Mesenchymal Stem Cells Conditioned Media (MSCs-CM): as a Substitute for Mesenchymal Stem Cells Therapy

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Abstract:

Background: According to recent research, the paracrine substances produced by mesenchymal stem cells (MSCs) appear to be the primary element responsible for the therapeutic action reported in these cells. MSC-CM, also known as the secretome of MSCs, is a rich source of paracrine factors and is being extensively studied for a variety of regenerative therapies, including wound healing and metabolic disorders.

Aim of the work: The current review provides the evaluation of Mesenchymal stem cells conditioned media outlining its clinical applications as well as its mechanism of action.

Conclusion: In summary, researchers have frequently emphasized the significance of Mesenchymal stem cells conditioned media administration as a new line for treating various diseases.

Keywords: Mesenchymal stem cells (MSCs); Mesenchymal stem cells conditioned media (MSCs-CM); metabolic disorders.

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Introduction:

The body frequently is unable to heal a damaged organ on its own. Tissue regeneration is therefore utilizing the latest developments in tissue engineering and regenerative medicine. The fields of regenerative medicine use scaffolds, growth factors, and stem cells. Stem cells

regenerate cellular microniches in the damaged organ, which leads to tissue regeneration **(Gunawardena et al., 2019)**.

MSCs:

MSCs live in the bone marrow stroma. Additionally, MSCs have been isolated from epidermis, adipose tissue, cord blood and vessel wall **(Gnecchi and Melo, 2009).** Stem cells have the unique ability to differentiate into a variety of specialized cells throughout the body. As a type of healing mechanism for the body, they may potentially divide indefinitely to replenish other cells as long as the person or animal is alive. When a stem cell splits, each new cell has the ability to either survive as a stem cell or become another type of cell with a more specialized purpose, such as a muscle cell, red blood cell, or brain cell **(Sandhaanam et al., 2013).**

MSCs immunomodulatory effect:

MSCs move to areas of injury, drawn by chemotactic signals generated by injured tissues. They influence cell survival and proliferation by secreting soluble substances and modulating the local and systemic immune response through interactions with both myeloid and lymphoid cells of the innate and adaptive immune systems. Although the processes by which MSCs influence and affect the immune response are still unknown, it is now obvious that the release of soluble factors, extracellular vesicles, and exosomes is behind their immunomodulatory function **(Alvites et al., 2022)**.

MSCs limitations:

However, several investigations have raised safety concerns about the use of in vitro grown MSCs. The expansion of cells outside their natural environment is thought to increase the risk of genomic instability or altered differentiation potential, and it may be associated with serious side effects such as tumors, teratomas, and severe immune reactions, possibly due to a lack of counter-immune surveillance and the influence of various culture induction factors **(Ntege et al., 2020).**

MSCs-CM:

Recently, evidence has emerged supporting the efficacy of MSC-conditioned medium (CM) or secretome in research aimed at determining its therapeutic potential for conditions such as osteoarthritis, spinal cord injury, cardiovascular illness, gastric mucosal damage, and colitis. MSC-CM includes a profusion of cytokines and a diverse range of bioactive substances released by MSCs. Characterization of the MSC-CM is critical since its therapeutic potential has been linked to cytokine combinations and their associated paracrine actions. Molecular analysis of the MSC-CM can reveal crucial therapeutically active components that can be further isolated and used **(Kumar et al., 2019)**.

Although both cell-based and cell-free treatments produced good outcomes, histopathological examination in the cell therapy-based technique yielded better findings. It might be owing to cell injection and the resulting extensive changes and regulation. However,

due to a paucity of cells following MSC-CM injection, we may require longer time to accomplish optimal tissue healing, which may be solved by increasing the number of injections or even the amount of MSC-CM **(Heidari et al., 2018)**.

Secretome may be more efficient than cell administration in terms of manufacture, storage, and handling . The use of MSC-CM reduces some safety problems associated with the transplantation of live cells, such as immunological compatibility, emboli formation, tumorigenicity, and infection transmission **(Sendon-Lago et al., 2021).**

MSCs-CM components:

Numerous protective bioactive compounds (secretome) including hormones, growth factors (GFs), lipid mediators, cytokines, chemokines, cell adhesion molecules, interleukin (IL), exosomes, microvesicles, and others are known to be produced by MSCs. Because these factors have paracrine actions that promote cell-to-cell contact, they have been recognized as important participants in tissue repair and regeneration. Collectively referred to as the secretome or conditioned media (CM), these released chemicals play a crucial part in regulating the interactions between neighboring tissues and cells in order to facilitate biological processes **(SMOLINSKÁ et al., 2023).**

Growth factors and cytokines such as basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), Macrophage Stimulating Protein (MSP), and insulin-like growth factor 1 (IGF-1) are present in the conditioned media generated from stem cells. These growth factors and cytokines are involved in angiogenesis and cell regeneration **(Noverina et al., 2019).**

MSCs-CM clinical applications:

Because MSCs have the ability to both secrete neurotrophic and anti-apoptotic proteins, which protect neurons from ischemia-induced damage and death, as well as modulate immunological responses, they can be neuroprotective. Exosomes, extracellular vesicles, and MSC-conditioned media are strongly linked to the therapeutic actions of MSCs in a variety of clinical states, such as inflammatory, degenerative, and ischemic disorders. Microglia damage and apoptosis were greatly reduced by CM, which also encouraged the microglia's anti-inflammatory effect **(Yu et al., 2021)**.

