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Therapeutic applications of human umbilical cord-derived mesenchymal stem cell secretome in chronic inflammatory diseases and cancer: A recent update

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ABSTRACT

Chronic inflammatory disorders and cancer remain major global health challenges driven by persistent immune activation and tissue damage. The human umbilical cord-derived mesenchymal stem cell (hUC-MSC) secretome has emerged as a promising cell-free therapeutic alternative owing to its potent anti-inflammatory, immunomodulatory, and regenerative properties. Comprising of cytokines, chemokines, growth factors, and extracellular vesicles enriched with bioactive miRNAs, the hUC-MSC secretome exerts its effects primarily through paracrine signaling. For this review, relevant literature was collected from established databases, including ScienceDirect, PubMed, and Google Scholar, using key terms such as "hUC-MSC secretome," "chronic inflammation," "exosomes," "tumor microenvironment," and "preconditioning." The search focused on studies published within the last five years, emphasizing *in vitro* and *in vivo* preclinical studies, original research, and review articles. Only studies specifically exploring hUC-MSC-derived secretomes were included, whereas those addressing cell-based therapies or secretomes from other MSC sources were excluded. Cumulative findings indicate that the hUC-MSC secretome alleviates chronic inflammation by releasing anti-inflammatory cytokines such as IL-10 and TGF-β, as well as regulatory miRNAs such as miR-29a-3p, miR-100-5p, and miR-125b-5p, which act via key signaling pathways including PI3K/AKT, Wnt/β-catenin, and JAK/STAT. These mechanisms collectively mediate anti-inflammatory responses, suppress epithelial-mesenchymal transition, enhance chemosensitivity, and promote tissue repair. This review aims to consolidate the emerging evidence that positions the hUC-MSC secretome as a next-generation cell-free therapeutic strategy for chronic inflammatory diseases, including major cancers, inflammatory bowel disease, rheumatoid arthritis, and neurodegenerative disorders, while highlighting current limitations and strategies to enhance the therapeutic efficacy and clinical applicability of the hUC-MSC secretome.

Abbreviations: hUC-MSC, Human umbilical cord-derived mesenchymal stem cells; EVs, Extracellular vesicles; MVs, Micro-vesicles; ECM, Extracellular matrix; VEGF, Vascular endothelial growth factor; TGF-β, Transforming growth factor-β; FGFs, Fibroblast growth factors; MiRNAs, MicroRNAs; TNF-α, Tumor necrosis factor-alpha; PDGF, platelet-derived growth factor; NF-κB, Nuclear factor kappa B; IFN-γ, Interferon-gamma; TME, Tumor microenvironment; EMT, Epithelial-mesenchymal transition; CRC, Colorectal cancer; IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; Th2, T helper 2 cells; Th17, T helper 17 cells; Treg, Regulatory T cells; RA, Rheumatoid arthritis; TLR4, Toll-like receptor 4.

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1. Introduction

Chronic inflammatory diseases account for over 50 % of all inflammation-driven deaths worldwide and represent a growing public health concern due to their increasing prevalence, morbidity, and mortality (Ansari et al., 2024; Furman et al., 2019). These conditions are characterized by persistent immune activation and unresolved inflammation, which lead to progressive tissue injury and contribute to the development of chronic inflammatory conditions such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), diabetes mellitus, neurodegenerative diseases, and various cancers (Chen et al., 2018; Blagov et al., 2024; Wylezinski et al., 2019). Current treatment strategies, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs), often offer only partial relief and can cause adverse effects such as osteoarthritis, gut ulceration, hepato-renal dysfunction, nausea, and fatigue when used long-term (Rainsford, 1999; Andersen et al., 2019). These limitations highlight the need for novel, safer, and more effective therapeutic strategies. In recent years, regenerative medicine has shifted attention to MSCs as promising candidates owing to their self-renewal capacity, multipotency, and immunomodulatory functions (Mao and Mooney, 2015; Naji et al., 2019; Ullah et al., 2015). MSCs can be isolated from multiple sources, including bone marrow, adipose tissue, and perinatal tissues such as placenta, amniotic membrane, and umbilical cord (Weiss and Dahlke, 2019). Among these, MSCs collected from human umbilical cord are attractive due to their non-invasive collection procedure, ease of isolation, differentiation, and transdifferentiation, and reduced immunogenicity compared to other adult tissue-derived MSCs (Nagamura-Inoue, 2014). However, the clinical application of MSC transplantation remains limited by concerns about tumorigenicity, immune compatibility, infectious transmission, and phenotypic instability during large-scale *in vitro* expansion (Lukomska et al., 2019; Hoang et al., 2022). The therapeutic efficacy of hUC-MSC is mainly mediated by their secretome, which includes cytokines, growth factors, and extracellular vesicles (EVs). The microenvironment influences the secretome composition and can be modulated by stimuli such as inflammatory factors, hypoxia, or 3D culture, enabling MSCs to modulate immunity, restore tissue homeostasis, and promote tissue repair (Tai et al., 2023). Studies show that hUC-MSCs produce considerably higher concentrations of cytokines and growth factors in their conditioned media than bone marrow-derived MSCs, often 10- to 100-fold greater, suggesting a correspondingly enhanced therapeutic potential (Yu. et al., 2019). Comparative proteomic analyses further demonstrate that fetal-derived MSCs, such as those from hUC-MSCs, possess a more diverse secretome profile than adult-derived MSCs, such as those from bone marrow or adipose tissue, implying broader functionality across regenerative and immunomodulatory pathways (Shin et al., 2021). Despite extensive research, the therapeutic potential of the hUC-MSC secretome in chronic inflammatory diseases and cancer remains underexplored, and its dual role in tumor biology and inflammation requires critical evaluation. While several reviews have summarized MSC biology and clinical use, very few have focused specifically on the hUC-MSC-derived secretome, which may offer unique therapeutic advantages over secretomes from other MSC sources. This review highlights recent advances in understanding the composition, mechanisms, and therapeutic applications of hUC-MSC secretome in inflammatory disorders and cancer. Furthermore, this review explores the challenges, enhancement strategies, and future perspectives for the optimization and clinical translation of hUC-MSC-derived secretome. For this review, relevant literature was obtained from PubMed, Google Scholar, and ScienceDirect, with a focus on studies published in the last five years. Only research specifically addressing hUC-MSC-derived secretomes was included, excluding cell-based therapies or secretomes from other sources of MSC.

