fulminant hepatic failure [67], stroke [68], osteosarcoma and mammary carcinoma [69], epilepsy [70], liver failure [71], wound healing [72], ischemia [73], lymphoma [74], and obesity [75]. All of the aforementioned studies except the study investigating its effects on aging demonstrated that the lysate was able to ameliorate in vitro and in vivo models.

Recently, MSC derivative therapy has been proven effective in treating pathologies that are autoimmune in nature. Apoptotic MSCs have demonstrated immunosuppressive properties in mouse models of GVHD [38], and extracellular vesicles have improved the symptoms associated with uveitis/uveoretinitis and type 1 diabetes mellitus [76]. In addition, exosomes have shown success in ameliorating autoimmune conditions including multiple sclerosis [77], Sjögren’s syndrome [78], graft versus host disease [59], systemic lupus erythematosus [79], and rheumatoid arthritis [80]. These results suggest the potential use of derivatives for other autoimmune conditions that lack entirely favorable treatment regimens, such as autoimmune pancreatitis.

**Conclusion**

In conclusion, employing MSCs in the treatment of autoimmune pancreatitis remains a promising putative cell therapy. However, the recent emergence of a variety of methods to produce MSC derivatives provides a newer and simpler approach that could have significant advantages over the use of cells themselves including simpler production, lower regulatory barriers, and easier systemic transport upon intravenous delivery.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

1. Guda N and Nojgaard C (2015) Recurrent acute pancreatitis and progression to chronic pancreatitis. *Pancreapedia: The Exocrine Pancreas Knowledge Base* 47, 653–666.
2. Okazaki K, Uchida K, Sumimoto K, Mitsuyama T, Ikeura T and Takaoka M (2014) Autoimmune pancreatitis: pathogenesis, latest developments and clinical guidance. *Ther Adv Chronic Dis* 5, 104–111.
3. Buchman AL (2001) Side effects of corticosteroid therapy. *J Clin Gastroenterol* 33, 289–294.
4. Goodman RR, Jong MK and Davies JE (2019) Concise review: The challenges and opportunities of employing mesenchymal stromal cells in the treatment of acute pancreatitis. *Biotechnol Adv*, 30005–30005.
5. Yang H (2011) South Korea’s stem cell approval. *Nat Biotechnol* 29, 857.
6. Sipp D, Robey PG and Turner L (2018) Clear up this stem-cell mess. *Nature* 561, 455–457.
7. Munir H and McGettrick HM (2015) Mesenchymal stem cell therapy for autoimmune disease: risks and rewards. *Stem Cells and Dev* 24, 2091–2099.
8. Wang D, Zhang H, Liang J, Wang H, Hua B, Feng X, Gilkeson GS, Farge D, Shi S and Sun L (2018) A long-term follow-up study of allogeneic mesenchymal stem/stromal cell transplantation in patients with drug-resistant systemic lupus erythematosus. *Stem Cell Reports* 10, 933–941.
9. Wang L, Huang S, Li S, Li M, Shi J, Bai W, Wang Q, Zheng L and Liu Y (2019) Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: a prospective phase I/II study. *Drug Des Devel Ther* 13, 4331–4340.
10. Wu H and Mahato RI (2014) Mesenchymal stem cell-based therapy for type 1 diabetes. *Discov Med* 17, 139–143.
11. Dulamea A (2015) Mesenchymal stem cells in multiple sclerosis – translation to clinical trials. *J Med Life* 8, 24–27.
MSC derivatives for autoimmune pancreatitis

Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shi J, Chen L, Lv S et al. (2012) Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem Cells Transl Med 1, 725–731.

Hu J, Zhao G, Zhang L, Qiao C, Di A, Gao H and Xu H (2016) Safety and therapeutic effect of mesenchymal stem cell infusion on moderate to severe ulcerative colitis. Exp Ther Med 12, 2983–2989.

Lu X, Wang X, Nian H, Yang D and Wei R (2017) Mesenchymal stem cells for treating autoimmune dacyroadenitis. Stem Cell Res Ther 8, 126.