Numerous research have examined the potential advantages of using MSC-conditioned media in various disease models, since they have the capacity to regenerate cardiac, neuronal, and osteogenic cells **(Rajan et al., 2016)**.

In order to improve the poor wound-healing conditions, MSC-CM has the potential to be a safe and effective therapeutic modality for the development of cell-free regenerative strategies that can eliminate reactive oxygen species , and restore the proliferation and migration of keratinocytes **(Li et al., 2015).**

MSC-CM improves psoriasis vulgaris. MSC-CM is anticipated to include a diverse spectrum of cytokines and growth factors that can act directly on resident skin cells and hence aid in skin regeneration **(Seetharaman et al., 2019).**

MSC-CM administration significantly reduced hyperalgesia and edema during both acute and chronic phases of Complete Freund's adjuvant (CFA) induced arthritis. This was aligned with a reduction of serum levels of tumor necrosis factor-alpha (TNF-α) and spinal Nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) **(Nazemian et al., 2018).**

MSCs-CM mechanisms of action:

At the moment, it is unknown how MSCs' paracrine actions contribute to their therapeutic benefits. It has been proposed that paracrine factors may mediate regeneration by activating and recruiting resident/circulating stem cells and progenitor cells to the site of injury, where they collaborate to repair damaged tissues **(Shen et al., 2015)**.

Furthermore, the media could be involved in apoptosis prevention. The observation of a decrease in pro-apoptotic gene expression and an increase in anti-apoptotic gene expression validated conditioned media's anti-apoptotic action. More precisely, it was shown that it had increased the anti-apoptotic gene Bcl2, suggesting that it has anti-apoptotic properties. After oxidative damage to cells lowers the potential of the mitochondrial membrane, chemicals that promote apoptosis are released from the intermembrane gap into the cytoplasm, activating the caspase signaling cascade (caspase 3 is an enzyme that executes apoptosis which was found to be down regulated by the media) **(Ra et al. 2021)**.

MSCs-CM role in metabolic disorders:

Tan et al., (2021) reported that human adipose mesenchymal stem cells conditioned media (hAMSCs-CM) alleviated hepatic steatosis, reduced weight gain, improved insulin sensitivity, and increased energy expenditure in HFD-induced metabolic disorders. Furthermore, the anti-obesity effects of hAMSCs-CM in HFD-induced obese mice was due to their prevention of adipogenesis, improvements in glucose metabolism and glycogen production, and anti-inflammatory properties.

Human Wharton's jelly mesenchymal stem cells hWJ-MSCs-CM might regain glycemic control by improving pancreatic function. Without the issues associated with cell treatment, CM therapy can improve renal function by adjusting microalbuminuria, creatinine levels, and GFR, as well as liver function by controlling hepatic enzyme activity in diabetic rats **(Karimi et al., 2024).**

An increasing number of studies have indicated a link between aberrant miRNA expression and hepatocyte damage. Conditioned medium from human umbilical cord blood mesenchymal stem cells (UCB-MSC-CM) is important in cell healing because it regulates

miRNA expression and alters the cell environment. UCB-MSC-CM protected hepatocytes from oxidative damage by regulating proliferation, apoptosis, and inflammation.
(Ma et al., 2021)

Renal artery injection of human umbilical cord mesenchymal stem cells (hUC-MSCs) condition medium decreased inflammation, oxidative stress, and collagen deposition, reduced renal interstitial fibrosis, promoted tubular epithelial cell proliferation, and inhibited apoptosis. These findings suggest a viable way in treating renal fibrosis and chronic kidney diseases **(liu et al., 2018).**

Human MSC-CM demonstrated anti-fibrotic effects in a mouse model of intestinal fibrosis. The key mechanisms behind these effects appear to be due to the reduction of collagen production and downregulation of α-SMA expression **(Choi et al., 2024).**

A conditioned secretome of adipose-derived stem cells may block the manufacture of pro-inflammatory cytokines in colon tissue, lowering blood interleukin 6 (IL-6 levels). The successful inhibition of proinflammatory cytokines in colon tissue and serum may primarily contribute to the repair of injured colon tissue in a dextran sulfate sodium-induced acute colitis model **(Lee et al., 2021).**

Conclusion: To sum up, specialists have repeatedly underlined the usage of Mesenchymal stem cells conditioned media (MSCs-CM) as a treatment against a range of illnesses instead of MSCs itself. MSCs-CM could exert their action through the antiapoptotic and antioxidant effects. Research indicates that MSCs-CM is beneficial for treating metabolic disorders.

Recommendations:

On the light of the information provided by the current review, Mesenchymal stem cells conditioned media (MSCs-CM) can be used as a prophylactic treatment against various diseases. Further studies are needed for assessment of the mechanisms of action, role and applications of MSCs-CM.

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