2. hUC-MSCs and their secretome

hUC-MSCs are multipotent stromal cells isolated primarily from Wharton's jelly, the gelatinous tissue surrounding the umbilical vessels (Kamal and Kassem, 2020). hUC-MSCs have gained increasing attention due to several biological and practical advantages compared to bone marrow-derived MSCs (BM-MSCs) and adipose tissue-derived MSCs (AT-MSCs) (Barbon et al., 2023). hUC-MSCs exhibit low MHC class I and minimal MHC class II and costimulatory molecule expression, thereby reducing their immunogenic profile. This low immunogenicity makes them suitable for allogeneic transplantation, as they cannot effectively activate allogeneic T cells *in vitro* (Machado et al., 2013). The therapeutic potential of hUC-MSCs is primarily mediated through their secretome, a complex repertoire of bioactive molecules, including cytokines, chemokines, growth factors, EVs, proteins, lipids, and non-coding RNAs. The secretome can be divided into a soluble fraction, comprising cytokines such as IL-4, IL-6, IL-10, IFN-γ; chemokines like IL-8, MCP-1, RANTES; growth factors including VEGF, TGF-β, and HGF; proteins (HSP70, HSP90); lipids; and non-coding RNAs, and a vesicular fraction consisting of exosomes, microvesicles (MVs), and apoptotic bodies, as illustrated in Fig. 1 (Drobiova et al., 2023). These bioactive molecules are released into the conditioned medium during hUC-MSC culture, reflecting the paracrine and immunomodulatory potential of MSCs. Comparative proteomic studies indicate that hUC-MSCs secrete a broader and more enriched repertoire of bioactive molecules than adult tissue-derived MSCs, with reduced levels of MMPs and extracellular matrix (ECM) proteins that limit tissue degradation while enhancing chemokine and anti-inflammatory cytokine release (Shin et al., 2021; Arrigoni et al., 2020; Vizoso et al., 2019; Jafarinia et al., 2020). EVs, particularly exosomes, constitute a major functional component of the secretome, serving as nanosized carriers of proteins, lipids, nucleic acids, and metabolites that facilitate intercellular communication (Jafarinia et al., 2020). EVs are also enriched with growth factors, cytokines, and microRNAs, underscoring their central role in driving most of the therapeutic effects attributed to hUC-MSCs (Guo et al., 2022a; Yang et al., 2023; Zhou, 2019). Growth factors represent another critical component of the hUC-MSC secretome, including VEGF, TGF-β, HGF, PDGF, FGFs, EGF, and IGF, which promote angiogenesis, tissue remodeling, and immune modulation (Shi et al., 2018; Yan et al., 2017; Liu et al., 2022). Cytokines and chemokines further define the immunoregulatory profile of the secretome. Anti-inflammatory cytokines such as IL-10 and TGF-β suppress immune overactivation, while chemokines such as MCP-1, IL-8, and RANTES guide immune cell recruitment and angiogenesis, thereby aiding tissue repair. Comparative studies have shown that hUC-MSCs secrete significantly higher levels of IL-6, IL-8, G-CSF, and MCP-1 than MSCs derived from other sources, highlighting their distinctive capacity to modulate inflammatory microenvironments (Xu et al., 2022; Jothimani et al., 2022). Additionally, microRNAs (miRNAs) within hUC-MSC-derived exosomes have emerged as key regulators (Zheng et al., 2025). Jothimani *et al.* (2020) have demonstrated that hUC-MSC exosomes are enriched with miRNAs such as miR-29a-3p, miR-100-5p, miR-125b-5p, miR-143-3p, miR-146a-5p, and Let-7 family members, which regulate inflammation, apoptosis, and oncogenic pathways. Tumor-promoting miRNAs like miR-183-5p, miR-372-3p, and miR-373-3p were absent or minimally expressed, highlighting a favorable therapeutic profile (Jothimani et al., 2022). Within MSC-based therapeutics, both exosome-focused formulations and whole secretome products demonstrate therapeutic promise but differ in composition and functional efficacy. Exosomes provide concentrated and stable delivery of regulatory molecules, enhancing reproducibility, lowering immunogenicity, and enabling targeted delivery of miRNAs, chemotherapeutic agents, or gene-editing molecules to malignant or inflamed cells with minimal off-target toxicity (Drobiova et al., 2023). The whole secretome, in contrast, contains a broader spectrum of soluble factors and vesicular components that synergistically modulate cellular responses, enhancing

anti-inflammatory, tissue regenerative, and immunomodulatory effects. Secretome-based strategies offer a promising cell-free alternative that circumvents risks associated with direct cell transplantation, such as tumorigenicity, immune rejection, and phenotypic instability (Yu. et al., 2019; Vizoso et al., 2017; Pulido-Escribano et al., 2022).

3. Therapeutic mechanisms of hUC-MSC secretome

3.1. Anti-inflammatory and immunomodulatory effects

The hUC-MSC secretome regulates inflammation by coordinating the release of cytokines, chemokines, growth factors, and EV-associated miRNAs. These bioactive factors synergistically suppress excessive immune activation, promoting resolution and tissue repair (Machado et al., 2013). In particular, the secretome promotes M2 macrophage polarization by elevating IL-10, IL-4, and TGF-β, while reducing pro-inflammatory cytokines such as TNF-α, IL-6, IL-2, IL-17, and IL-1β. hUC-MSC secretome also modulates other immune cells by releasing chemokines and upregulating ICAM-1 and VCAM-1, thereby inducing T-cell arrest, apoptosis, or reprogramming (Kuppa et al., 2022; Li et al., 2024; Cruz-Barrera et al., 2020; Su et al., 2023). Cytokines such as IL-10 and TGF-β suppress pro-inflammatory signalling through STAT3-driven anti-inflammatory responses, while chemokines such as MCP-1 and IL-8 regulate leukocyte recruitment to prevent excessive infiltration (Tian et al., 2025; Choi et al., 2024). EVs released from hUC-MSC also play a crucial role in immunomodulation, with miR-21 and miR-146a attenuating TLR/NF-κB signaling by targeting key upstream mediators. This suppression also reduces pro-inflammatory gene expression and drives macrophages towards M2 phenotype (Pei et al., 2023; Hua et al., 2022). Growth factors within the hUC-MSC secretome also significantly contribute to its anti-inflammatory and tissue-protective properties. Tai et al. (2023) reported that TNF-α-primed hUC-MSCs release a secretome enriched in HGF and VEGF, which thereby activate PI3K/AKT, ERK, and eNOS pathways to enhance cell survival, stabilise endothelial function, and limit inflammatory tissue damage (Tai et al., 2023). Despite substantial insights into the secretome that mediate the anti-inflammatory and immunomodulatory actions, current evidence remains limited in explaining how these components function together within the dynamic inflammatory or tumor microenvironment (TME). However, a precise understanding of the mechanisms, including dosing, pathway crosstalk, and the potential for dual effects, remains a significant gap in current evidence (Vizoso et al., 2017).