Sánchez-Berná I, Santiago-Díaz C and Jiménez-Alonso J (2015) Immunomodulatory properties of stem mesenchymal cells in autoimmune diseases. Med Clin 144, 88–91.

Forbes S, Bond AR, Thirlwell KL, Burgoyne P, Samuel K, Noble J, Borthwick G, Colligan D, McGowan NWA, Lewis PS et al. (2020) Human umbilical cord perivascular cells improve human pancreatic islet transplant function by increasing vascularization. Sci Transl Med 12, 5907.

https://www.globenewswire.com/news-release/2016/02/24/813541/0/en/First-Allogeneic-Cell-Therapy-Product-Launched-in-Japan-by-Mesoblast-Licensee.html

Yang J, Su J, Xi S, Ke X, Zhu Y, Lin H, Zeng X, Liu B, Zhu M, Dai WY et al. (2019) Human umbilical cord mesenchymal stem cells pretreated with angiotensin-II attenuate pancreas injury of rats with severe acute pancreatitis. Biomed Pharmacoc 117, 109052.

Li Q, Song W, Ryu M, Nam A, An J, Ahn J, Bhang DH, Jung YC and Youn H (2018) TSG-6 secreted by human adipose tissue-derived mesenchymal stem cells ameliorates severe acute pancreatitis via ER stress downregulation in mice. Stem Cell Res Ther 9, 255–255.

Marquez-Curtis L, Janowska-Wieczorek A, McGann LE and Elliott JAW (2015) Mesenchymal stromal cells derived from various tissues: biological, clinical and cryopreservation aspects. Cryobiology 71, 181–197.

Davies JE, Walker JT and Keating A (2017) Concise review: Wharton’s jelly: the rich, but enigmatic, source of mesenchymal stromal cells. Stem Cells Transl Med 6, 1620–1630.

Boland LK, Burand AJ, Boyt DT, Dobroski H, Di L, Liszewski JN, Schrodt MV, Frazer MK, Santillan DA and Ankrum JA (2019) Nature vs. nurture: defining the effects of mesenchymal stromal cell isolation and culture conditions on resiliency to palmitate challenge. Front Immunol 10, 1080.

https://clinicaltrials.gov/ct2/show/NCT02291770

Vizoso F, Eiro N, Cid S, Schneider J and Perez-Fernandez R (2017) Mesenchymal stem cell secretome: toward cell-free therapeutic strategies in regenerative medicine. Int J Mol Sci 18, 1852.

Hwang NS, Zhang C, Hwang Y and Varghese S (2009) Mesenchymal stem cell differentiation and roles in regenerative medicine. Wiley Interdiscip Rev Syst Biol Med 1, 97–106.

Eggenhofer E, Benseler V, Kroemer A, Popp FC, Geissler EK, Schlitt HJ, Baan CC, Dahlke MH and Hoogduijn MJ (2012) Mesenchymal stem cells are short-lived and do not migrate beyond the lungs after intravenous infusion. Front Immunol 3, 297–297.

Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, Semprun-Prieto L, Delafontaine P and Prockop DJ (2009) Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell 5, 54–63.

Bazhanov N, Ylostalo J, Bartosh T, Tiblow A, Mohammadipoor A, Fossett A and Prockop D (2016) Intraperitoneally infused human mesenchymal stem cells form aggregates with mouse immune cells and attach to peritoneal organs. Stem Cell Res Ther 7, 27.

Weiss DJ, English K, Krasnodembskaya A, Isaza-Correa J, Hawthorne JJ and Mahon BP (2019) The necrobiosis of mesenchymal stromal cells affects therapeutic efficacy. Front Immunol 10, 1228.

Bakhtyar N, Jeschke M, Herer E, Sheikhosslam M and Amini-Nik S (2018) Exosomes from acellular Wharton’s jelly of the human umbilical cord promotes skin wound healing. Stem Cell Res Ther 9, 193.

