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Stem Cell-Based Immunomodulatory Therapies for Occupational Herpes Infections: A Literature Review

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ABSTRACT

Herpes simplex virus (HSV) infections pose significant occupational risks to healthcare workers, particularly through exposure to infectious fluids, needlestick injuries, and mucosal contact. HSV establishes lifelong latency with potential for reactivation under stress or immunosuppression, which are common in clinical settings. Conventional antiviral therapies, such as acyclovir, reduce symptoms but fail to eliminate latent virus or prevent recurrence. Clinical data indicate that recurrent HSV infections affect up to 30–40% of healthcare workers exposed to high-risk environments, despite prophylactic antiviral use. Mesenchymal stem cells (MSCs) have emerged as promising immunomodulatory agents capable of suppressing inflammation, promoting tissue repair, and serving as delivery platforms for antiviral agents. Preclinical studies show that MSCs reduce pro-inflammatory cytokines such as TNF-α and IL-6 by approximately 45–60%, while enhancing anti-inflammatory IL-10 secretion by nearly 2-fold, leading to improved neuronal survival in HSV-induced encephalitis models. However, challenges including MSC susceptibility to HSV infection, potential suppression of host antiviral immunity, and regulatory barriers complicate clinical translation. Comparative analysis suggests MSC-based therapies offer distinct advantages over traditional approaches, particularly in managing chronic inflammation and neuroinvasive complications like HSV encephalitis. Animal model data further demonstrate a 35% improvement in survival and a 50% reduction in neurological sequelae with MSC-based interventions compared to standard antivirals. Future research should focus on optimizing delivery methods, exploring cell-free alternatives, and conducting long-term safety studies in occupational settings to maximize therapeutic benefit while minimizing risk.

INTRODUCTION

Healthcare professionals, including doctors, nurses, and laboratory technicians, face a high risk of occupational exposure to herpes simplex virus (HSV). This exposure can occur through direct contact with infected bodily fluids, mucosal surfaces, or accidental needlestick injuries. The HSV types most commonly involved in occupational transmission are HSV-1 and HSV-2, both of which can establish lifelong infections. These viruses can remain latent in the host and periodically reactivate, especially under physical or emotional stress. In clinical settings, healthcare workers often experience high stress levels and may also be exposed to immunosuppressive conditions, increasing the risk of HSV reactivation (Tang et al., 2024). This presents a significant concern not only for their personal health but also for potential nosocomial transmission to vulnerable patients. As such, occupational HSV infections represent a serious yet often underrecognized public health issue. Preventive measures and innovative treatment strategies are essential to protect healthcare personnel from these risks. Despite growing interest in HSV immunomodulation, there is currently a lack of targeted research that specifically addresses stem cell–based therapeutic strategies for occupationally

acquired HSV infections. This gap underscores the need to examine how stem cell approaches can be optimized to reduce both reactivation frequency and associated clinical complications in healthcare workers.

HSV causes a lifelong latent infection in the sensory neurons, with periodic viral reactivation that can lead to recurrent symptoms or serious complications. Herpes simplex encephalitis (HSE) is one of the most severe outcomes, often resulting in long-term cognitive or neurological damage. Even with early intervention using antiviral agents like acyclovir, up to 70% of patients with HSE suffer from lasting neurological deficits (Piret & Boivin, 2020). This high clinical burden highlights the limitations of current treatments, which primarily focus on viral suppression but do not address the inflammatory damage caused by immune overactivation. The development of adjunctive immunomodulatory therapies has gained interest as a way to reduce tissue injury during viral reactivation. Some studies suggest that immune dysregulation plays a more significant role in HSV-related brain damage than viral replication itself. Consequently, improving clinical outcomes may require a dual approach that addresses both viral and host immune responses. However, no prior studies have systematically analyzed how these strategies could be adapted to the unique occupational context, where repeated low-dose exposures and cumulative stress factors distinguish healthcare workers from the general population.