3.2. Anti-tumor effects

The hUC-MSC secretome has emerged as a promising anti-cancer

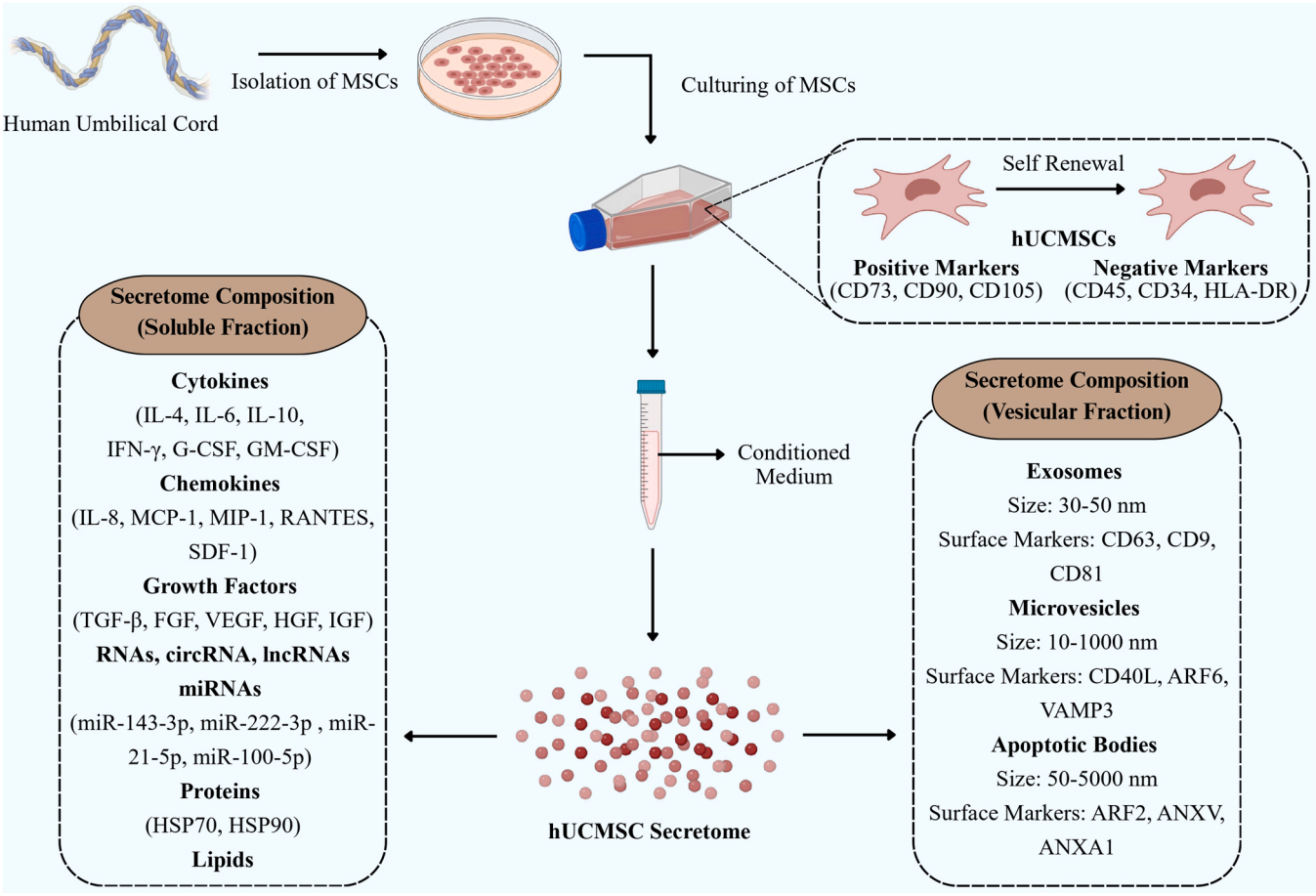

Fig. 1. Isolation, culture, and secretome composition of human umbilical cord mesenchymal stem cells (hUC-MSCs). Human MSCs can be isolated from the Wharton's jelly of the umbilical cord and expanded *in vitro*. hUC-MSCs are positive for CD73, CD90, and CD105, while negative for CD34, CD45, and HLA-DR. The hUC-MSC secretome, collected from conditioned medium, is divided into soluble and vesicular fractions. The soluble fraction contains cytokines (IL-4, IL-6, IL-10, IFN-γ, G-CSF, GM-CSF), chemokines (IL-8, MCP-1, MIP-1, RANTES, SDF-1), growth factors (TGF-β, FGF, VEGF, HGF, IGF), RNAs (circRNAs, lncRNAs), miRNAs (miR-143-3p, miR-222-3p, miR-21-5p, miR-100-5p), proteins (HSP70, HSP90), and lipids. The vesicular fraction comprises extracellular vesicles, including exosomes (size: 30-50 nm; surface markers: CD63, CD9, CD81), microvesicles (size: 10-1000 nm; surface markers: CD40L, ARF6, VAMP3), and apoptotic bodies (size: 50-5000 nm; surface markers: ARF2, ANXV, ANXA1). The secretome reflects the paracrine activity of hUC-MSCs and mediates their immunomodulatory, regenerative, and signaling functions. MSC = mesenchymal stem cell; hUC-MSC = human umbilical cord mesenchymal stem cell.

strategy owing to its ability to reprogram the TME, inhibit tumor proliferation, enhance apoptosis, and suppress metastasis through a diverse repertoire of paracrine factors (Shojaei et al., 2019; Mirabdollahi and Sadeghi-Aliabadi, 2020). The anti-tumor activity of the hUC-MSC secretome is driven by inhibitory molecules such as DKK-1, P10, and BMPs, as well as cytotoxic factors like TRAIL and TNF-α, which induce apoptosis in malignant cells. The secretome also contains anti-angiogenic and immunomodulatory components that suppress major oncogenic pathways, including PI3K/AKT, Wnt/β-catenin, JAK/STAT, NF-κB, MAPK, and TGF-β/SMAD, thereby reducing tumor survival, metastasis, and Epithelial-mesenchymal transition (EMT) (Hmadcha et al., 2020; Li et al., 2021a,b; Zhang et al., 2025). hUC-MSC secretome also disrupts stromal and vascular components of the tumor niche by inhibiting PDGF/PDGFR signaling to limit angiogenesis and vascular remodeling, while simultaneously suppressing cancer-associated fibroblast activation and enhancing $CD8^+$ T-cell-mediated immune surveillance (Vizoso et al., 2017; Sousa et al., 2023; Merindol et al., 2011). EV-associated miRNAs such as miR-100-5p, miR-145-5p, miR-34a-5p, and let-7 family members further suppress PI3K/AKT/mTOR, STAT3, and Wnt/β-catenin pathways, thereby reducing EMT, proliferation, and chemoresistance while enhancing apoptosis (Lu et al., 2023; Jothimani et al., 2022). The hUC-MSC secretome, exerting coordinated immunomodulatory, anti-inflammatory, and anti-tumor effects by influencing multiple cellular pathways, restoring immune balance, and suppressing tumor-supportive signaling networks, is illustrated in Fig. 2. Despite its robust anti-tumor potential, the hUC-MSC secretome shows context-dependent dual roles in cancer. Reports highlight that MSC-exosomes isolated from different sources, doses, and timings, and across cancer types, may be associated with the dual effect. Studies have suggested that this dual effect of MSC-secretome and MSC-exosomes is mainly due to the variability in conditioning and paracrine effect of MSCs (Xue et al., 2020). Findings from KEGG and secretome analysis by Vaiasicca et al. (2024) highlight that gestational-MSC-derived factors strongly engage WNT, TGF-β, and TNF-α signaling pathways in cancer. While these mediators support immune regulation and anti-inflammatory activity, they can also promote angiogenesis, EMT, and metastasis under certain microenvironmental conditions (Vaiasicca et al., 2024).

4. Applications of hUC-MSC secretome in cancer

hUC-MSCs secretome exhibits a dual nature, depending on the composition of its paracrine factors within the TME (Starska-Kowarska,