Gonzalves F, Luk F, Korevaar S, Bouzid R, Paz A, López-Iglesias C, Baan C, Merino A and Hoogduijn M (2017) Membrane particles generated from mesenchymal stromal cells modulate immune responses by selective targeting of pro-inflammatory monocytes. Sci Rep 7, 12100.

vanKoppen A, Joles JA, vanBalkom Bas W M, Lim SK, deKleijn D, Giles RH, Verhaar MC and Dussaule J (2012) Human embryonic mesenchymal stem cell-derived conditioned medium rescues kidney function in rats with established chronic kidney disease. PLoS ONE 7, e38746.

Timmers L, Lim SK, Arslan F, Armstrong JS, Hoefer IE, Dovendans PA, Piek JJ, El Oakley RM, Choo A, Lee CN et al. (2008) Reduction of myocardial infarct size by human mesenchymal stem cell conditioned medium. Stem Cell Res 1, 129–137.

Galleu A, Riff-Vasquez Y, Trento C, Lomas C, Dolcetti L, Cheung TS, Von Bonin M, Barbieri L, Halai K, Ward S et al. (2017) Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation. Sci Transl Med 9, 7828–7839.

Chang C, Leu S, Sung H, Zhen Y, Cho C, Chen A, Tsai T, Chung S, Chai H, Sun CK et al. (2012) Impact of apoptotic adipose-derived mesenchymal stem cells on attenuating organ damage and reducing mortality in rat...
sepsis syndrome induced by cecal puncture and ligation. J Transl Med 10, 244–244.
36 Chen H, Lin K, Wallace CG, Chen Y, Yang C, Leu S, Chen Y, Sun C, Tsai T, Chen YL et al. (2014) Additional benefit of combined therapy with melatonin and apoptotic adipose-derived mesenchymal stem cell against sepsis-induced kidney injury. J Pineal Res 57, 16–32.
37 Sung P, Chang C, Tsai T, Chang L, Leu S, Chen Y, Gao L, Cen S, Wang P, Xie Z, Liu Z, Deng W, Su H, Yao Y, Fan X, Jiang D, Zhang Y, Li X, Xu Z, Fang S, Zhang Y, Yu Z, Jiang D, Liang X, Liao S, Zhang Z, Morrison TJ, Jackson MV, Cunningham EK, Lai RC, Arslan F, Lee MM, Sze NSK, Choo A, Chen Collino F, Pomatto M, Bruno S, Lindoso RS, Tapparo M, Sicheng W, Quesenberry P and Camussi G (2016) Exosomal miR-223 contributes to mesenchymal stem cell-derived exosomes mediate mitochondrial transfer to rescue anthracycline-induced cardiomyopathy. Stem Cell Reports 7, 749–763.
42 Morrison TJ, Jackson MV, Cunningham EK, Kissenpfennig A, Mcauley DF, O’Kane CM and Krasnodembskaya AD (2017) Mesenchymal stromal cells rescue cognitive impairments after TBI. Stem Cell Rev Rep 13, 226.
43 Lai RC, Arslan F, Lee MM, Sze NSK, Choo A, Chen TS, Salto-Tellez M, Timmers L, Lee CN, El Oakley RM et al. (2010) Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. Stem Cell Res 4, 214–222.
44 Li QC, Liang Y and Su ZB (2019) Prophylactic treatment with MSC-derived exosomes attenuates traumatic acute lung injury in rats. Am J Physiol Lung Cell Mol Physiol 316, L1107–L1117.
46 Wu P, Zhang B, Shi H, Qian H and Xu W (2018) MSC-exosome: a novel cell-free therapy for cutaneous regeneration. Cytototherapy 20, 291–301.
49 Lee C, Mitsialis SA, Aslam M, Vitali SH, Vergadi E, Konstantinou G, Sdrimas K, Fernandez-Gonzalez A and Kourembanas S (2012) Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. Circulation 126, 2601–2611.
50 Zhou Y, Xu H, Xu W, Wang B, Wu H, Tao Y, Zhang B, Wang M, Mao F, Yan Y et al. (2013) Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis in vivo and in vitro. Stem Cell Res Ther 4, 34–34.
52 Kim D, Nishida H, An SY, Shetty AK, Bartosh TJ and Prockop DJ (2016) Chromatographically isolated CD63+CD81+ extracellular vesicles from mesenchymal stromal cells rescue cognitive impairments after TBI. Proc Natl Acad Sci USA 113, 170–175.
53 Tan CY, Lai RC, Wong W, Dan YY, Lim SK and Ho HK (2014) Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. Stem Cell Res Ther 5, 76.
54 Rager TM, Olson JK, Zhou Y, Wang Y and Besner GE (2016) Exosomes secreted from bone marrow-derived mesenchymal stem cells protect the intestines from experimental necrotizing enterocolitis. J Pediatr Surg 51, 942–947.
59 Fang S, Xu C, Zhang Y, Xue C, Yang C, Bi H, Qian X, Wu M, Ji K, Zhao Y et al. (2016) Umbilical cord-derived mesenchymal stem cell-derived exosomal miRNAs suppress myofibroblast differentiation by inhibiting the transforming growth factor-β/SMAD2 pathway during wound healing. Stem Cells Transl Med 5, 1425–1439.
60 Bonafe de R, Scambi I, Peroni D, Potrich V, Boschi F, Benati D, Bonetti B and Mariotti R (2016) Exosome derived from murine adipose-derived stromal cells: neuroprotective effect on in vitro model of amyotrophic lateral sclerosis. Exp Cell Res 340, 150–158.
63 Wang X, Gu H, Qin D, Yang L, Huang W, Essandoh K, Wang Y, Caldwell CC, Peng T, Zingarelli B et al. (2015) Exosomal miR-223 contributes to mesenchymal
R. R. Goodman and J. E. Davies