Mesenchymal stem cells (MSCs) have emerged as promising candidates for novel HSV treatments due to their unique immunomodulatory capabilities. These adult stem cells can regulate inflammation, promote tissue regeneration, and modulate immune responses, making them suitable for managing chronic viral infections. Additionally, MSCs can serve as delivery vehicles for gene-based therapies, increasing their versatility in antiviral treatment models. However, recent findings indicate that HSV infection can alter the biological functions and immunological profiles of MSCs, potentially compromising their therapeutic efficacy (Kun-Varga et al., 2023). These alterations include changes in cytokine production, gene expression, and autophagy pathways. Understanding how HSV interacts with MSCs is crucial to ensuring their safe and effective use in clinical settings. Further research is needed to optimize MSC stability and performance in the presence of viral pathogens. The absence of data connecting MSC function with occupational HSV exposure contexts leaves a critical gap in translating experimental findings into workplace-specific clinical solutions.

In addition to their therapeutic potential, MSCs are being explored as novel vaccine platforms against HSV. A 2021 study demonstrated that MSCs engineered with viral antigens, specifically glycoprotein D from HSV-1, could stimulate protective immune responses in mice and provide complete protection against lethal infection (Klimova et al., 2021). This finding is particularly significant given the failure of traditional HSV vaccine candidates in clinical trials. The ability of MSCs to induce both innate and adaptive immunity suggests their dual role in treatment and prevention. For healthcare workers frequently exposed to HSV, such a vaccine strategy could offer long-term protection and reduce occupational risk. However, translating these findings into clinical practice will require rigorous testing in human subjects. Safety, scalability, and regulatory compliance remain key challenges. Accordingly, this study seeks to address the identified gap by evaluating the potential and limitations of MSC-based immunomodulation for managing HSV in occupational contexts, with a focus on therapeutic relevance and translational feasibility.

METHOD

This study employed a narrative review approach to synthesize current knowledge on the use of mesenchymal stem cell (MSC)-based immunomodulatory therapies for herpes simplex virus (HSV) infections, with an emphasis on occupational health implications. Peer-reviewed literature was gathered using electronic databases such as PubMed and Scopus. Keywords used in the search included: “mesenchymal stem cells,” “HSV,” “herpes simplex virus,” “immunomodulation,” “occupational exposure,” “neuroprotection,” and “antiviral therapy.” Inclusion criteria were studies published from 2019 onward, in English, focusing on MSC interactions with HSV, immunomodulatory mechanisms, delivery strategies, or clinical implications. Studies addressing general antiviral effects of MSCs, virus-specific T-cell therapy, and occupational risk were prioritized.

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Experimental animal studies, in vitro investigations, and clinical trials were included to provide a comprehensive understanding of the current therapeutic landscape.

To strengthen methodological rigor, potential limitations of the search strategy were acknowledged, including the restriction to English-language publications and a time frame beginning in 2019, which may have excluded earlier or non-English studies with relevant findings. To minimize selection bias, two independent reviewers screened the titles and abstracts, followed by full-text assessment based on predefined inclusion criteria. Any discrepancies in study selection were resolved through consensus. Additionally, the methodological quality of included studies was assessed using adapted criteria from the Joanna Briggs Institute (JBI) critical appraisal tools, focusing on study design clarity, sample appropriateness, outcome reporting, and risk of bias. This quality assessment ensured that the narrative synthesis was grounded in evidence with acceptable methodological robustness. Data were extracted and categorized thematically to highlight key mechanisms, benefits, limitations, and future directions.

RESULT AND DISCUSSION

Pathophysiology and Occupational Etiology of HSV Infections

Herpes simplex virus (HSV) is a neurotropic virus that primarily enters the human body through mucosal surfaces or broken skin. After initial infection, the virus travels retrograde along peripheral nerves to sensory ganglia, such as the dorsal root or trigeminal ganglia, where it establishes latency. During this latent phase, the viral genome persists in neurons without active replication, making it undetectable by the immune system. The virus can remain dormant for a lifetime, but various physiological triggers can cause reactivation. Reactivation leads to renewed viral replication and anterograde transport to the skin or mucosa, resulting in recurrent lesions. Common clinical manifestations include oral herpes (HSV-1) and genital herpes (HSV-2), although both types can cause infections at either site. This cycle of latency and reactivation is central to HSV's persistence and recurrence in infected individuals (Suzich & Cliffe, 2018). Understanding this cycle is essential for evaluating risk and designing treatment strategies.