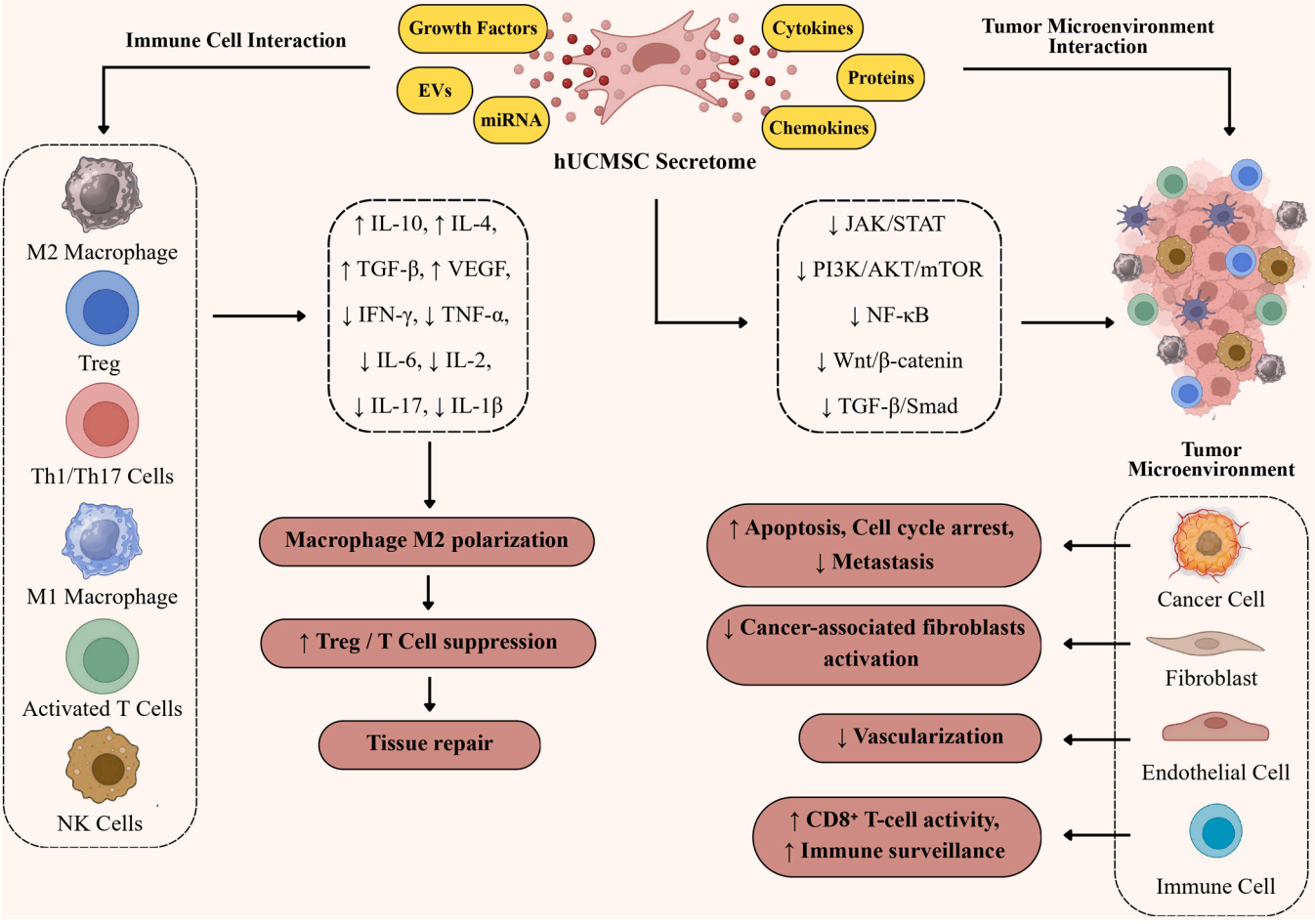

Fig. 2. Immunomodulatory and antitumor effects of the hUC-MSC secretome. The hUC-MSC secretome, comprising growth factors, cytokines, chemokines, proteins, extracellular vesicles (EVs), and miRNAs, exerts dual effects on immune cells and the tumor microenvironment (TME). Immune modulation: The secretome acts on M2 macrophages, Tregs, Th1/Th17 cells, M1 macrophages, activated T cells, and NK cells, promoting M2 polarization and Treg/T cell suppression via modulation of cytokines and signaling molecules (↑IL-10, ↑TGF-β, ↑VEGF; ↓IL-4, ↓IFN-γ, ↓TNF-α, ↓IL-6, ↓IL-2, ↓IL-17, ↓IL-1β), facilitating tissue repair. Antitumor activity: In the TME, which includes cancer cells, fibroblasts, endothelial cells, and immune cells, the secretome inhibits tumor progression by: downregulating oncogenic signaling pathways (JAK/STAT, PI3K/AKT/mTOR, NF-κB, Wnt/β-catenin, TGF-β/Smad); inducing apoptosis and cell cycle arrest while reducing metastasis; decreasing cancer-associated fibroblast activation; suppressing vascularization; and enhancing CD8+ T-cell activity and immune surveillance. hUC-MSC = human umbilical cord mesenchymal stem cell; EV = extracellular vesicle; TME = tumor microenvironment.

2024). The balance between pro- and anti-tumorigenic mediators secreted by hUC-MSCs critically influences tumor progression, as these bioactive molecules can either suppress or facilitate carcinogenesis within the neoplastic niche (Starska-Kowarska, 2024). Exosomes are key functional components of the hUC-MSC secretome with significant therapeutic potential in cancer therapy due to their biocompatibility and drug-carrying capacity (Gemayel et al., 2023; Zhang et al., 2019). Their intrinsic biocompatibility and low immunogenicity enable prolonged circulation and effective tissue penetration, while their lipid bilayer protects encapsulated therapeutic cargos from enzymatic degradation (Ren et al., 2016). Significantly, exosomes preferentially accumulate within tumor tissues via receptor-ligand interactions and the enhanced permeability and retention (EPR) effect, allowing targeted delivery of therapeutics to malignant cells with minimized off-target toxicity and improved therapeutic efficacy (Abbaszadeh et al., 2020; Zhao et al., 2024). Although these features support their translational promise, ongoing comparative analyses are clarifying how exosome origin, dose, and route of administration influence therapeutic consistency. In endometrial cancer, hUC-MSC-derived EVs deliver the tumor-suppressive miR-302a, which is downregulated in EC. Restoring miR-302a suppresses cyclin D1, inhibits AKT signaling, and reduces cancer cell proliferation and migration, consistent with its anti-proliferative and pro-apoptotic roles reported in melanoma, breast, and cervical cancers (Li et al., 2019). Similarly, in colorectal cancer (CRC), (Li et al., 2021a,b) studies demonstrated that hUC-MSCs EVs carrying miR-3940-5p significantly attenuate tumor cell invasion and metastatic potential by downregulating integrin alpha-6 (ITGA6) and TGF-β expression, thereby interfering with EMT signaling (Guo et al., 2022a; Li et al., 2021a,b). In breast cancer, hUC-MSC-derived secretome was shown to reduce VEGF activity by downregulating miR-16 and VEGF mRNA, leading to decreased angiogenesis and tumor proliferation (ElBadre et al., 2023). Similarly, hUC-MSC-derived EVs have been shown to inhibit bladder carcinoma growth by reducing phosphorylation of Akt kinase while increasing cleaved caspase-3 expression, thereby promoting apoptotic signaling in malignant cells (Eiro et al., 2022). Together, these studies underscore the broad anti-tumor activities mediated by MSC-derived EVs, although inter-studies variability indicates that therapeutic effects may depend on the specific molecular cargo enriched under different culture conditions. miR-145-5p, frequently downregulated in multiple cancers including pancreatic ductal adenocarcinoma (PDAC), CRC, and hepatocellular carcinoma (HCC), exerts tumor-suppressive effects when delivered via hUC-MSC-derived exosomes. Ding *et al.* (2017) showed that exosomal miR-145-5p inhibits PDAC proliferation and invasion, induces cell-cycle arrest, and suppresses Smad3 (Yaghoubi et al., 2019). Additionally, hUC-MSC exosomes reduced proliferation, migration, and glycolytic metabolism in HCC and CRC, with miR-486-5p targeting PIK3R1 and neuropilin-2 to impair cancer stemness and metabolic reprogramming (Cui et al., 2024). hUC-MSC-derived exosomal miR-3940-5p inhibits EMT via ITGA6 and TGF-β1 suppression (Li et al., 2019), while miR-320a in lung cancer targets SOX4, blocking Wnt/β-catenin signaling to reduce proliferation, migration, and invasion and promote apoptosis (Xie and Wang, 2022). In ovarian cancer, hUC-MSC-derived exosomal miR-146a restores chemosensitivity by targeting LAMC2 and inhibiting PI3K/Akt signaling, reversing resistance to docetaxel and taxanes (Qiu et al., 2020). Likewise, miR-18a-5p-enriched hUC-MSC exosomes suppress proliferation, migration, invasion, and chemoresistance, reducing tumor growth both *in vitro* and *in vivo* (Wang and Ding, 2023). In HCC, hUC-MSC-derived exosomal miR-451a targets ADAM10 to suppress EMT, reducing invasiveness and enhancing paclitaxel sensitivity, highlighting its potential to improve chemotherapy responses (Dong et al., 2021; Lin et al., 2022).

