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Exosome-based Therapy

Overcoming challenges in MSC-sEV therapeutics: insights and advances after a decade of research

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A B S T R A C T

Over the past decade, mesenchymal stromal cell-derived small extracellular vesicles (MSC-sEVs) have emerged as promising therapeutics, shifting the focus from MSC engraftment or differentiation to their secretion of sEVs—particularly those under 200 nm—that mediate regenerative and immunomodulatory functions. Transitioning from cell therapies to sEV-based therapies offers clinical advantages, including reduced challenges with cell viability, storage, and administration, and improved pharmacological predictability. However, manufacturing MSC-sEV products faces challenges in defining critical quality attributes (CQAs) for consistent identity and potency. Variability arises from differences in cell sources, culture conditions, enrichment techniques, and the inherent heterogeneity of MSCs. Even the use of immortalized clonal MSC lines may not fully eliminate variability, as factors such as developmental processes, epigenetic modifications, or genetic drift could lead to the re-emergence of heterogeneity. Establishing robust potency CQAs is further complicated by the complex, multimodal modes of action of MSC-sEV products, which involve diverse mechanisms impacting various cell types and processes. Traditional models of EV mediated signalling suggesting direct internalization of sEVs by target cells are increasingly challenged due to inefficient EV-uptake and the high therapeutic efficacy observed. Instead, the Extracellular Modulation of Cells by EVs (EMCEV) model proposes that MSC-sEVs exert their effects by modulating the extracellular environment, enabling a "one EV to many cells" interaction. In conclusion, while MSC-sEV products hold significant therapeutic promise due to their multimodal action and functional redundancy, manufacturing challenges and the complexity of defining potency CQAs remain hurdles to clinical translation. A pragmatic approach focusing on identifying key potency-related CQAs based on specific mechanisms of action—while recognizing that "the process defines the product"—may facilitate the advancement of MSC-sEV therapeutics into clinical applications.

Key Words: MSC-sEV (Mesenchymal Stromal Cell-small Extracellular Vesicles), critical quality, attributes (CQAs), Extracellular Modulation of Cells by EVs (EMCEV), mode of action, (MoA), mechanism of action (MechA).

Introduction: Translation Shift From MSC to MSC-sEV

The discovery of MSC-sEV (Mesenchymal Stromal Cell-small Extracellular Vesicles) has significantly advanced from early observations suggesting that the therapeutic efficacy of MSCs was not reliant on their engraftment or differentiation. A pivotal 2002 review by Chopp and Li already stated that both implantation and intravenous injection of MSCs led to equally rapid functional recovery despite the low survival and differentiation rates of the administered cells [1]. This led to the hypothesis that MSCs which constitutively secrete a variety of cytokines and chemokines such as G-CSF, SCF, LIF, M-CSF, IL-6, and IL-11 [2] repair tissue by secreting trophic factors [3].

Initial efforts to identify these trophic factors focused on small molecules, but a key discovery showed that the therapeutic activity was primarily associated with a fraction larger than 1000 kDa [4]. In 2009, Bruno *et al.* demonstrated that MSC-derived *microvesicles* (80–1000 nm) could mitigate glycerol-induced acute kidney injury in mice [5]. Subsequent investigations focusing on size revealed that vesicles smaller than 200 nm, particularly around 160 nm, were responsible for these renal protective effects [6]. Additionally, Lai *et al.* [7] reported that *exosomes*, a specific type of vesicle measuring approximately 100–130 nm, exhibited therapeutic activity [7]. Multiple studies since then have reinforced

List of abbreviations: MSC-sEV, (Mesenchymal Stromal Cell-small Extracellular Vesicles); critical quality attributes, (CQAs); Extracellular Modulation of Cells by EVs, (EMCEV); mode of action, (MoA); the mechanism of action, (MechA)

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the importance of sEVs, which encompass exosomes and small microvesicles, as significant mediators of MSC-derived therapeutic effects. These studies consistently show that MSC-derived EV enriched samples offer comparable or even superior efficacy to that of their parental cells [5,8,9,10].