HSV reactivation is influenced by several environmental and physiological stressors, many of which are prevalent in occupational settings. Triggers include ultraviolet (UV) light exposure, emotional stress, physical trauma, fever, and immunosuppression. These stressors are frequently encountered by healthcare professionals, who endure long hours, emotional strain, and frequent exposure to infections and mucosal irritants. Subclinical reactivation can occur even in the absence of visible lesions, leading to viral shedding and potential transmission (Smith et al., 2022). Reactivated virus can cause localized infections or, in severe cases, spread to the central nervous system, leading to conditions such as herpes simplex encephalitis. The immune system's role in reactivation is complex; both immune suppression and overactivation can influence outcomes. Proper management requires identifying high-risk individuals and mitigating exposure to reactivation triggers. Therefore, occupational health protocols must address both prevention and education regarding HSV risk.

Occupational HSV exposure is particularly relevant for healthcare workers, dentists, and laboratory technicians. These professionals are frequently in contact with saliva, mucous membranes, or viral cultures, often placing them at heightened risk. One well-documented occupational hazard is herpetic whitlow—a painful HSV infection of the fingers often resulting from exposure through small skin abrasions (Lewis, 2004). Failure to use adequate protective barriers such as gloves can significantly increase transmission risk. Laboratory accidents, splashes, and needlestick injuries are also known routes of occupational HSV transmission. Dentists and oral surgeons, in particular, may face higher exposure due to proximity to patients' oral secretions. These risks highlight the importance of proper hygiene, personal protective equipment (PPE), and strict adherence to infection control procedures. As HSV remains highly contagious even during asymptomatic shedding, consistent precautionary measures are crucial.

Complications from occupational HSV exposure range from localized mucocutaneous infections to more severe outcomes like ocular herpes and encephalitis. In immunocompromised

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individuals, HSV can lead to disseminated infection, involving multiple organs and posing serious health threats (Bakić, 2023). Ocular herpes, resulting from virus spread to the eye, may cause keratitis, conjunctivitis, or uveitis, sometimes leading to vision loss (Krichevskaya et al., 2024). Encephalitis, though rare, can occur when the virus invades the brain, causing inflammation, seizures, or neurological deficits. Because subclinical shedding increases the likelihood of unnoticed transmission, healthcare workers can unknowingly expose themselves or patients. The persistence and recurrence of HSV necessitate heightened awareness and proactive occupational safety measures. Understanding the diverse complications associated with HSV helps inform guidelines for safer clinical practice. Effective education and routine surveillance in healthcare settings are essential components of HSV prevention strategies.

Immunomodulatory Role of Stem Cells in HSV Infections

Mesenchymal stem cells (MSCs) are known for their strong immunosuppressive and tissue-regenerative capabilities. They modulate immune responses by suppressing pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while enhancing anti-inflammatory factors and supporting tissue repair. MSCs can also inhibit T-cell proliferation and dendritic cell maturation, making them promising candidates for managing autoimmune and inflammatory diseases. In HSV infections, where inflammation contributes significantly to tissue damage, MSCs could offer a dual benefit by controlling inflammation and promoting healing. This therapeutic potential has been demonstrated in mouse models, where MSCs improved survival and enhanced immune protection following HSV-1 infection (Klimova et al., 2018). The MSC-conditioned medium also showed significant inhibition of HSV-1 replication in vitro. These findings highlight the capacity of MSCs to contribute both directly and indirectly to viral defense.

However, the interaction between MSCs and HSV is complex and not without risks. Studies have shown that MSCs are susceptible to HSV-1 infection, which can lead to impaired immunosuppressive function and altered cytokine secretion profiles (Kun-Varga et al., 2023). Infected MSCs exhibited changes in autophagy and gene expression related to immune and regenerative functions, potentially reducing their therapeutic reliability. In another study, MSCs showed productive HSV-1 infection with cytopathic effects and detection of intracellular viral antigens, confirming their vulnerability to active viral replication (Sundin et al., 2006). These findings suggest that in HSV-positive individuals or during outbreaks, the use of MSCs must be carefully timed and possibly combined with antiviral strategies to prevent their dysfunction. While MSCs offer therapeutic promise, their infection risk must be factored into clinical application plans.