5. Applications of hUC-MSC secretome in inflammatory disorders

5.1. Inflammatory bowel disease

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition arising from an abnormal immune response in genetically susceptible individuals. Its relapsing nature leads to symptoms such as abnormal pain, diarrhea, and weight loss, while increasing the risk of complications, including strictures, abscesses, and CRC (Din et al., 2024). In UC mouse models, hUC-MSC exosomes downregulate IL-1β and IL-6, suppress macrophage ferroptosis by increasing GPX4 expression, and activate Nrf2 signaling through the delivery of miR-23b-3p, thereby alleviating DSS-induced colitis (Liu et al., 2023). Similarly, hUC-MSC-exosomes enriched miR-378a-5p suppress NLRP3 inflammasome activation in colonic macrophages, reduce IL-1β and IL-18 release along with caspase-1 cleavage, and protect against DSS-induced colitis by limiting pyroptotic cell death (Cai et al., 2021). These mechanistic insights indicate potential anti-inflammatory roles, although their relevance in complex human IBD physiology remains to be fully explored. Beyond UC, hUC-MSC-exosomes also demonstrate therapeutic potential in Crohn's disease-like inflammation. In DSS-induced colitis, exosomes enriched with miR-302d-3p reduced macrophage infiltration, regulated lymph angiogenesis, and inhibited AKT phosphorylation by targeting VEGFR3, revealing a novel immune regulatory mechanism relevant to CD pathogenesis (Zhang et al., 2022). (Wang et al., 2020a,b) demonstrated that hUC-MSC-derived exosomes modulate inflammation by post-translational regulation of cullin1 via transfer of the ubiquitin-like protein NEDD8, thereby modulating the CRL/NF-κB signaling axis to suppress pro-inflammatory cytokine synthesis and release (Wang et al., 2020a,b). Additionally, hUC-MSCs exert anti-inflammatory effects by enhancing T helper 2 (Th2) and regulatory T (Treg) responses, while hUC-MSC-derived exosomes mimic these immune-modulatory properties, reinforcing their potential as a cell-free therapy for IBD (Yang et al., 2021). Through tumor necrosis factor-stimulated gene 6 (TSG-6), hUC-MSC-derived exosomes suppress pro-inflammatory cytokine production and upregulate anti-inflammatory mediators, thereby preserving intestinal barrier integrity and regulating Th2 and Th17 immune responses in mesenteric lymph nodes (Mao et al., 2017). Moreover, mucosal healing, now recognized as a critical therapeutic goal in IBD, encompasses the resolution of inflammation, restoration of epithelial structure, and recovery of mucosal function (Moriichi et al., 2021; Gui et al., 2022). Studies indicate that hUC-MSC-exosomes, upon intraperitoneal administration, can effectively target the intestinal epithelium, where they are internalized by epithelial cells to promote mucosal regeneration (Barnhoorn et al., 2020). In experimental DSS- and TNBS-induced mice colitis models, Liang et al. (2023). demonstrated that hUC-MSC-exosome treatment significantly reduced inflammatory cell infiltration, preserved crypt architecture, and improved epithelial integrity, reflecting significant attenuation of mucosal injury (Duan et al., 2020; Joo et al., 2021; Liang et al., 2023). miRNA profiling revealed that pro-inflammatory hsa-miR-21-5p, typically overexpressed in IBD, was downregulated in hUC-MSC-exosomes while let-7a-5p, let-7f-5p, and miR-100-5p were upregulated (Johnston et al., 2018). The Let-7 family supports intestinal homeostasis by suppressing inflammation and promoting paneth cell differentiation (Guo et al., 2018a,b), whereas miR-100 enhances Wnt/β-catenin signaling by inhibiting its negative regulators DKK1 and ZNRF3, thereby promoting epithelial proliferation and mucosal repair (Barnhoorn et al., 2020).

5.2. Rheumatoid arthritis

Chronic autoimmune diseases such as rheumatoid arthritis (RA) cause inflammation in the synovial joints, which can lead to progressive joint destruction, disability, and systemic consequences. RA is primarily

associated with abnormal immune cell infiltration and synovial inflammation, resulting in an imbalance between anti-inflammatory and pro-inflammatory factors (Guo et al., 2018a,b; Kumar Muruganantham and Veerabathiran, 2024). hUC-MSCs secretome contains potent immunoregulatory molecules, including IL-10, prostaglandin E2 (PGE2), and TGF-β, which collectively suppress pro-inflammatory cytokine production and promote Treg differentiation (Kim et al., 2020). *In vivo* studies using collagen-induced arthritis (CIA) rat models have demonstrated that administration of hUC-MSC-derived exosomes significantly alleviates joint inflammation and cartilage damage in a dose-dependent manner. This therapeutic effect was associated with reduced T cell proliferation, increased apoptosis, and restoration of the Treg/Th17 balance (Xu et al., 2021). Additionally, miRNA profiling revealed that miR-140-3p from hUC-MSCs contributes substantially to the observed anti-arthritic effects in CIA models (Huang et al., 2022). Notably, hUC-MSC EVs exhibit greater efficacy in ameliorating arthritis than MSCs from other tissue sources and even exceed that of conventional disease-modifying antirheumatic drugs such as methotrexate (Shimizu et al., 2023). hUC-MSC-derived EVs modulate immunity by suppressing pro-inflammation, promoting M2 macrophage polarization, and restoring the Th17/Treg balance. Their miRNA cargo reduces fibroblast-like synoviocytes' proliferation and migration, while growth factors and exosomal miRNAs enhance chondrocyte survival, stimulate ECM synthesis, and limit cartilage degradation (Bertolino et al., 2023). Consistently, treatment with hUC-MSC-derived EVs in CIA rat models significantly decreased joint inflammation and histopathological damage. This improvement coincided with elevated levels of anti-inflammatory cytokines (IL-10, TGF-β) and reduced pro-inflammatory IL-17, reflecting a shift toward an immunosuppressive microenvironment (Guo et al., 2018a,b).

5.3. Neurodegenerative disorders

The hUC-MSC secretome supports the CNS by promoting neurogenesis, angiogenesis, and neuronal survival, while reducing apoptosis, glial scarring, and inflammation, thereby enhancing neural repair and functional recovery in various neurodegenerative disorders (Yuan et al., 2023). Recent studies increasingly highlight the strategic potential of intranasal administration of MSC-derived secretomes and EVs for the treatment of neurological diseases (Farfán et al., 2020; Santamaria et al., 2021). While intranasal administration of MSC-derived secretome and EVs has been widely explored across various neurological disorders, studies specifically employing hUC-MSCs secretome remain underexplored. Among the limited evidence available, Thomi et al. (2019) demonstrated that intranasally administered hUC-MSCs exosomes can efficiently traverse the nasal-brain axis, providing preventive neuroprotection, reducing neuroinflammation, and improving functional recovery following perinatal brain injury (Thomi et al., 2019). Their findings support the notion that intranasal delivery of MSC-derived exosomes and bioactive factors, including neurotropic molecules and miRNA vesicles, can bypass the blood-brain barrier via olfactory and trigeminal pathways, thereby enhancing treatment of Parkinson's disease (PD), epilepsy, autism, and neuroinflammatory disorders (Thomi et al., 2019; Wei et al., 2025). Although several studies have identified networks of signaling pathways and transcriptional regulators that control neural progenitor differentiation, the precise molecular mechanisms through which hUC-MSC secretome modulates neural progenitor behaviour remain to be fully elucidated. In multiple sclerosis, an autoimmune demyelinating disorder confined to the CNS and characterized by inflammation, astrocyte proliferation, and neurodegeneration, hUC-MSCs exhibit unique neuroprotective potential (Hauser and Cree, 2020). Compared to BM-MSCs and other sources of MSCs, hUC-MSCs secrete higher levels of neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), and basic fibroblast growth factor (bFGF), along with cytokines including IL-6, IL-8, and IL-11. This neurotrophin-rich secretome confers hUC-MSCs with a stronger predisposition toward ectodermal and neural lineage differentiation (Tesiye et al., 2022). In PD, which involves dopaminergic neuronal loss leading to motor impairments such as rigidity, bradykinesia, tremor, and postural instability, hUC-MSCs exert neuroprotective effects by secreting GDNF and brain-derived neurotrophic factor (BDNF) (Wang et al., 2024a,b). These molecules enhance the survival of dopaminergic neurons, improve synaptic plasticity, and support dopamine metabolism. Furthermore, anti-inflammatory cytokines such as TGF-β and IL-10 within the hUC-MSC secretome suppress neuroinflammation, thereby slowing disease progression (Kandeel et al., 2023). Moreover, hUC-MSC exosomes contribute significantly to neuroprotection by modulating key inflammatory pathways. In disease models of intracerebral hemorrhage (ICH), hUC-MSC exosomes inhibit Toll-like receptor 4 (TLR4) expression, thereby suppressing downstream NF-κB signaling and attenuating excessive neuroinflammation (Wilkinson et al., 2018; Nan et al., 2025). In *in vitro* studies, hUC-MSC exosomes decreased the hemin-induced astrocyte activation and restored mitochondrial function, while *in vivo*, hUC-MSC exosomes alleviate brain edema, preserve blood-brain barrier integrity, and limit neutrophil and macrophage infiltration (Nan et al., 2025). These effects correlate with decreased expression of inflammatory mediators, including IL-1β and TNF-α, and downregulation of TLR4, NF-κB/p65, and p-p65 proteins, collectively improving neurological outcomes in ICH models (Nan et al., 2025). hUC-MSC-derived exosomes also show therapeutic potential in Alzheimer's disease (AD). Ding et al. (2018) reported that intravenously administered exosomes crossed the blood-brain barrier and were selectively taken up by microglia, promoting a shift from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype. This was accompanied by suppression of NF-κB signaling, reduced amyloid-β plaque burden, and improved cognitive function, primarily mediated through exosomal miRNAs and proteins targeting the TLR4/NF-κB axis (Ding et al., 2018). Across cancer, inflammatory, and neurological disorders, the hUC-MSC secretome exerts its effects via paracrine mechanisms, modulating oncogenic signalling, modulating immune responses, and providing neurotrophic and anti-inflammatory support. Together, these mechanisms account for the therapeutic disease-specific impact, which is summarized in Table 1.