MSC derivatives for autoimmune pancreatitis

57 Ono M, Kosaka N, Tominaga N, Yoshioka Y, Takeshita F, Takahashi R, Yoshida M, Tsuda H, Tamura K and Ochiya T (2014) Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. Sci Signal 7, ra63.

58 Roccaro AM, Sacco A, Maiso P, Azab AK, Tai Y, Reagan M, Azab F, Flores LM, Campigotto F, Weller E et al. (2013) BM mesenchymal stromal cell-derived exosomes facilitate multiple myeloma progression. J Clin Invest 123, 1542–1555.

59 Kordelas L, Rebmann V, Ludwig AK, Radtke S, Ruesing J, Doepppner TR, Epple M, Horn PA, Beelen DW and Giebel B (2014) MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. Leukemia 28, 970.

60 Aslam M, Baveja R, Liang OD, Fernandez-Gonzalez A, Lee C, Mitsialis SA and Kourembanas S (2009) Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. Am J Respir Crit Care Med 180, 1122–1130.

61 Batrakovka EV and Kim MS (2016) Development and regulation of exosome-based therapy products. Wiley Interdiscip Rev Nanomaterials Nanobiotechnol 8, 744–757.

62 Linares R, Tan S, Gounou C, Arraud N and Brisson AR (2015) High-speed centrifugation induces aggregation of extracellular vesicles. J Extracell Vesicles 4, 2909.

63 Wittner KW, Buzás EI, Bemis LT, Bora A, Lässer C, Lötvvall J, Nolet-T Hoen EN, Piper MG, Sivaraman S, Skog J et al. (2013) Standardization of sample collection, isolation and analysis methods in extracellular vesicle research. J Extracell Vesicles 2, 20360.

64 Li P, Mao Z, Peng Z, Zhou L, Chen Y, Huang P, Truica CI, Drabick JJ, El-Deiry W, Diao M et al. (2015) Acoustic separation of circulating tumor cells. Proc Natl Acad Sci USA 112, 4970–4975.

65 Hsu MF, Yu SH, Chuang SJ, Kuo TK, Singal PK, Huang CY, Kao CL and Kuo CH (2018) Can mesenchymal stem cell lysate reverse aging? Aging 10, 2900–2910.

66 Albersen M, Fandel TM, Lin G, Wang G, Banie L, Lin C and Lue TF (2010) Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. J Sex Med 7, 3331–3340.