Consequently, interest in MSC-EVs—more specifically in small MSC-EVs (MSC-sEVs)—as a novel therapeutic agent increased over the years. The transition from living cell therapies to non-living sEV therapies holds significant potential for clinical translation, as it mitigates challenges related to cell viability during manufacturing, storage, and administration [11]. Additionally, sEVs exhibit more predictable pharmacological activity because they are less susceptible to environmental changes than living cells. Their small size also reduces the risk of embolism, a concern with the intravenous administration of larger MSCs and allows sterilisation of the MSC-sEV product by filtration. However, due to their physical similarity to viruses, standard viral removal methods such as nanofiltration or chromatography, as well as virus inactivation techniques like low pH or heat treatments, cannot be applied to eliminate viruses from the final product. Nevertheless, the risk of viral contamination in sEVs can be effectively managed following the guidelines outlined in ICH Q5A (ICH_Q5A(R2)_Guideline_2023). The primary sources of viral contamination are the source cell lines (cell substrates) and exogenous adventitious viruses introduced during production. To mitigate this risk, a comprehensive viral testing program should be applied to the source cell lines, along with the implementation of validated virus removal and inactivation strategies during production.

Additionally, MSC EVs could potentially be a cheaper option than MSCs for several reasons:

1. Sustained Production: MSC-based therapies rely on primary cells that require continuous replenishment through the isolation of new MSCs and extensive quality control testing. This costly process can be avoided by using immortalized MSC lines to produce EVs.
2. Simplified Harvesting: The extraction of viable MSCs involves cell dissociation, which is more expensive and labor-intensive compared to collecting conditioned medium for MSC-EV production.
3. Easier Storage & Stability: MSCs require cryopreservation at −150°C, whereas MSC-EVs can be stored at −80°C . Additionally, lyophilized EVs have been reported to maintain stability at ambient temperatures, further reducing storage costs.
4. Comparable Dosing Requirements: Both MSCs and MSC-EVs typically require multiple doses for therapeutic applications, but EVs offer logistical advantages in production, storage, and administration.

Manufacturing challenges in translation

Manufacturing MSC-sEV products for clinical applications presents unique challenges, particularly in defining the CQAs crucial for establishing the identity and potency of MSC-sEV preparations. A panel of representatives from organizations including SOCRATES, ISEV, ISCT, and ISBT has recommended that MSC-sEV preparations be characterized by a set of measurable parameters: the concentration of 50−200 nm particles, protein content, abundance of MSC-positive and -negative markers, and the ratio of membrane lipids to proteins. Additionally, assessment of biochemical activity—such as the enzyme activity of an MSC-sEV marker like CD73—should be provided. Collectively, these parameters are intended to define the identity of MSC-sEV products [12]. However, these parameters are still insufficient to fully capture the complexity and variability inherent in MSC-sEV compositions across different manufacturing processes. For example, despite sharing common proteins characteristic of MSCs and MSC-EVs, a meta-analysis revealed significant proteomic differences in MSC-EV preparations from various laboratories [13].

Variations in MSC-sEV compositions can stem from distinct manufacturing practices, such as differences in cell sources; cell culture media and supplements; the nature of the cell culturing process (e.g., two-dimensional vs. three-dimensional cultures); and the methods used for EV enrichment. Notably, the use of biological materials like animal sera or human platelet lysate as cell culture media supplements can profoundly impact the composition of EV populations [14].

Among these factors, selecting an appropriate cell source for EV product manufacturing stands out as a highly empirical aspect of the process. The most commonly used cells for MSC-sEV manufacture are primary MSCs from adult tissues like bone marrow aspirates [15] or adipose tissue [16], or from perinatal medical waste materials [17] such as the placenta [18] and umbilical cord [19] as reviewed. Additionally, MSCs were derived from pluripotent stem cells such as embryonic stem cells [20] and induced pluripotent stem cells [21].

Notably, the advantage of using primary MSCs as sEV source is that their therapeutic potential has been extensively evaluated in clinical research and can easily compared with respective sEV products in the preclinical setting. However, the use of primary MSCs and also MSCs derived from pluripotent stem cells as cellular sources of sEV products presents unique manufacturing challenges. These challenges include inherent heterogeneity and limited lifespan, which can hinder reproducibility and scalability [22,23].

