IV Exosomes

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OVERVIEW

With regenerative therapeutics gaining the attention of researchers and clinicians across the world, exosomes have been widely recognized as a potential treatment avenue for a range of degenerative conditions and diseases. Exosomes are small vesicles that are secreted by many different types of cells, making them abundantly available in extracellular fluids. These vesicles were initially viewed as cellular garbage, but in recent years researchers have discovered numerous clinical applications of exosome properties from drug delivery techniques to regenerative therapeutics (1).

Exosomes carry numerous components, such as lipids, proteins, microRNA, and nucleic acids, and deliver this cargo to target cells that subsequently carry out a response based on the contents of the exosome. As such, both exosomes and their contents have the ability to alter cellular communication by influencing factors in tissue microenvironments (1). Exosomes are also able to target specific cells by expressing target-specific surface proteins, so they can be used as tissue-specific delivery systems. This distinctive feature of exosomes has revealed how they may be applicable in drug delivery techniques.

Clinically, exosomes have been demonstrated to have immense therapeutic potential in regenerative medicine. Many clinical studies have shown that exosome injections directly into damaged tissues may elicit cell processes that promote tissue regeneration and repair in patients with osteoarthritis (OA), spinal cord injuries (SCIs), and intervertebral disc degeneration (3-10). Studies have also demonstrated that exosome therapy can also be administered intravenously (exosome infusion) and have indicated promising results in the treatment of peripheral nerve injury, aging-related conditions such as frailty and inflammatory diseases such as COVID-19-induced severe acute respiratory distress syndrome (ARDS), and graft-versus-host disease (11, 12, 13, 14, 15, 18). Currently, there are many clinical trials investigating the role of MSC-derived exosome therapy in treatment of chronic pain conditions, age-related loss of function and diseases, pulmonary infections, lung diseases, ARDS, chronic wounds, dry eye, ischemic stroke, and even psychiatric conditions such as depression and schizophrenia (13, 16, 17, 18).

Regenerative research has mainly focused on exosomes derived from umbilical cord, amniotic fluid, or bone mesenchymal stem cells (MSCs) because these MSC-derived exosomes have the ability to mediate biological function by altering gene expression through release of microRNA-containing exosomal cargo, enhancing the multipotency and self-renewing properties of MSCs (1, 2). For example, MSC-derived exosomes can elicit therapeutic effects by enhancing cellular viability, trophicity, neoangiogenesis, cell proliferation and modulation of immune cells (19, 20). Although the exact mechanisms by which exosome therapy exerts these regenerative processes is not completely understood, the regenerative potential of MSC-derived exosomes is thought to be attributed to their ability to transfer exosomal cargo to recipient cells to induce physiological alterations that favor regeneration (10). Studies examining the role of exosomes in treatment of inflammatory diseases such as OA, rheumatoid arthritis, and chronic regional pain

syndrome have revealed that exosome therapy may improve pain symptoms with fewer side effects by eliciting immunoprotective and anti-inflammatory responses through paracrine action of exosomal cargo (18, 21, 22, 23, 24).

Recently, the contents of exosomal cargo have been widely studied as a novel therapeutic tool for the treatment of myriad diseases. Studies show MSC-derived exosomal cargo contains several growth factors, anti-inflammatory cytokines, miroRNAs, and other bioactive substances (10). Many of the growth factors found in MSC-derived exosomes, such as vascular endothelial growth factor (VEGF), play significant roles in wound healing and tissue regeneration (29,30). Studies have shown that the cytokines found in MSC-derived exosomal cargo have great potential for immunomodulation following injury (29, 33). These cytokines can regulate immune cell behavior and can promote tissue recovery (29, 34). The microRNAs found in MSC-derived exosomes have been demonstrated to have remarkable therapeutic potential in promoting wound healing in myriad tissue types through downstream gene regulation of targets such as hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1) and nerve growth factor (NGF) (29, 30, 31, 32). Interestingly, the substances contained in exosomal cargo not only exert biological effects on surrounding tissue, but the regenerative properties of microRNAs, growth factors, and cytokines synergistically compound, amplifying the therapeutic effects of exosome therapy (29).