67 Parekkadan B, vanPoll D, Suganuma K, Carter EA, Berthiaume F, Tilles AW and Yarmush ML (2007) Mesenchymal stem cell-derived molecules reverse fulminant hepatic failure (MSC-CM reverses FHF). PLoS ONE 2, e941.

68 Jeon D, Chu K, Lee S, Jung K, Ban J, Park D, Yoon H, Jung S, Yang H, Kim BS et al. (2013) Neuroprotective effect of a cell-free extract derived from human adipose stem cells in experimental stroke models. Neurobiol Dis 54, 414–420.

69 Gauthaman K, Fong C, Arularasu S, Subramanian A, Biswas A, Choolani M and Bongso A (2013) Human Wharton’s jelly stem cell conditioned medium and cell-free lysate inhibit human osteosarcoma and mammary carcinoma cell growth in vitro and in xenograft mice. J Cell Biochem 114, 366–377.

70 Chu K, Jeon D, Lee S, Jung K, Lee S and Roh J (2010) A cell-free extract from human adipose stem cells protects mice against epilepsy. Annal Neuro 68, S38.

71 Khubutiya M, Temnov A, Vagabov V, Sklifas A, Rogov K and Zhgutov Y (2015) Effect of conditioned medium and bone marrow stem cell lysate on the course of acetaminophen-induced liver failure. Bull Exp Biol Med 159, 118–123.

72 Mishra P, Mishra P and Banerjee D (2012) Cell-free derivatives from mesenchymal stem cells are effective in wound therapy. World J Stem Cells 4, 35–43.

73 Rajasingh J, Lambers E, Hamada H, Bord E, Thorne T, Goukassian I, Krishnamurthy P, Rosen KM, Ahluwalia D, Zhu Y et al. (2008) Cell-free embryonic stem cell extract-mediated derivation of multi-potent stem cells from NIH3T3 fibroblasts for functional and anatomical ischemic tissue repair. Cir Res 102, e107–e117.

74 Lin H, Fong C, Biswas A, Choolani M and Bongso A (2014) Human Wharton’s jelly stem cells, its conditioned medium and cell-free lysate inhibit the growth of human lymphoma cells. Stem Cell Rev Rep 10, 573–586.

75 Lee C, Hsiao W and Lee O (2017) mesenchymal stem cell-based therapies alleviate high-fat diet-induced obesity. Cytotherapy 19, S224.

76 Shigemoto-Kuroda T, Oh JY, Kim D, Jeong HJ, Park SY, Lee HJ, Park JW, Kim TW, An SY, Prokop DJ et al. (2017) MSC-derived extracellular vesicles attenuate immune responses in two autoimmune murine models: type 1 diabetes and uveoretinitis. Stem Cell Reports 8, 1214–1225.

77 Riaziifar M, Rezza Mohammadi M, Pone EJ, Yeri A, Lässer C, Segaliny AI, McIntyre LL, Vilas Shelke G, Hutchins E, Hamamoto A et al. (2019) Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders. ACS Nano 13, 6670–6688.

78 Hai B, Shigemoto-Kuroda T, Zhao Q, Lee RH and Liu F (2018) Inhibitory effects of iPSC-MSCs and their extracellular vesicles on the onset of sialadenitis in a mouse model of Sjögren’s syndrome. Stem Cells Int 2018, 2092315.

79 Sharma J, Hampton JM, Valiente GR, Wada T, Steigelman H, Young MC, Spurbeck RR, Blazeck AD,
Bösh S, Jarjour WN et al. (2017) Therapeutic development of mesenchymal stem cells or their extracellular vesicles to inhibit autoimmune-mediated inflammatory processes in systemic lupus erythematosus. *Front Immunol* **8**, 526.

Chen Z, Wang H, Xia Y, Yan F and Lu Y (2018) Therapeutic potential of mesenchymal cell-derived miRNA-150-5p-expressing exosomes in rheumatoid arthritis mediated by the modulation of MMP14 and VEGF. *J Immunol* **201**, 2472–2482.