Challenges of primary MSCs as cellular sources of MSC-sEVs

Despite the extensive evaluation of primary MSCs in over 1700 clinical trials, including numerous Phase III studies, only 13 MSC-based products have received market authorization globally—one in Europe and none in the United States in 2023 [24]. Notably, Mesoblast's Remestemcel-L, which demonstrated therapeutic efficacy in a single-arm Phase III trial for pediatric acute graft-versus-host disease (aGVHD) [25] faced two market authorization rejections before finally being approved on December 18, 2024 (FDA, 2024). In contrast, on December 13, 2024, the European Commission withdrew marketing authorization for Alofisel, the only MSC-based product previously authorized in Europe (EMA, 2024). Based on data from another larger study (ADMIRE-CD-II), EMA decided that Alofisel's benefits no longer outweighed its associated risks. These recent events emphasize the importance of robust efficacy and potent CQAs for MSC products to ensure their reliability under real-world conditions.

The FDA's 2020 briefing document on product characterization for Remestemcel-L highlighted a critical manufacturing challenge in this field: the absence of CQAs that are conclusively linked to clinical performance to ensure that the products have consistent acceptable quality fda-briefing-document-on-remestemcel-l-am-session.pdf.

The US FDA has noted that primary MSCs present unique challenges due to their limited expansion capacity and finite lifespan, necessitating the regular production of cell banks from different donors. Because the characteristics and biological activities of primary MSCs vary widely depending on tissue origin and donor, establishing well-defined CQAs is essential. This ensures that new cell banks can be robustly qualified to maintain consistent and acceptable quality.

A key question is whether MSC-sEV products would encounter the same issues of variability caused by tissue and donor heterogeneity observed in MSC products. A systematic literature review revealed that MSC-sEVs exhibit regenerative and immunomodulatory potential independent of the starting material for MSC expansion, EV production, and isolation methods [26]. However, such conclusions need confirmation through direct head-to-head comparisons. In a recent study, Madel *et al.* directly compared MSC-sEV preparations produced in the same laboratory, using either the same or different MSC donors and employing similar methods for MSC expansion and EV

production [27]. They observed differences in *in vivo* and *in vitro* immunomodulatory activities among independent MSC-sEV preparations, even when they used MSCs from same the same cell stocks. This suggests that while MSC-sEV preparations in principle exhibit regenerative and immunomodulatory potential, the quality of this potential may be influenced by intrinsic and extrinsic variabilities in the manufacturing process, including the heterogeneity of MSC cell source. MSCs are highly heterogeneous due to variability among tissues of origin, individual donors, clonal subpopulations, and even at the single-cell level [28,29]. Except for the heterogeneity of the cell source, other variabilities in the manufacturing process can be mitigated by strict adherence to Good Manufacturing Practices (GMP).

The primary reason that the heterogeneity issue of primary MSCs cannot be fully addressed by GMP is their limited lifespan. If primary MSCs had an infinite lifespan, they could be cloned and expanded to generate an infinite supply of identical clonal cells, thereby eliminating cellular heterogeneity. In line with this reasoning, Chen *et al.* proposed immortalizing and cloning the cells to generate an infinite supply of clonal cells to directly address this issue [30]. More recently, this approach has been adopted and successfully used by others [31,32].

Immortalized, clonally expanded MSCs offer the potential for more consistent and scalable production of MSC-sEVs. However, it is important to recognize that even clonal MSC lines may not maintain cellular homogeneity indefinitely. Heterogeneity can re-emerge due to processes such as asymmetric cell division [33], epigenetic changes [34] or spontaneous mutations. To address this, careful selection of monoclonal MSC lines with stable genomic and functional characteristics is essential, though it requires significant time and resources. Maintaining consistent passage numbers across all production batches is critical to minimizing variability; any deviation in passage number would necessitate stringent bioequivalence testing to ensure the product's identity and potency across passage numbers. Due to the inherent heterogeneity of MSC preparations derived from primary tissues or pluripotent stem cells, independently established monoclonal MSC lines are likely to originate from distinct subclones of primary cells. Consequently, even though these cells and their EVs share common MSC and MSC-sEV markers, the lines may exhibit significant differences in their biological properties, as reflected in variations in proteomic profiles and RNA content. Therefore, using immortalized monoclonal lines does not negate the importance of defining MSC-sEV identity and potency through both the manufacturing process and the cell source, underscoring the principle that 'the process defines the product.'

