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MODERN PERSPECTIVES ON CELL THERAPY USING EXOSOMES IN EXPERIMENTAL TRAUMATIC BRAIN INJURY

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Abstract

Traumatic brain injury (TBI) remains one of the leading causes of mortality and long-term disability worldwide, particularly among young and working-age populations. Despite significant advances in neurocritical care and neurosurgical techniques, effective therapeutic strategies aimed at promoting neural repair and preventing the secondary systemic consequences of TBI remain limited. This review provides a comprehensive overview of current experimental approaches to cell-based therapy for TBI, with particular emphasis on mesenchymal stem cells (MSCs) and MSC-derived exosomes. The pathophysiology of TBI involves primary mechanical injury followed by a complex cascade of secondary pathological events, including neuroinflammation, hypoxia, oxidative stress, and disturbances in cerebral microcirculation. Microglial activation is considered a key driver of secondary brain injury, contributing to sustained neuroinflammatory responses and subsequent neurodegenerative changes. Although endogenous regenerative mechanisms, including activation of neural stem cells and the release of neurotrophic factors, are initiated following injury, they are insufficient

to achieve complete functional recovery. MSCs have demonstrated considerable therapeutic potential owing to their ability to home to injured tissues, modulate inflammatory responses, and promote neuroregeneration. More recently, increasing attention has focused on MSC-derived exosomes, which represent a promising cell-free therapeutic alternative with several favorable characteristics, including low immunogenicity, high stability, and the capacity to cross the blood–brain barrier. Experimental studies have demonstrated that exosomes transfer bioactive molecules, including RNAs and proteins, to recipient cells, thereby modulating gene expression and promoting functional recovery. In conclusion, MSC-derived exosomes represent a promising and rapidly evolving therapeutic strategy for the treatment of TBI and its systemic consequences. Nevertheless, further experimental studies are required to elucidate their mechanisms of action, biodistribution, and interactions with target cells in both the central nervous system and peripheral organs.

Key words: traumatic brain injury; cell therapy; mesenchymal stem cells; exosomes; neuroinflammation; neuroregeneration; microglia; blood–brain barrier; experimental models; regenerative medicine.

Traumatic brain injury (TBI) remains one of the most significant challenges in contemporary medicine because of its high prevalence and increasing annual incidence worldwide [1]. Despite substantial advances in medical science and improvements in neurocritical care and neurosurgical management, TBI continues to be associated with high rates of mortality and long-term disability, particularly among young and working-age individuals [2].

According to the World Health Organization (WHO), TBI ranks third among the leading causes of death and disability worldwide, following cardiovascular and oncological diseases [3]. Notably, even mild TBI has been shown to result in persistent cognitive, social, and occupational impairment, leading to reduced work capacity and imposing a substantial medical, social, and economic burden.

TBI pathogenesis is classically divided into two interconnected phases: primary and secondary brain injury [4, 5]. Primary injury occurs immediately following the mechanical insult and is characterized by direct damage to neurons, astrocytes, oligodendrocytes, and other glial cells. These pathological changes result in diffuse axonal injury, disturbances in cerebral blood flow and cerebrospinal fluid circulation, subarachnoid and intraventricular hemorrhages, hydrocephalus, and venous congestion [5-7].

Secondary brain injury develops as an inflammatory response developing in reaction to the primary damage. It has been shown that within the first hours after TBI, secondary injury is

accompanied by hypoxia, hypoxemia, and hypercapnia, resulting in disruption of cerebral oxygen homeostasis. These alterations are subsequently followed by impaired cerebral microcirculation and tissue oxygenation, ultimately leading to ischemic brain injury [7-10].

Accumulating experimental evidence indicates that microglial dysfunction plays a central role in the development of secondary brain injury following TBI. In response to traumatic injury, microglia become activated and maintain a sustained inflammatory and immune response, thereby contributing to persistent neuroinflammation and the subsequent development of epileptogenic and neurodegenerative processes [10, 11]. Neuroinflammation has also been implicated in the pathogenesis of moderate and severe TBI, hypoxic-ischemic brain injury following stroke, chronic infections, and a wide range of neurodegenerative disorders [12, 13].

Microglia are the first resident immune cells of the central nervous system to respond to brain injury and neuroinflammation. Their activation is closely associated with astroglial responses and results in a broad spectrum of phenotypic and functional changes that depend on the nature and severity of the injury. Owing to their remarkable phenotypic plasticity, microglia continuously adapt to alterations within the local neural microenvironment. Consequently, these cells play a dynamic role in regulating neuroinflammatory responses, influencing both tissue repair and the progression of neuronal dysfunction and neurodegeneration [13, 14].

In addition to local pathological alterations within the brain, growing experimental evidence indicates that TBI induces a systemic response affecting multiple organs and physiological systems [15, 15]. These systemic effects are manifested by a wide range of morphological and functional alterations not only at the site of injury but also in peripheral organs. During the acute phase of severe TBI, hepatic and renal dysfunction may develop, accompanied by functional disturbances involving the coronary vasculature and myocardium [17]. Furthermore, experimental studies have demonstrated that even mild TBI induces significant hemodynamic and morphological changes in the liver, myocardium, and kidneys in both sexually mature and immature rats [18].

Concurrently with neuroinflammation, endogenous regenerative mechanisms are activated following TBI. These processes include enhanced angiogenesis and neurogenesis mediated by the proliferation of neural stem cells (NSCs) within the subventricular zone and the hippocampus [18, 19]. Experimental studies in animal models have demonstrated a two- to four-fold increase in the number of stem cells within the ipsilateral subventricular zone compared with the contralateral hemisphere [19]. These findings suggest that activated NSCs migrate toward the injured region and contribute to neuronal and glial repair processes [20].