6. Challenges and limitations of hUC-MSC secretome-based therapy

Despite the encouraging therapeutic potential of hUC-MSCs and their secretome in regenerative and cell-free therapies, several challenges continue to impede their widespread clinical adoption. Obtaining MSCs in sufficient quantities for clinical use is inherently difficult, as large-scale expansion requires prolonged *in vitro* culture, which often increases cellular senescence, increases the risk of genomic instability, and compromises their therapeutic potency (Wang et al., 2024a,b). Cell-based infusion therapies also carry risks, including microvascular obstruction and embolus formation due to cell aggregation, raising significant concerns about the safety of systemic administration (Coppin et al., 2019). Additionally, donor-related variability, including differences in age, health status, genetic background, and tissue of origin, contributes to significant biological heterogeneity, making it difficult to achieve consistent standardization and reproducibility in cell-based therapeutic applications (Wang et al., 2020a,b; Mastrolia et al., 2019). Evaluating *in vivo* safety, optimal dosage, biodistribution, and therapeutic potency of cell-based therapeutics remains challenging, as infused cells exhibit dynamic behaviors, variable responses to the host microenvironment, and can undergo off-target migration or differentiation (Bashor et al., 2022). Practical limitations, such as complex cryopreservation procedures, the need for continuous low-temperature storage during transport, high production costs, and the restricted availability of large therapeutic doses on demand, further constrain the feasibility and scalability of cell therapy in clinical use (Gostage et al.,

Table 1
Summary of the therapeutic applications of hUC-MSC secretome in cancer and inflammatory disorders. The table highlights the key paracrine factors and EV-associated molecules identified in various disease models, indicating whether their expression levels are increased (↑), decreased (↓), or inhibited (⊥), along with their corresponding mechanisms of action.

Inflammatory disorders/Conditions		hUC-MSC paracrine factors	Mechanistic effect	References
Cancer	Endometrial cancer	↑ miR-302a	↓ Cyclin D1, ⊥ AKT signaling → inhibits proliferation & migration	(Li et al., 2019)
	Colorectal cancer	↑ miR-3940-5p, ↑ miR-486-5p	↓ ITGA6, ↓TGF-β, ↓ PIK3R1 → inhibits EMT, stemness, and glycolysis	(Li et al., 2021a,b; Guo et al., 2022a,b; Cui et al., 2024)
	Breast cancer	↓ miR-16, ↓ VEGF	↓ angiogenesis and tumor growth	(ElBadre et al., 2023)
	Bladder carcinoma	hUC-MSC EVs	↓ p-Akt (phosphorylated Akt), ↑ cleaved caspase-3	(Sousa et al., 2023; Eiro et al., 2022)
	Prostate cancer	hUC-MSC EVs	↓ PI3K/AKT pathway, ↑ p53 expression, ↑ anti-inflammatory cytokines	(Sousa et al., 2023; Yaghoubi et al., 2019)
	Pancreatic ductal adenocarcinoma	↑ miR-145-5p	↓ Smad3 → induces cell-cycle arrest and apoptosis	(Yaghoubi et al., 2019)
	Hepatocellular carcinoma	↑ miR-451a	⊥ ADAM10 → suppresses EMT and increases chemosensitivity	(Dong et al., 2021; Lin et al., 2022)
	Lung cancer	↑ miR-320a	↓ SOX4 → inhibits Wnt/β-catenin signaling → ↓ proliferation and metastasis	(Xie and Wang, 2022)
	Ovarian cancer	↑ miR-146a, ↑ miR-18a-5p	↓ LAMC2, ↓ PI3K/AKT activity → reverses chemoresistance	(Wang and Ding, 2023)
Inflammatory bowel disease	Inflammatory bowel disease	↓ miR-21-5p, ↑ let-7a-5p/ let-7f-5p/miR-100-5p, miR-100	activates Wnt/β-catenin for epithelial repair; regulate Th2 and Th17 immune responses	(Wang et al., 2020a,b; Yang et al., 2021; Barnhoorn et al., 2020; Johnston et al., 2018; Guo et al., 2018a,b)
	Ulcerative colitis	↓ IL-1β, ↓ IL-6, ↑ GPX4, ↑ Nrf2, ↑ miR-23b-3p	activates Nrf2 pathway; reduces ferroptosis and inflammation	(Liu et al., 2023)
		↑ miR-378a-5p	↓ NLRP3 inflammasome, ↓ IL-1β/IL-18 → limits pyroptosis	(Cai et al., 2021)
	Crohn's disease	↑ miR-302d-3p	↓ VEGFR3, ⊥ AKT phosphorylation → reduces macrophage infiltration and lymphangiogenesis	(Zhang et al., 2022)
Rheumatoid Arthritis		↑ miR-140–3p	↓ fibroblast-like synoviocyte (FLS) proliferation and migration	(Huang et al., 2022)
		↑ IL-10, ↑ PGE2, ↑ TGF-β	↓ IL-6 and TNF-α → anti-inflammatory response	(Kim et al., 2020; Xu et al., 2021)
		hUC-MSC EVs	↑ Treg/Th17 ratio, ↑ M2 macrophage polarization → immune homeostasis	(Xu et al., 2021)
Neurodegenerative Disorders	Multiple sclerosis	↑ GDNF, ↑ NT-3, ↑ NT-4, ↑ NGF, ↑ bFGF	promotes remyelination and neurogenesis	(Hauser and Cree, 2020; Tesiye et al., 2022)
	Parkinson's disease	↑ GDNF, ↑ BDNF, ↑ TGF-β, ↑ IL-10	protects dopaminergic neurons and reduces neuroinflammation	(Kandeel et al., 2023)
	Intracerebral hemorrhage	↓ TLR4, ↓ NF-κB/p65, ↓ IL-1β, ↓ TNF-α	Suppress NF-κB signaling, reduces neuroinflammation, and BBB damage	(Wilkinson et al., 2018; Nan et al., 2025)
	Alzheimer's disease	hUC-MSC EVs	↑ miRNAs targeting TLR4/NF-κB axis → ↑ M2 microglia polarization, ↓ Aβ plaques, ↑ cognition	(Ding et al., 2018)

2025). These challenges have driven the exploration of hUC-MSC secretome-based, cell-free therapies as a potentially safer, more scalable, and clinically accessible alternative. However, despite these advantages, secretome-based treatment is associated with inherent biological and technical challenges that must be addressed for effective clinical application. A primary biological challenge lies in preserving the stability and bioactivity of the secretome. Comprising a dynamic mixture of cytokines, growth factors, EVs, and other biomolecules, the secretome is inherently sensitive to degradation under improper storage or transport conditions, potentially compromising its therapeutic potency (Najar et al., 2022). Therefore, the development of optimized preservation techniques and standardized storage conditions is crucial for maintaining its efficacy over time. Another critical issue is the lack of standardization in secretome composition. Variations in MSC tissue source, donor characteristics, culture environment, and processing methods can markedly influence the profile and concentration of bioactive components, leading to batch-to-batch inconsistency and unpredictable therapeutic outcomes (Stepanenko et al., 2018). This variability is conceptually similar to the heterogeneity observed in cell therapy, further emphasizing the need for standardized manufacturing procedures and quality control measures that can reduce inconsistencies across production. Establishing unified protocols for MSC culture, secretome collection, and characterization is thus essential for reproducibility and clinical reliability. Commercial-scale manufacturing requires adherence to good manufacturing practice (GMP) guidelines to ensure safety, purity, and reproducibility. Moreover, cold chain logistics are indispensable for preserving the integrity of temperature-sensitive molecules, adding to production cost and complexity (Ma et al., 2024). Regulatory challenges further complicate clinical translation of secretome-based therapy. Current frameworks for cell-free biologics are still evolving, with ambiguity regarding product classification, safety evaluation, and quality standards. Consequently, obtaining regulatory approval demands extensive preclinical validation and rigorously designed clinical trials, which are often time-consuming and financially demanding (Weiss and Dahlke, 2019). Large-scale, controlled clinical trials are imperative to establish efficacy, elucidate mechanisms of action, and confirm long-term safety in human subjects (Prado-Yupanqui et al., 2025). While hUC-MSC-derived secretome therapy holds immense promise as a next-generation regenerative and immunomodulatory approach, addressing challenges related to biological stability, standardization, scalable production, regulatory approval, and clinical validation will be pivotal for its successful clinical translation.