Challenges in establishing potency CQAs for MSC-sEV products

Establishing robust potency CQAs represents a significant challenge in the development of MSC-sEV products [35]. This process requires a comprehensive understanding of both the mode of action (MoA) and the mechanism of action (MechA) of these therapeutic agents, as well as the identification of specific attributes that drive their therapeutic effects [35]. While the terms MoA and MechA are often used interchangeably, they represent distinct concepts in pharmacology.

The MoA describes the general biological and anatomical changes induced by a substance, focusing on its broader physiological or cellular effects, e.g. cell migration, cell proliferation or apoptosis, immune modulation or extracellular matrix remodelling [35–38].

In contrast, the MechA delves into the molecular processes underlying these MoA detailing the specific interactions between the drug and its molecular targets, such as enzymes or receptors. It also explains whether these interactions involve inhibition, activation, agonism, or antagonism.

While identifying the MoAs of MSC-EV products in eliciting specific therapeutic processes is relatively straightforward, the MechA detailing the interaction of MSC-EV attributes and the target molecules that regulate these processes—such as enzymes and receptors—have only been identified and elucidated for a subset of these MechA, as detailed below.

Relationship between mode and mechanism of action of MSC-sEVs

Studies often describe the MoA of MSC-sEV products for specific diseases as multimodal, meaning they impact multiple cell types and processes. However, these observed MoA may not be direct consequences of the MSC-sEVs themselves. For instance, the administration of MSC-sEV products in ischemic stroke and other neurological pathologies is associated with extensive immunomodulation. Various cell types—including immune cells like neutrophils, monocytes, lymphocytes, and microglia, as well as nonimmune cells such as endothelial cells, neural progenitor cells, and astrocytes—have been implicated [9,39]. However, it remains unclear whether this modulation is direct, indirect, or context-dependent. For example, in *in vitro* assays, it is evident that MSC-sEVs influence the activities of monocytes and macrophages as well as of T cell function [40,41]. More detailed analyses have shown that the impact of MSC-sEVs on T cells is mediated indirectly through signals originating from monocytes. In the absence of these cells, MSC-sEVs do not recognizably affect T cell functions [41]. Additionally, Loh *et al.* demonstrated that MSC-sEVs can inhibit neutrophil activity indirectly. Specifically, MSC-sEVs efficiently suppress complement-mediated activation of neutrophils, preventing the secretion of neutrophil extracellular traps (NETs) and IL-17, though they do not affect PMA-mediated activation [42]. This inhibition occurs through CD59, a membrane protein on MSC-EVs that prevents the formation of the terminal complement complex C5b9. These findings suggest that the efficacy of MSC-sEVs on specific cell types depends on their physiological or pathological context, making it challenging to determine which cell types are directly or indirectly affected by MSC-sEVs.

Even if the MoA could be established, it may involve several processes. For example, in MSC-sEV mediated repair of osteochondral defect, multiple action modes have been identified, including increased cellular proliferation and infiltration, enhanced cartilage matrix synthesis, and the promotion of a regenerative immune response [43]. In the case of enhanced cartilage matrix synthesis, there was an observed increase in the production of cartilage extracellular matrix components such as sulfated glycosaminoglycan, type II collagen and type VI collagen, but not fibrotic type I collagen. This suggests that the enhancement of cartilage matrix synthesis is mediated by different and possibly independently regulated processes. Indeed, Zhang *et al.* further demonstrated that phosphorylated AKT, a key signalling molecule, upregulated COL2A but not s-GAG gene transcription, indicating that the upregulation of COL2A and s-GAG gene transcription is mediated by different signal transduction pathways—that is, different MechA [43].

It is possible for MSC-sEV preparations to initiate multiple MechA in a single disease scenario because they carry a diverse cargo of proteins, nucleic acids, and metabolites. This diversity allows them to interact with various cellular targets and drive different mechanisms of action. Identifying and understanding these mechanisms is important for pinpointing potency CQAs and advancing the clinical application of MSC-sEVs [35].