In parallel, several neurotrophic factors, including brain-derived neurotrophic factor (BDNF), neurotrophins, and interleukin-10, are released and contribute to tissue regeneration. Nevertheless, endogenous NSCs alone are insufficient to achieve complete functional recovery because of the persistent and robust immune-inflammatory response that accompanies TBI [21].

Taken together, the complex pathophysiological mechanisms and considerable clinical burden associated with TBI highlight the urgent need for novel therapeutic strategies aimed at promoting neurological recovery while preventing secondary systemic complications. This need is particularly relevant in mild TBI, which is increasingly recognized as a systemic disorder rather than an isolated brain injury. Consequently, considerable research efforts have been directed toward the development of experimental cell-based therapeutic approaches for TBI.

The aim of the work was to provide a comprehensive overview of current experimental approaches to cell-based therapy for traumatic brain injury, with particular emphasis on mesenchymal stem cells and MSC-derived exosomes.

Various stem cell populations have been investigated for the treatment of TBI, including totipotent stem cells, progenitor cells at different stages of differentiation, fetal and adult brain-derived cells, embryonic neuronal cells, mesenchymal stem cells (MSCs), and endothelial progenitor cells [22, 23]. Among these, MSCs have attracted the greatest attention owing to their favorable biological characteristics and broad therapeutic potential. MSCs can be isolated from multiple tissue sources, including bone marrow, adipose tissue, placenta, umbilical cord, and amniotic membrane, among others [23].

MSC-based therapy has demonstrated considerable promise in regenerative medicine for the treatment of injuries affecting both the central nervous system and peripheral organs, including the heart, kidneys, and liver [24, 25]. Following transplantation, exogenous MSCs exhibit the ability to home to sites of tissue injury, where they interact with cells of the brain parenchyma. These cells suppress the expression of axonal growth inhibitory molecules while stimulating the production of neurotrophic and plasticity-associated factors that enhance neurite outgrowth, promote neuroregeneration, and facilitate functional neurological recovery following brain injury [25].

Experimental studies have demonstrated that MSC administration via different routes, including intra-arterial, intravenous, and intracerebral delivery, produces beneficial therapeutic effects following TBI [26]. Interestingly, the distribution of transplanted MSCs within the brain is influenced by the route of administration. Following intracerebroventricular transplantation, MSCs migrate predominantly toward the lesion border zone, including the ipsilateral brain

parenchyma and hippocampus [25, 26], whereas relatively few cells are detected within the contralateral hemisphere [27]. In contrast, intravenously administered MSCs exhibit a broader biodistribution and migrate not only to the injured brain but also to peripheral organs, including the heart, lungs, liver, kidneys, and spleen [27, 28].

Recent studies have demonstrated that MSCs, similar to other stem cell populations, actively synthesize and secrete large numbers of exosomes into the extracellular environment [29–31]. Exosomes are nanosized membrane-bound extracellular vesicles, approximately 30–100 nm in diameter, that are released by virtually all cell types. They contain a diverse cargo of bioactive molecules, including messenger RNA (mRNA), microRNA (miRNA), and proteins, which participate in intercellular communication under both physiological and pathological conditions [30]. MSC-derived exosomes exhibit several favorable biological characteristics, including low immunogenicity, prolonged stability in the peripheral circulation, and the ability to cross the blood–brain barrier [29, 30]. Consequently, intravenous administration of MSC-derived exosomes has demonstrated promising therapeutic effects in experimental TBI as well as in models of internal organ injury [31].

Experimental evidence indicates that exosomes transfer proteins and regulatory RNAs to recipient cells, thereby modulating gene expression through epigenetic mechanisms and altering cellular function. Furthermore, recent studies have demonstrated that MSC-derived exosomes improve cognitive function in experimental models of TBI in both rats and mice [31].

Importantly, exosome-based therapy avoids several potential complications associated with the transplantation of viable proliferating cells. Compared with cell-based therapies, exosomes possess a favorable safety profile, as they are incapable of replication, do not induce microvascular embolism, and can be stored for prolonged periods without significant loss of biological activity [32]. Consequently, elucidating the mechanisms responsible for the regenerative properties of MSC-derived exosomes has become a major focus of current experimental research.

A comprehensive understanding of their therapeutic effects on functional brain recovery, together with their underlying molecular mechanisms, will be essential for the successful development of MSC-derived exosomes as an effective therapeutic strategy for TBI and its associated complications [31, 32].

Thus, based on the available experimental evidence, it can be concluded that intravenous administration of mesenchymal stem cell (MSC)-derived exosomes currently represents one of the most extensively investigated therapeutic approaches for the treatment of TBI. These exosomes promote regenerative processes not only within the injured brain but also in peripheral

organs affected by TBI. However, significant gaps remain in our understanding of the pathogenetic mechanisms underlying exosome transport across the blood–brain barrier, the delivery of their protein and RNA cargo to target parenchymal cells, and their effects on morphological and functional alterations in internal organs following TBI, particularly after mild injury.

A more comprehensive understanding of these mechanisms will not only facilitate the development of effective therapeutic strategies for the treatment of TBI and its systemic consequences but may also contribute to the design of novel preventive approaches in the management of brain trauma. Therefore, further experimental studies aimed at elucidating these fundamental mechanisms are essential for establishing the scientific basis required for the safe and effective clinical translation of MSC-derived exosome therapy for traumatic brain injury.

Conclusions

1. MSC-derived exosomes represent a promising and rapidly evolving therapeutic strategy for the treatment of TBI and its systemic consequences.

2. Further experimental studies are required to elucidate their mechanisms of action, biodistribution, and interactions with target cells in both the central nervous system and peripheral organs.

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