7. Strategies to enhance the therapeutic potential of hUC-MSC secretome

Enhancing the therapeutic efficacy of the hUC-MSC secretome is crucial for improving its clinical performance in chronic inflammatory disorders. Multiple strategies have been developed to optimize both the quality and stability of the secretome derived from hUC-MSC by modulating the MSC microenvironment and employing advanced bioengineering and culture systems. These methods aim to boost the secretion of anti-inflammatory and immunomodulatory factors while maintaining stability, scalability, and reproducibility for various clinical applications. While hUC-MSCs naturally secrete a wide range of bioactive molecules, several studies have demonstrated that their secretory potential can be significantly enhanced through targeted stimulation or environmental conditioning, collectively termed "preconditioning" (Işıldar et al., 2024). Such interventions include exposing cells to hypoxic conditions, inflammatory cytokines, 3D culture environments, or pharmacological agents that alter their paracrine signaling, as illustrated in Fig. 3. Among these, hypoxic preconditioning is one of the most extensively explored approaches. Culturing hUC-MSCs under hypoxic conditions has been shown to improve their proliferative and migratory behaviour by modulating paracrine signaling pathways and enhancing the secretion of trophic and pro-survival factors (Olcar et al., 2024). This oxygen-deprived microenvironment upregulates genes that support cell survival, angiogenesis, and tissue repair, thereby improving the ability of MSCs to endure harsh *in vivo* conditions following transplantation (Hu and Li, 2018; Harrell et al., 2019). Inflammatory preconditioning represents another powerful strategy to boost the immunomodulatory and secretory functions of MSCs. Exposing cells to inflammatory mediators such as TNF-α, interferon-gamma (IFN-γ), IL-17, TGF-β, activates pathways like NF-κB, MAPK, JAK/STAT, Wnt/β, etc. that increase their capacity to release soluble immunosuppressive molecules, influencing both innate and adaptive immune responses (Gorgun, 2021; Sarsenova et al., 2022; Su et al., 2023). This adaptive process enhances MSC resilience, longevity, and anti-inflammatory efficacy after transplantation. For instance, stimulation with TNF-α or IFN-γ not only amplifies the release of immunoregulatory cytokines but also enhances MSCs' capacity to modulate immune cell differentiation and suppress inflammatory responses (Ferreira et al., 2018; Su et al., 2023). Likewise, hypoxia-based priming promotes the secretion of survival and angiogenic factors such as VEGF, chemokines, and growth factors, allowing MSCs to better adapt to the hostile microenvironment of injured tissues (Li et al., 2023). Another emerging approach involves culturing MSCs in a 3D microenvironment rather than the conventional 2D monolayer. The 3D culture setup, such as spheroids and microbeads, provides a more physiologically relevant context, supporting intricate cell-cell and cell-matrix interactions and improving transcriptional and metabolic activity. This system has been reported to significantly increase the secretion of cytokines and growth factors, such as FGF, TGF-β1, and IL-6, compared to traditional 2D cultures (Tolstova et al., 2024; Kim et al., 2018). Moreover, preconditioning the secretome using pharmacological agents such as chlorzoxazone and rapamycin has been shown to enhance the secretion of bioactive factors, thereby improving its therapeutic potential (Miceli et al., 2021). Upon stimulation, MSCs dynamically

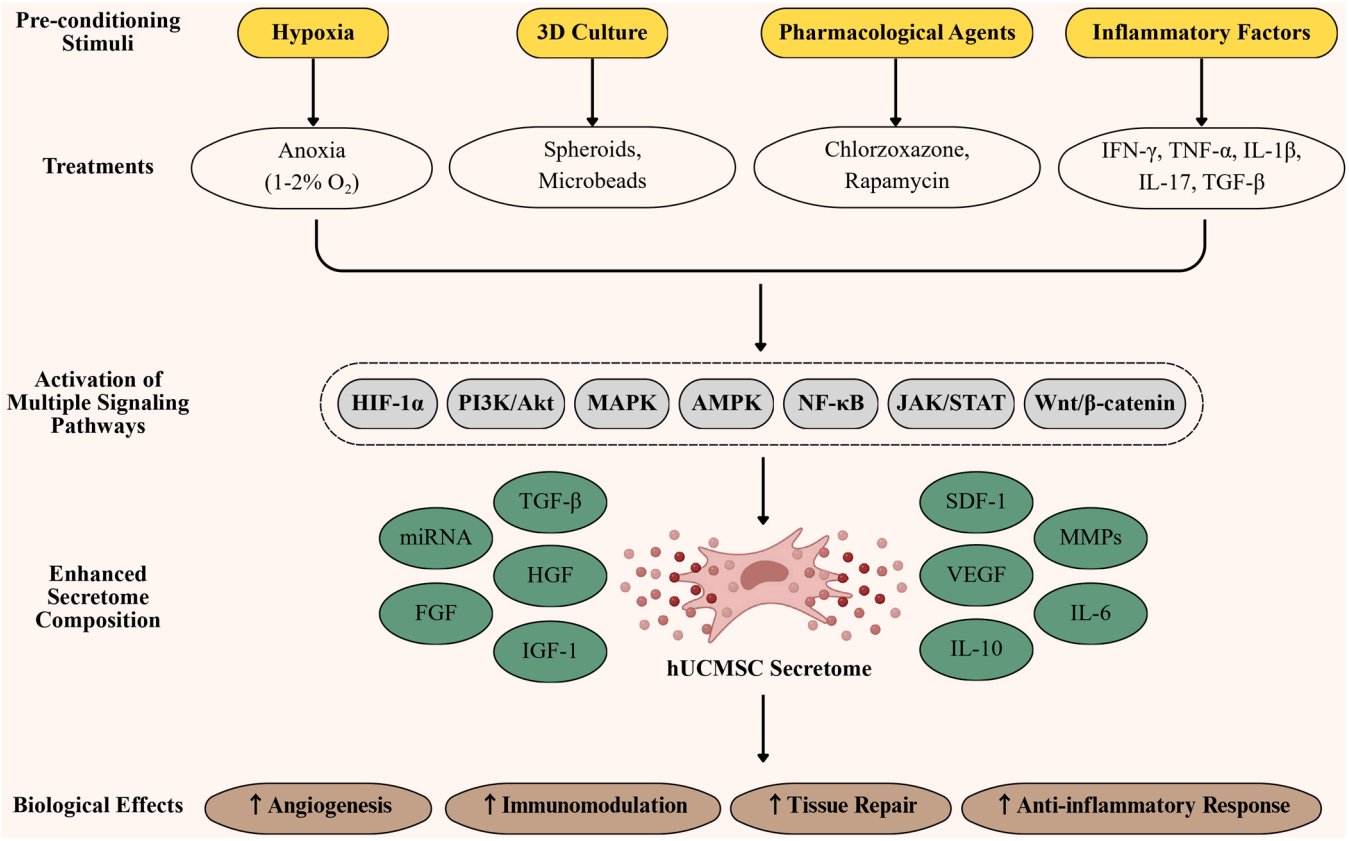

Fig. 3. Strategies for pre-conditioning hUC-MSCs to enhance secretome potency and biological effects. Various pre-conditioning stimuli are used to improve the therapeutic potential of the hUC-MSC secretome, including hypoxia (1-2% O_2), 3D culture systems (spheroids, microbeads), pharmacological agents (chlorzoxazone, rapamycin), and inflammatory factors (IFN-γ, TNF-α, IL-1β, IL-17, TGF-β). These treatments activate multiple signaling pathways in hUC-MSCs, such as HIF-1α, PI3K/Akt, MAPK, AMPK, NF-κB, JAK/STAT, and Wnt/β-catenin. Activation of these pathways enhances secretome composition, increasing levels of bioactive molecules including miRNAs, TGF-β, HGF, FGF, IGF-1, SDF-1, VEGF, MMPs, IL-6, and IL-10. The enhanced secretome subsequently promote biological effects such as angiogenesis, immunomodulation, tissue repair, and anti-inflammatory responses. hUC-MSC = human umbilical cord mesenchymal stem cell; HGF = hepatocyte growth factor; FGF = fibroblast growth factor; IGF-1 = insulin-like growth factor-1; VEGF = vascular endothelial growth factor; MMP = matrix metalloproteinase.