Challenges in validating mechanism of action hypotheses

To validate a MechA hypothesis for MSC-sEVs, it is essential that the concentration and spatiotemporal distribution of the EVs and their active components allow interaction with their targets to produce a timely, pharmacologically relevant response.

Consequently, the spatiotemporal biodistribution of exogenous EVs has been a major area of research, as highlighted in recent

reviews [44,45]. However, this research is often complicated by the nonspecific or variable labelling artefacts associated with the different dyes used to track EVs [46]. This issue is particularly problematic with widely used lipophilic dyes such as PKH or DiR [47–50]. Furthermore, as it was observed for the Exoria dye, even suitably appearing EV labelling dyes may not label all EV populations in MSC-EV products equally well, thus biasing interpretations of biodistribution experiments [50,50]. Moreover, the labelling process itself may compromise the biological integrity of EVs. For example, iodination of MSC-sEVs has been shown to reduce the enzymatic activity of CD73, 5' ectonucleotidase present on the surface of both MSCs and MSC-sEVs [38].

Given the complexities associated with labelling EVs for biodistribution studies, our understanding of EV biodistribution and persistence is still evolving. This necessitates further investigation, along with rigorous validation and reassessment of existing notions. Additionally, reported half-lives of intravenously administered EVs vary considerably—from minutes to days [51–53]. These discrepancies may result from differences in the efficiency of dyes used to label distinct EV subpopulations with varying half-lives or possibly reflect the tracking of the dye itself rather than the EVs. Regardless of their biodistribution, depending on whether the half-life is on the scale of minutes or days, pharmacologically relevant interactions between EVs and target cells could be either highly transient or prolonged measuring in seconds or days, respectively.

In addition to these challenges with spatiotemporal distribution and half-life, the widely accepted notion that EVs interact with target cells by direct internalization and delivery of their cargo into the cytoplasm is increasingly being challenged. Two seminal studies have shown that less than 1% of EVs are internalized by target cells, and of these, only a small fraction escape the endosome to deliver their cargo intracellularly [54,55]. This highly inefficient internalization is now widely recognized, as evidenced by the recent surge in EV engineering efforts to enhance cellular uptake and endosomal escape by incorporating fusogenic proteins such as VSV-G into engineered EVs [56,57]. However, given the extremely low efficiency of less than 1%, any enhancement would need to be substantial—potentially increasing efficiency by several orders of magnitude—to have a meaningful impact. If these observations are universally true for EVs, including MSC-sEVs, such low EV internalization would preclude a mechanism of action that relies on EV internalization.

Despite the inefficient internalization of EVs by cells, MSC-sEV preparations are widely reported to have high therapeutic efficacy in preclinical animal models. For instance, Tan *et al.* observed that a typical intravenous dose of MSC-sEVs per mouse is about 1–10 μg of protein, whereas the corresponding dose for monoclonal antibodies is around 200 μg of protein [58]. This suggests that EVs, which carry hundreds of proteins, are more effective per unit of protein mass than monoclonal antibodies. Such high efficacy challenges the current model of EV-cell interactions, where EVs are thought to either be internalized by cells or bind to cell surface receptors. Even if internalization were highly efficient, it would at best result in a "one EV to one cell" interaction. Instead, the observed efficacy of MSC-sEVs suggests that the MechA involves a different stoichiometric model—likely a "one EV to many cells" model.