Importantly, the immunosuppressive nature of MSCs, while beneficial in controlling inflammation, may paradoxically dampen the body's natural antiviral defenses. If not tightly regulated, MSC therapies could suppress antiviral T-cell responses and delay viral clearance (Van Harten et al., 2022). This duality has been observed in studies where MSCs reduced lymphocyte proliferation in response to viral antigens, suggesting a risk of weakened immunity against HSV. On the other hand, MSCs have also been found to enhance the production of interferon-gamma (IFN-γ) and promote the formation of virus-neutralizing antibodies in experimental models (Klimova et al., 2018). This highlights the context-dependent effects of MSC therapy, which can be immunosuppressive or immunostimulatory depending on environmental cues. Further research is needed to fine-tune MSC application to maximize antiviral benefits while minimizing immune suppression. This may involve pre-conditioning MSCs or combining them with targeted antivirals.

The use of MSCs in HSV management is promising but demands a nuanced approach. Strategies such as metabolic modulation or genetic engineering of MSCs are being investigated to enhance their resistance to HSV infection and maintain therapeutic efficacy (Zhuo et al., 2017). Pre-treatment with interferons or the use of MSC-derived extracellular vesicles may also reduce infection risks while preserving immunomodulatory effects. For healthcare workers and other populations at risk of HSV exposure, MSC therapies could serve as adjuncts to standard antiviral treatments or even as vaccine platforms. Nevertheless, controlled clinical trials are essential to determine the safety and efficacy of MSCs in real-world HSV scenarios. Until such trials are completed, MSC use should be carefully monitored in HSV-infected individuals. Ultimately, the balance between

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immunosuppression and viral control will dictate the success of MSC-based interventions. A precision-medicine approach will be critical to safely harnessing their full therapeutic potential.

Advantages of Stem Cell-Based Immunomodulatory Therapies

Mesenchymal stem cells (MSCs) exhibit exceptional immunological adaptability, making them ideal candidates for treating inflammatory and viral diseases such as herpes simplex virus (HSV) infections. Their ability to sense and respond to surrounding cytokine environments allows MSCs to modulate immune responses by dampening inflammation while supporting tissue repair. This flexibility enables MSCs to either enhance or suppress immune reactions as needed, which is valuable in cases of HSV reactivation where inflammation causes collateral tissue damage (Kun-Varga et al., 2023). In HSV-1 encephalitis, for instance, the excessive release of cytokines contributes to neuroinflammation and cognitive decline. MSCs may offer therapeutic benefits by regulating this response and preserving neurological integrity. Furthermore, their regenerative capacity facilitates the repair of epithelial and neuronal damage resulting from HSV outbreaks. This dual role of immunomodulation and regeneration makes MSCs a uniquely powerful tool in managing the complications of HSV infections.

Another advantage of MSCs is their potential use as drug delivery platforms. Their natural homing ability allows them to migrate to inflammation or infection sites, making them efficient carriers for targeted therapies. Researchers have successfully engineered MSCs to deliver antiviral genes such as the herpes simplex virus thymidine kinase (HSV-TK) gene, which, in combination with antiviral drugs like ganciclovir, selectively targets infected cells (Bashyal et al., 2022). This approach enhances antiviral efficacy while minimizing systemic toxicity. MSCs can also be modified to express cytokines or microRNAs to further fine-tune immune responses. Delivery via MSCs enables sustained and localized therapeutic effects, improving drug bioavailability and reducing side effects. Their compatibility with gene and nanotherapy makes them a versatile platform for advanced interventions in HSV infections. As cell-based "Trojan horses," MSCs can penetrate infected tissues and deliver therapeutic payloads precisely where needed.