adjust their secretory profile toward an anti-inflammatory, pro--regenerative phenotype that orchestrates transient yet potent tissue repair processes. For example, Yang et al. (2021) have reported that exosomes derived from TNF-α-stimulated hUC-MSCs exerted robust anti-inflammatory effects in UC models, mitigating intestinal inflammation and restoring immune balance (Yang et al., 2021). Hu et al. (2024) performed GO and KEGG pathway analyses, revealing that IFN-γ-primed hUC-MSCs are enriched in immune regulation pathways, while TNF-α-primed cells are associated with chemokine signaling and leukocyte migration; IL-4 priming, in contrast, enhances cell adhesion and ECM-related processes. Another study demonstrated that IFN-γ stimulation enhances the immunosuppressive potential across multiple MSC lines, with morphological parameters correlating with the degree of enhanced immunoregulatory activity (Hu et al., 2024).

8. Future perspectives and translational outlook

The anti-inflammatory and immunomodulatory properties of the hUC-MSC secretome make it a suitable candidate for the treatment of cancer, RA, IBD, and other chronic inflammatory conditions. Engineered hUC-MSC secretome components may further enhance cytotoxic T-cell and NK-cell responses, reduce tumor-associated inflammation, and deliver anti-inflammatory cytokines and miRNAs through exosomes to modulate immune dysregulation. Additionally, miRNAs with neuroprotective and regenerative effects could be harnessed to treat neurodegenerative diseases such as AD and PD, as well as to promote recovery following spinal cord injuries (Brennan et al., 2020). Developing a cost-effective manufacturing process and addressing logistical challenges related to distributing and storing secretome products will be critical to their widespread adoption in clinical practice. In parallel, a comprehensive translational outlook must also address safety, optimal dosing, and pharmacokinetic parameters. Factors such as donor variability, isolation methods, and differences in bioactive cargo can influence both immunogenicity and off-target effects. Moreover, the lack of standardized dosing metrics, whether based on particle counts, protein content, or particle concentration, continues to limit cross-study comparability. While exosomes exhibit relatively predictable yet rapid clearance with organ-specific biodistribution, soluble secretome components follow more complex pharmacokinetic patterns. These challenges underscore the need for systematic dose-response analyses and well-defined pharmacokinetic studies in future research. With advances in personalization, innovative delivery systems, and combination therapies, hUC-MSC-derived secretome could revolutionize the treatment landscape for chronic inflammatory conditions and cancer. Despite promising preclinical outcomes, translating these findings into clinical-grade formulations demands robust GMP-compliant production systems and well-defined quality control parameters. Ensuring batch-to-batch consistency, purity, and potency of secretome-based products is critical to maintaining therapeutic efficacy and patient safety. To achieve this, future research must focus on systematic optimization of secretome production, including refining preconditioning regimens, such as hypoxia, cytokine priming, or pharmacological induction, and implementing bioreactor-based dynamic culture systems that better mimic *in vivo* conditions. These strategies can reproducibly enhance the yield and bioactivity of secreted factors, accelerating the development of secretome-based therapeutics suitable for clinical use (Vizoso et al., 2017; Miceli et al., 2021). Moreover, integrating multi-omics technologies, including transcriptomics, proteomics, and metabolomics, can provide a deeper understanding of the molecular mechanisms driving secretome composition and function (Clark et al., 2022). This systems-level approach could enable the rational design of "next-generation secretome", where the secretion profile is intentionally tuned toward specific therapeutic outcomes such as anti-inflammatory, anti-fibrotic, or pro-regenerative responses. Combining genetic engineering with preconditioning techniques may also allow precise modulation of key paracrine factors to maximize immunomodulatory and regenerative potential (Alvites et al., 2022). Within MSC-based therapeutics, exosome-focused formulations and complete secretome products have emerged as complementary strategies. Exosomes offer a more stable, well-defined, and easily standardized vesicle-based therapy, whereas the broader secretome contains a diverse array of synergistic soluble factors. Their clinical suitability varies according to disease context, regulatory requirements, scalability, and safety considerations. Emerging biomaterial-based carriers, such as EV-loaded scaffolds, injectable hydrogels, and nanoparticle systems, represent promising tools for controlled, localized delivery that reduces systemic clearance and enhances therapeutic precision (Bari et al., 2019; Harrell et al., 2019). These innovations, when combined with 3D bioreactor systems, could pave the way for scalable, cost-effective, and reproducible production pipelines for secretome-derived products. To enable clinical translation, regulatory agencies will require precise definitions of secretome-based products, standardized potency assays, and validated quality control metrics. Early clinical trials must prioritize dose selection, pharmacokinetics, safety, and reproducibility to establish a reliable therapeutic profile (Wang et al., 2025).

9. Conclusion

The hUC-MSC secretome represents a powerful next-generation tool in regenerative and anti-inflammatory therapeutics. By virtue of its rich cytokine, growth factor, and EV composition, the hUC-MSC secretome exerts multifaceted effects that modulate immune responses, attenuate chronic inflammation, and promote tissue repair and regeneration. Recent evidence underscores its therapeutic efficacy across a broad spectrum of chronic inflammatory disorders, including RA, IBD, neurodegenerative conditions, and cancer, through mechanisms that involve the suppression of pro-inflammatory signaling, promotion of angiogenesis and neurogenesis, and restoration of tissue homeostasis. Despite these advances, the translation of secretome-based therapies into clinical practice remains constrained by challenges related to product standardization, stability, large-scale production, and regulatory approval. Preconditioning strategies such as hypoxia, cytokine stimulation, and pharmacological modulation, along with 3D culture systems and bioreactor-based manufacturing, offer promising solutions to enhance the consistency and potency of the secretome. Moreover, the integration of omics-based profiling, genetic engineering, and controlled delivery platforms such as hydrogels and nanocarriers may facilitate precision tuning of the secretome toward disease-specific therapeutic outcomes. hUC-MSC-derived secretome holds immense promise as a cell-free therapeutic platform capable of addressing the underlying mechanisms of chronic inflammation and tissue degeneration. Continued interdisciplinary research combining stem cell biology, bioengineering, and clinical sciences will be pivotal in overcoming existing translational barriers and realizing its full clinical potential. With sustained innovation and regulatory harmonization, hUC-MSC secretome therapies could redefine the future of regenerative medicine and chronic disease management.

Ethics Approval and Consent to Participate

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Consent for publication

All authors have approved the final version of the manuscript and

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CRediT authorship contribution statement

Keerthi Nethaji: Writing – original draft, Visualization. **P Ashiq Shibili:** Writing – original draft, Visualization. **Amit Dey:** Writing – review & editing. **Sibin Nambidi:** Writing – review & editing. **Antara Banerjee:** Conceptualization, Funding acquisition, Writing – review & editing. **Silvia Barbon:** Writing – review & editing. **Surajit Pathak:** Writing – review & editing. **Asim K Duttaroy:** Writing – review & editing

Declaration of Competing Interest

None. All authors declare that there are no conflicts of / or competing interests.

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Data availability

No data was used for the research described in the article.

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