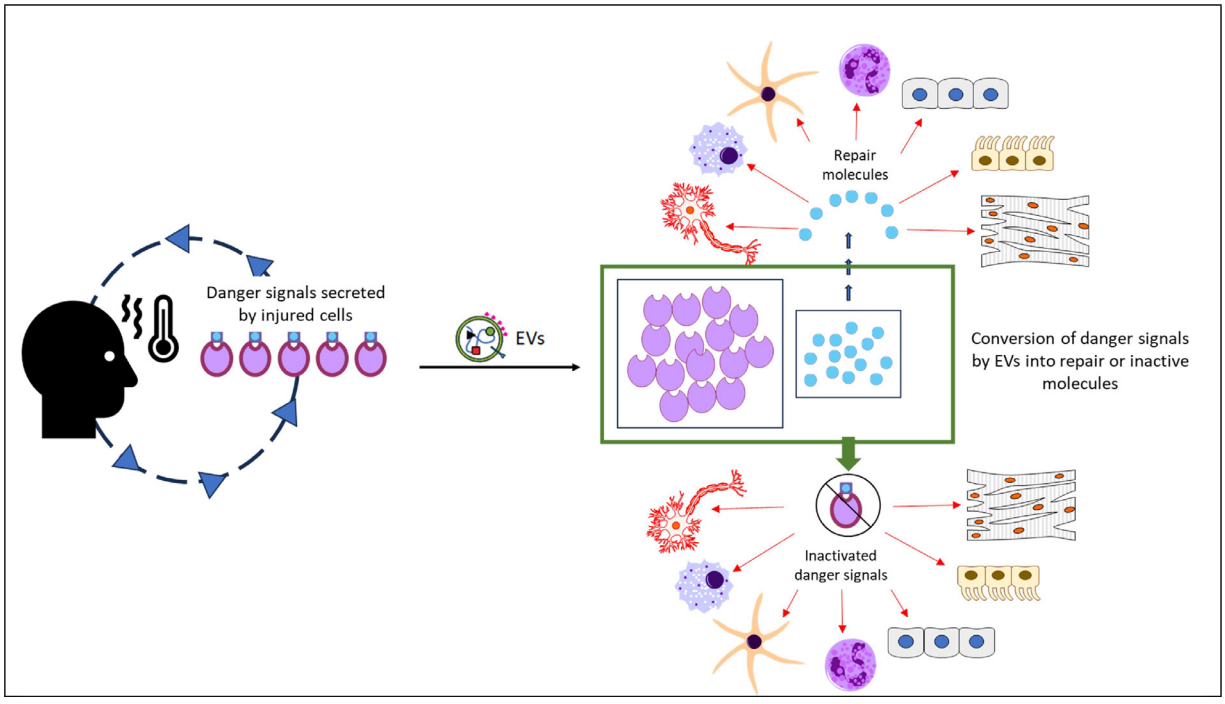

Fig. 1. EMCEV: a model for MSC-EV functional activity through indirect EV-Target cell interactions. When tissue or cellular injury occurs—whether due to disease or trauma—damaged cells release or activate a range of signaling molecules such as inflammatory cytokines, DNA and ATP into the extracellular space to coordinate an effective response to neutralize the primary tissue insult. Many of these molecules serve as danger signals to trigger proinflammatory processes, often amplifying the tissue damage and preventing repair processes. MSC-EVs counteract these harmful effects. There is evidence that MSC-EVs play a role in neutralizing or converting danger-signaling molecules in the extracellular environment into anti-inflammatory molecules or in preventing the transduction of pro-inflammatory signals. A well-established example is the conversion of extracellular ATP into the anti-inflammatory molecule adenosine. In this process, CD73 on MSC-EVs catalyzes the conversion of AMP, a cleavage product of ATP generated by CD39, into adenosine. Another example is MSC-EV-associated CD59, which inhibits the formation of the C5b-9 terminal complement complex. This complex plays a central role in transducing pro-inflammatory signals across tissue-specific blood barriers. Furthermore, MSC-EVs interact with various immune cell types, such as through the TLR-4 receptor, to regulate immune cell activity and promote the resolution of inflammation. These mechanisms likely operate in combination with other activities in a context-dependent manner. From a stoichiometric perspective, it is more plausible that MSC-EVs exert their functional effects primarily within extracellular environments, without requiring cellular internalization. Once the injury resolves and pro-inflammatory molecules return to baseline levels, the activity of MSC-EVs becomes unnecessary and subsequently diminishes. This adaptive mechanism ensures that MSC-EV activity is aligned with the dynamic needs of the tissue, preventing unnecessary or excessive intervention in the absence of injury. (Color version of figure is available online.)