EXOSOME THERAPY FOR MUSCULOSKELETAL DISEASES

Numerous pre-clinical and clinical trials have demonstrated the promising safety and efficacy of exosome therapy for treatment of various musculoskeletal diseases such as osteoarthritis (OA), complex regional pain syndrome (CRPS), intervertebral disc degeneration (IDD), and peripheral nerve injury (3-10, 22).

OSTEOARTHRITIS

OA is a common chronic degenerative joint disease that presents with symptoms such as joint pain, joint stiffness and loss of joint function (25). Animal models of osteoarthritis have revealed that exosome therapy can induce the migration of and proliferation of chondrocytes, effectively preventing OA from further progressing (26). Pre-clinical data suggests that MSC-derived exosome therapy can effectively relieve pain symptoms of OA, accelerate healing, and promote tissue regeneration (3-6, 21, 25, 27). Further, these studies demonstrate that MSC-derived exosome therapy can significantly protect cartilage from damage and halt the progression of OA (3-6, 21, 25, 27). Recent studies suggest that MSC-derived exosome therapy is a safe and effective therapeutic for OA because the size of exosomes permits efficient migration to target tissues without getting trapped in microvasculature and because exosomal therapy allows for a high concentration of regenerative factors to be directly administered to patients (28, 29). Numerous completed and ongoing clinical trials have indicated the safety and efficacy of intra-articular exosome injection for symptom relief and treatment of knee osteoarthritis (36, 37, 38, 39).

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is a debilitating pain disorder characterized by excessive and prolonged pain and inflammation following injury. As CRPS is particularly difficult to treat due to limited therapeutic options, exosome therapy has emerged as a promising treatment alternative for CRPS patients. Animal models of CRPS have revealed specific microRNA that are altered in the disease which may bear downstream consequences that contribute to symptomatic pain and inflammation (40, 41). These studies suggest that exosome injections may play an immunoprotective role by restoring altered microRNAs and therefore attenuating inflammatory pain (40). Further, studies suggest that treatment with several exosome-derived microRNAs can reduce inflammatory cytokines known to be elevated in CRPS patients (42). Additionally, human studies have revealed that exosome therapy may reduce the likelihood of developing CRPS in patients with fractures (43).

INTERVERTEBRAL DISC DEGENERATION

Intervertebral disc degeneration (IDD) is a common source of low back pain that is caused by various degenerative musculoskeletal disorders. Recent research has suggested that exosome therapy may delay or even prevent IDD occurrence by modulating cell organelle stress and inhibiting disc cell death (44, 45). Further, exosome therapy has been shown to halt the progression of IDD through antioxidant and anti-inflammatory actions (45, 46). MSC-derived exosomes offer a significant opportunity to treat IDD safely and effectively because their cargo supplies degenerating tissue with factors that promote wound healing and tissue regeneration (47). With regard to IDD, exosomes may exert regenerative effects by altering dysregulated gene expression in target cells and by providing target cells with resistance to oxidative stress (48, 49). In vivo studies utilizing MSC-derived exosome therapy have indicated that exosome treatment may alleviate inflammation and promote disc regeneration in IDD animal models (50, 51). At current, a clinical trial is investigating the safety and efficacy of intradiscal exosome injection for patients suffering from chronic low back pain due to IDD (52).

EXOSOME INFUSION THERAPY

As regenerative research continues to expand, many potential clinical applications of exosome therapy have been discovered. Intravenous exosome therapy (exosome infusion) has gained growing interest as a prospective treatment option for a variety of conditions from long-lasting COVID-19 symptoms to unfavorable aging-related processes.