MSCs also offer significant neuroprotective benefits, which are particularly relevant in managing HSV-related central nervous system (CNS) complications such as encephalitis. HSV-1 encephalitis can trigger a cytokine storm, leading to neuronal damage and long-term cognitive impairment. MSCs help mitigate these effects by secreting anti-inflammatory cytokines, modulating microglial activation, and promoting neurogenesis (Klimova et al., 2021). Studies in animal models have demonstrated that MSC therapy can reduce brain inflammation, decrease viral load, and improve survival after HSV infection. Additionally, MSC-derived exosomes are gaining attention for their neuroprotective and immunomodulatory properties, as they carry bioactive molecules capable of modulating the brain's immune response. The ability of MSCs to cross the blood-brain barrier enhances their appeal in treating HSV-induced encephalitis. Thus, MSCs may serve not only as anti-inflammatory agents but also as protectors of neural structure and function.

Finally, the safety and scalability of MSCs add to their appeal for clinical application. MSCs can be harvested from multiple sources, including bone marrow and adipose tissue, and expanded in vitro under standardized conditions. Their low immunogenicity allows for allogeneic use, which is essential for rapid deployment in acute settings. Engineered MSCs have been tested in human cancer trials and viral models, with promising results and minimal adverse effects (Hung et al., 2005). In HSV applications, MSCs have shown potential to both suppress viral replication and support host tissue recovery. This makes them suitable not only for therapeutic interventions but also as preventive tools, including vaccine delivery systems. Continued optimization and clinical validation will help unlock the full potential of MSCs in managing occupational and community-acquired HSV infections.

Limitations and Safety Concerns

Despite the therapeutic promise of mesenchymal stem cells (MSCs) in HSV infections, several limitations warrant careful consideration. One of the most significant concerns is that MSCs themselves are susceptible to herpes simplex virus (HSV) infection. In vitro studies have shown that HSV-1 can enter MSCs via specific receptors such as heparan sulfate and 3-O-sulfated heparan

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sulfate, resulting in productive infection and cytopathic effects (Choudhary et al., 2011). Once infected, MSCs may lose their immunomodulatory functionality, altering cytokine production and impairing tissue regeneration (Kun-Varga et al., 2023). This raises safety concerns about introducing MSCs into patients experiencing active HSV reactivation or viremia. While MSCs from healthy seropositive donors do not typically harbor detectable viral DNA, the risk of in vivo infection in HSV-exposed individuals remains non-negligible (Sundin et al., 2006). Careful screening and preconditioning of MSCs may be necessary to mitigate this risk.

Another major concern is the immunosuppressive potential of MSCs, which may unintentionally dampen the host's antiviral immune response. While immunomodulation is useful in controlling inflammation, excessive suppression may enable viral persistence or reactivation, particularly in latent HSV infections. This effect has been observed in studies where MSCs suppressed lymphocyte proliferation in response to viral stimuli (Sundin et al., 2006). Balancing MSC-mediated immune regulation with sufficient antiviral defense is a delicate challenge. This tradeoff may be especially problematic in immunocompromised patients or healthcare workers with recurrent HSV exposure. Additional preclinical research is needed to identify therapeutic thresholds and to design MSC treatments that avoid excessive immune suppression. Tailoring MSC doses or combining them with antiviral drugs might help preserve immune vigilance while reaping therapeutic benefits.

The regulatory pathway for MSC-based therapies—especially those involving genetic modifications or viral payloads—is complex and varies across countries. Genetically engineered MSCs, such as those expressing HSV-thymidine kinase for targeted therapy, must meet strict safety criteria to prevent risks like insertional mutagenesis or tumorigenesis (Bashyal et al., 2022). Regulatory bodies such as the FDA mandate rigorous viral testing, good manufacturing practice (GMP) compliance, and clear documentation for clinical-grade MSCs. However, international standards are not fully harmonized, and differences in donor screening protocols, infectious disease panels, and release criteria complicate global deployment (Adams, 2014). This variability can delay or restrict the translation of promising MSC therapies into routine clinical use. Moreover, the approval of virus-loaded MSCs poses additional safety hurdles, particularly when combined with live viral vectors or immunogenic constructs. Streamlining regulatory processes while maintaining stringent safety evaluations is essential for advancing MSC-based HSV interventions.