Addressing challenges to elucidate a mechanism of action

To elucidate the mechanism of action of MSC-sEVs, we previously proposed a roadmap that begins by identifying the pathological processes (i.e., MoA) modulated by the EVs and evaluating their alignment with the spatiotemporal distribution of MSC-sEV candidate attributes. This process is followed by establishing a direct cause-and-effect relationship (i.e., MechA) between these MSC-sEV candidate attributes and the modulated biological processes [35].

However, due to challenges with spatiotemporal tracking and half-life of intravenously administered EVs, it may be more practical in the short term to focus on understanding MechA in situations where EVs are locally administered and expected to remain at the administration site, such as intra-articular injections. Intra-articular administration of adeno-associated virus (AAV) has been shown to localize within the articular capsule [59], and a similar localization can be expected for intra-articular administration of EVs.

Current models of EV interactions with cells often focus on direct EV-cell engagement, which fails to fully explain the high therapeutic efficacy. Direct EV-cell engagement implies a restrictive "one EV−one cell" interaction, which does not account for the broader therapeutic outcomes observed. To address this limitation, Tan *et al.* introduced the Extracellular Modulation of Cells by EVs (EMCEV) model [58]. This model proposes that MSC-sEVs exert their therapeutic effects not solely through direct cell contact but by influencing multiple cells indirectly. They achieve this by modulating the extracellular environment, enabling a "one EV-many cells" interaction—a mechanism that better explains the extensive therapeutic impact of MSC-sEVs (Figure 1).

As an illustration of the EMCEV model, Tan *et al.* cite a study where intra-articular administration of MSC-sEVs significantly enhanced collagen type II deposition, aiding osteochondral repair in a rat model of joint injury [43]. Notably, based on the enzymatic activity of CD73 present in the MSC-sEV dose used and the estimated volume of synovial fluid in a rat articular capsule, Tan *et al.* estimated that adenosine—a molecule with potent anti-inflammatory and tissue-regenerative properties [60] could be generated in pharmacologically relevant concentrations of 0.3 to 3.0 uM within seconds. This rapid adenosine production exemplifies how MSC-sEVs may mediate extracellular modifications that facilitate therapeutic effects on multiple cells simultaneously, an effect not limited by the half-life of MSC-sEVs [58].

Another challenge to the validation of the MechA is the redundancy i.e. each MoA could be driven by several MechA. For example, an angiogenesis MoA can be enhanced by several mechanism of action using factors such as VEGF, FGF, Ang-1, Ang-2, TNFα, and MMPs, to singly or synergistically promote vascular growth. Angiogenesis promoting factors have been detected in different MSC-sEV preparations [13] and could potentially provide functional redundancy to ensure that no single mechanism of action is solely critical for an angiogenesis mode of action. This redundancy likely explains why MSC-sEV preparations with different characteristics from various MSC sources can yield comparable therapeutic outcomes.

Conclusion: a holistic perspective of the mode and mechanism of action in the context of MSC-sEV therapeutic potency

MSC-sEVs have shown significant therapeutic potential across a wide range of diseases, as evidenced by both clinical trials and preclinical animal studies. This broad efficacy is largely attributed to the complex cargo carried within or on the surface of MSC-sEVs, enabling a multimodal mode of action. Each mode of action may be mediated by various independent or interdependent MechA. Consequently, different MSC-sEV prepared using different manufacturing processes may exhibit similar efficacy despite variations in potency-related CQAs

While adopting a comprehensive perspective that considers all potential factors and pathways influenced by MSC-sEVs would be ideal for developing potency CQAs, this approach is highly complex and impractical. A more feasible strategy is to focus on identifying key potency-related CQAs based on specific MechA, while embracing the principle that "the process defines the product." This targeted approach recognizes the uniqueness of the processes that produce the product, enabling a comprehensive evaluation of MSC-sEV potency without necessitating exhaustive analysis of every possible pathway.

Declaration of competing interest

BG is a scientific advisory board member of Mursla Ltd. and PL Bioscience as well as a co-founder of Exosia Ltd.

Author Contributions

SKL conceptualized and drafted the manuscript. BG critically reviewed and revised the manuscript.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, B.G. and SKL used ChatGPT to improve the language and readability. Both authors reviewed and edited the content as needed and take full responsibility for the content of this manuscript.

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