LONG-TERM COVID-19

Exosome infusions have demonstrated immense potential in the treatment of lung-related diseases like pulmonary fibrosis and ARDS. In the wake of the COVID-19 pandemic, the need for effective and safe treatment options for pulmonary fibrosis conditions has become essential. Pulmonary fibrosis is a condition in which the lung tissue becomes inflamed or scarred. There

are many causes of pulmonary fibrosis, such as environmental pollutants, viral infection, and interstitial lung disease. To date, there are no pharmacological or interventional cures for pulmonary fibrosis, and treatment options are limited to the prevention of further lung tissue damage and symptom relief. In addition to pulmonary fibrosis conditions, COVID-19 infection can cause myriad and long-lasting respiratory problems. Severe COVID-19 infection can cause excessive production of pro-inflammatory cytokines that results in further host tissue damage and can contribute to a potentially fatal systemic inflammatory response called a cytokine storm. In COVID-19 patients, cytokine storms can cause acute-respiratory distress syndrome, the most common cause for COVID-19 infection-related morbidity and mortality (56). Recent studies have shown that MSC-derived exosomes can inhibit pro-inflammatory cytokine release, leading to reduced inflammation in pulmonary fibrosis patients (53). Similarly, many preclinical and clinical studies have indicated that exosome infusions can reduce COVID-19 cytokine storm complications like ARDS by exerting anti-inflammatory and immunomodulatory effects (57, 58, 59, 60). This finding is especially exciting because ARDS has been shown to be present in over 90% of patients who have died from COVID-19 (61). Currently, there are over 90 clinical trials investigating how exosome therapy can be used in the treatment of pulmonary fibrosis conditions related to COVID-19.

Further, exosome infusions can provide significant improvement in patients with long-term COVID-19 symptoms. After COVID-19 infection, some patients may present with symptoms that last far longer than the duration of the active viral infection, a condition called long-term COVID-19 or COVID-19 long hauler. These symptoms can include persistent shortness of breath, fatigue, joint pain, brain fog, depression and anxiety (62). In patients with COVID-19 long hauler, exosome infusions can significantly improve respiratory function and oxygen saturation measurements (63). Exosome infusions may improve COVID-19 long hauler symptoms by harnessing the regenerative capacity of exosomal cargo to stimulate tissue regeneration and improve lung function. The intrinsic regenerative properties of exosomal cargo may play a key role in the search for COVID-19 long hauler treatments.

AGE-RELATED CONDITIONS

Additionally, exosome infusions have been a topic of interest in the development of treatment options for age-related conditions such as some cardiovascular diseases, age-related frailty and age-related neurological conditions. Age and cardiovascular risk factors have been demonstrated to reduce host stem cell availability and function, leading to restricted cardiac regeneration in aging populations (64). MSC-derived exosome infusions may have the potential to rejuvenate host stem cells through secretion of exosomal cargo containing microRNAs that promote regeneration processes (64). Further, many age-related conditions are associated with a reduction in specific exosomal contents thought to be involved with multiple biological processes that contribute to the pathogenesis of these diseases. For example, age-related bone frailty is associated with reduced Galectin-3, a signaling molecule involved in bone cell maturation (65). As exosome therapy utilizes exosomes from healthy donors, MSC-derived

exosome infusions have emerged as a potential intervention for age-related bone frailty. In addition to age-related cardiovascular and age-related frailty conditions, exosome dysfunction is also implicated in myriad age-related neurological conditions. Acute ischemic strokes (AIS) account for over 87% of the strokes in the United States (6). AIS occurs when an artery in the brain becomes blocked by a blood clot, and the strongest non-modifiable risk factor for AIS is aging (66). Preclinical data suggests that MSC-derived exosome infusions may promote neurogenesis following AIS (66, 67, 68). Currently, a clinical trial is investigating the safety and efficacy of MSC-derived exosome infusions for AIS patients. The regenerative capacity of exosomal cargo shows immense potential for exosome infusions as future age-related disease treatment options.

CONCLUSION

Regenerative research has only begun to uncover the therapeutic potential of exosome therapy. Exosome therapy is an extremely safe treatment option for myriad conditions ranging from musculoskeletal disorders to chronic pain to long-term COVID-19 symptoms. Further, exosome therapy draws upon the human body's natural processes to stimulate wound healing and promote tissue regeneration and will be central to future developments in regenerative medicine.

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