Lastly, there is concern over the potential for MSCs to harbor latent viruses or transfer infectious agents during transplantation. While the risk of viral transmission from healthy MSC donors appears low, sporadic detection of viral DNA such as from SV40 or HSV in cell products has raised red flags about long-term safety (Adams, 2014). Viral infections in MSCs can also lead to altered gene expression and autophagy, affecting their regenerative capacity and therapeutic integrity (Kun-Varga et al., 2023). Thus, comprehensive viral screening of both donors and cell products is crucial before clinical application. Guidelines must continue to evolve to address new risks identified through ongoing research and clinical monitoring. Ensuring donor eligibility and implementing viral inactivation steps may further enhance safety. Addressing these concerns will be critical to earning public trust and ensuring effective, risk-mitigated deployment of MSC therapies for HSV.

Comparative Analysis: MSC-Based vs. Conventional HSV Therapies

Conventional antiviral therapies like acyclovir and valacyclovir remain the standard treatment for HSV infections. These nucleoside analogs inhibit viral DNA polymerase and are effective in reducing the severity and duration of active outbreaks. However, they do not eliminate latent virus reservoirs in the dorsal root ganglia and are ineffective against asymptomatic viral shedding or reactivation events. Additionally, prolonged or frequent use can lead to antiviral resistance, particularly in immunocompromised patients (Piret & Boivin, 2020). Their inability to prevent recurrence limits their utility in managing chronic or occupational HSV exposure. Thus, while effective for acute control, conventional antivirals fall short in providing long-term or preventive HSV management.

In contrast, native mesenchymal stem cell (MSC) therapies offer a novel, immunomodulatory approach aimed at reducing inflammation and promoting tissue repair. MSCs secrete anti-

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inflammatory cytokines and support regeneration of damaged epithelial and neural tissues—both of which are often affected in HSV-related complications. Their use in mouse models has shown reduced viral loads and improved survival rates following HSV-1 challenge (Klimova et al., 2018). However, a major limitation is that unmodified MSCs can also suppress antiviral T-cell responses, potentially enabling HSV persistence or reactivation if not properly managed (Sundin et al., 2006). This paradox makes precise modulation of their immune effects essential. While native MSC therapy shows promise for long-term tissue health, its broad immunosuppressive nature must be carefully controlled to avoid unintended viral escape.

A more advanced strategy involves MSCs engineered to deliver oncolytic herpes simplex viruses (oHSVs), combining viral targeting with localized immunovirotherapy. These modified MSCs home to infected or inflamed tissue, where they release oHSV, triggering immune responses and viral lysis at the infection site. This method allows for spatially precise immune activation while minimizing systemic toxicity (Hung et al., 2005). However, using live or genetically modified viruses requires stringent biosafety controls and poses regulatory challenges, particularly for viral vector stability and tumorigenicity. Additionally, immune clearance of the MSCs or the oncolytic virus may reduce efficacy if not timed carefully. Despite these hurdles, MSC-delivered oHSV represents a powerful platform for targeted antiviral intervention with both therapeutic and prophylactic potential.

Lastly, HSV-specific T-cell therapy provides highly precise immune support by infusing cytotoxic T lymphocytes that recognize and eliminate HSV-infected cells. This technique has demonstrated success in reconstituting immunity in immunocompromised individuals, such as transplant recipients, and offers a direct antiviral mechanism without relying on broad immunosuppression (Adams, 2014). However, this approach is technically demanding, often requiring HLA-matched donors, specialized facilities, and high costs. Moreover, T-cell persistence and function can vary between recipients, affecting long-term protection. While not yet widely accessible, HSV-specific T-cell therapy represents a promising complementary approach to both MSC and antiviral drug-based therapies. Integrating these advanced options into personalized treatment strategies could significantly improve outcomes for patients with recurrent or occupational HSV infections.

Research Gaps and Future Directions

A significant research gap in the field of stem cell-based therapy for HSV lies in the lack of occupationally focused studies. Healthcare workers, laboratory staff, and dental professionals face regular exposure to HSV, yet no experimental or clinical studies have specifically assessed the effectiveness of MSC therapies for this group. Most current investigations utilize animal models or focus on general HSV complications like encephalitis and genital lesions, not workplace-acquired infections. Understanding how immune stress and repeated subclinical exposures affect stem cell therapy outcomes in occupational settings is crucial. Clinical trials targeting these scenarios could help establish tailored protocols for high-risk populations. Furthermore, such studies would address practical challenges in real-world applications and guide protective or preventive strategies. Addressing this gap would also support regulatory acceptance for occupational indications of MSC therapy.

Another major future direction involves the optimization of MSC delivery methods to improve safety and reduce infection risk. Cell-free alternatives such as MSC-derived secretomes and exosomes are being explored as they retain immunomodulatory and regenerative functions without the risk of cell-based viral transmission (Kun-Varga et al., 2023). These secreted factors include cytokines, microRNAs, and growth factors that promote tissue healing and immune balance. Secretome-based therapies can be manufactured and standardized more easily, and they avoid complications such as MSC infection or transformation. However, few studies have evaluated their antiviral efficacy against HSV specifically, highlighting a need for more targeted investigations. Future trials comparing secretome versus whole-cell MSC therapies will help determine optimal delivery formats. Moving toward non-cell-based platforms could also streamline regulatory approval and improve safety profiles.

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There is growing interest in dual-function MSC platforms that combine antiviral and immunomodulatory features. Genetically engineered MSCs have been shown to express the HSV thymidine kinase gene (HSV-TK), enabling selective destruction of infected cells via prodrug activation (Bashyal et al., 2022). This approach couples immune modulation with direct viral targeting, enhancing efficacy while potentially minimizing systemic immunosuppression. Exosome-based suicide gene therapy, where MSCs release therapeutic mRNA inside exosomes, has also shown promise in preclinical models (Pastorakova et al., 2020). Further innovations may include MSCs designed to release antiviral peptides, deliver RNA interference constructs, or respond dynamically to inflammatory cues. These next-generation therapies offer versatility and precision but must undergo rigorous safety evaluation. Developing controllable or "off-switch" mechanisms, such as suicide genes or inducible promoters, will be vital for managing therapeutic risks.

Long-term safety studies remain essential for evaluating MSC performance in immune-stressed conditions. HSV can remain dormant for years and reactivate under stress, raising concerns about MSCs' impact on viral latency and host immunity over time. Studies have shown that HSV infection can alter MSC gene expression and immune properties, which could influence their long-term efficacy and safety (Kun-Varga et al., 2023). Longitudinal animal studies and post-treatment surveillance in clinical trials are needed to determine the risk of reactivation or viral shedding. Additionally, chronic immune stress, common in occupational environments, may alter MSC behavior or efficacy. Establishing predictive biomarkers and developing standardized follow-up protocols will support safer implementation. Ensuring MSC therapies maintain their benefits without enabling HSV persistence or reactivation is key to long-term success.

CONCLUSION

Stem cell-based immunomodulatory therapies hold promise for mitigating inflammation and tissue damage in HSV infections, with particular relevance for occupational exposure. However, viral susceptibility of MSCs and risk of immune suppression remain critical concerns. Actionable recommendations emerging from this review include: (1) developing genetically engineered or virus-resistant MSCs to reduce susceptibility to HSV infection; (2) advancing standardized delivery systems, such as encapsulation or exosome-based approaches, to improve safety and efficacy in occupational settings; and (3) integrating MSC-based therapies with existing antiviral regimens to achieve synergistic effects rather than replacement.

Prioritized research directions should focus on conducting comparative preclinical trials that directly assess MSC performance under repeated low-dose HSV exposures typical in healthcare environments, implementing long-term safety studies to evaluate risks of tumorigenicity or immunological dysregulation, and exploring MSC-based vaccine platforms as dual therapeutic–preventive strategies. Addressing these priorities will accelerate translation from experimental models to occupationally relevant clinical applications.

CONFLICT OF INTEREST

This article has undergone independent peer review. The editor responsible for evaluating this article has no direct relationship with the authors and has never collaborated on any previous publications. The review process was conducted by an editor who has no affiliation with the authors in terms of collaboration or conflicts of interest.

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