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Review Article



# The Advantages of Mesenchymal Stem Cell-Derived Extracellular Vesicles as Drug Delivery Systems

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## Abstract

Extracellular vesicles (EVs) are nanosized particles, secreted by most, if not all cell types, enclosed by a bilayer phospholipid membrane, and mediate crucial intercellular communications by carrying and transporting many active biological molecules. These naturally occurred nanoparticles are emerging as a promising drug delivery system. In particular, EVs from mesenchymal stem cells (MSC-EVs) offer numerous advantages as drug delivery vehicles due to their unique features, as briefly reviewed below in Figure 1.

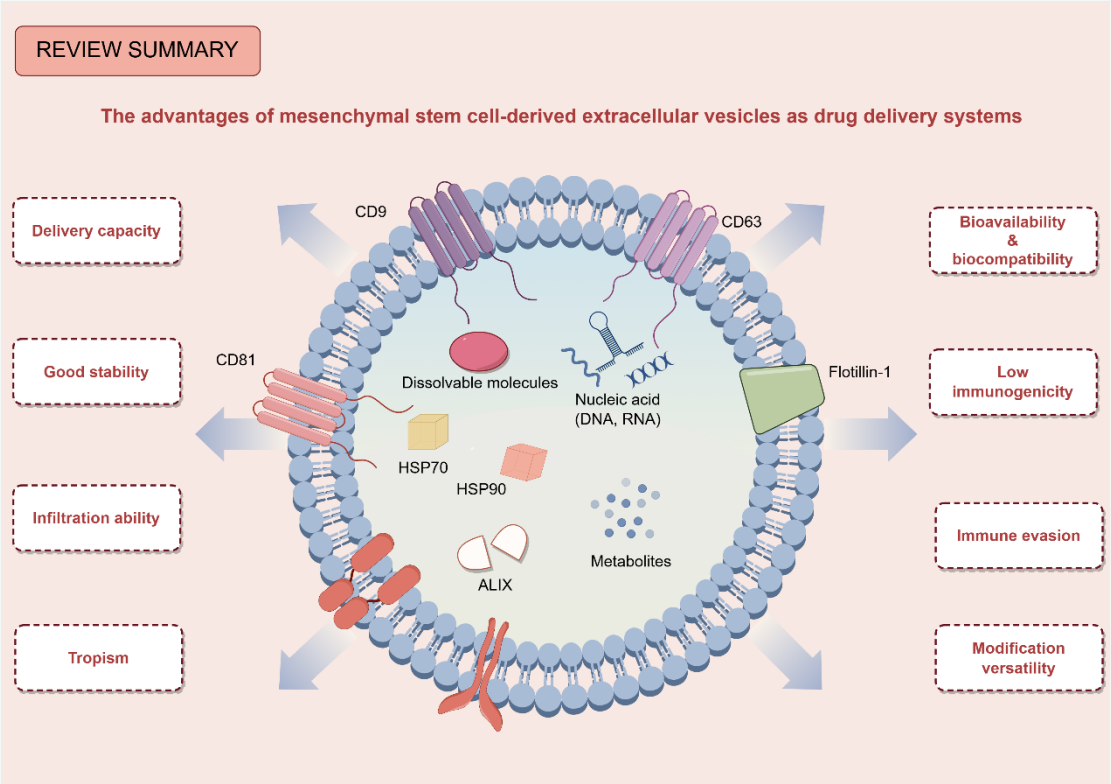


**Figure 1:** Summary of the Advantages of Mesenchymal Stem Cell-Derived Extracellular Vesicles as Drug Delivery Systems.

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## THE CAPACITY TO DELIVER BOTH SOLUBLE CARGOES AND MEMBRANE BOUND THERAPEUTIC MOLECULES

MSC-EVs have the capability to deliver a variety of therapeutic cargoes, including soluble agents like small molecule drugs and RNAs as well as membrane-integrated therapeutic molecules such as proteins and antibodies [1,2]. By encapsulating these therapeutic molecules, MSC-EVs not only enhance the stability and bioavailability of the drugs but also enable co-delivery of synergistic drugs [3,4]. For example, chemotherapy drugs doxorubicin with miR-159 or 5-fluorouracil (5-FU) with miR-21i could be co-delivered for synergistic anticancer therapies [5,6]. Previously we genetically transduced MSCs to express the proapoptotic tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [7] and found the transduced cells secreted EV-membrane incorporated TRAIL

(EV-T) [8]. Further we encapsulated the chemotherapy dinaciclib (Dina) into EV-T to fabricate a complexed nanodrug Dina@EV-T, which overcame TRAIL resistance and showed strikingly augmented anticancer efficacy by either intravenous (i.v.) [4] or nebulized administration [9]. Additionally, the CDK9-targetting siRNA could be loaded into EV-T for precision anticancer medicine [10]. Therefore, MSC-EV mediated co-delivery of drugs enables high efficacy of combinatory therapies.

## GOOD STABILITY BOTH *IN VITRO* AND *IN VIVO*

As the natural drug carrier, MSC-EVs have shown good stability both *in vitro* and *in vivo [9]*. The membrane structure of EVs forms a natural and biocompatible platform to not only protect the enclosed drugs from premature degradation by enzymes and other degradative processes, but also help in maintaining the stability of labile therapeutics. The *in vivo* stability of EVs was proposed to be further enhanced by the coating of an albumin-enriched protein corona and consequent immune evasion [11].

## THE ABILITY TO INFILTRATE AND PENETRATE TISSUES AND THE BLOOD-BRAIN BARRIER

EVs have innate capacity to cross various biological barriers including the blood-brain barrier (BBB) [12]. The tissue permeability of nanomedicines was traditionally assumed to be mainly mediated by the enhanced permeability and retention (EPR) effect. However, the advancements in this area have unveiled a possible transcytosis mechanism, by which EVs can migrate through endothelial cells [13]. This property highlights the attractive potential of EV-based therapies for brain disorders and tumors [14]. Indeed, MSC-EVs have been recently harnessed to successfully deliver therapeutic siRNAs to the striatum of mice brain, leading to the synergistic alleviation of neuronal death in a model of Parkinson's disease (PD) [12].

## TISSUE AND ORGAN TROPISMS

The tropism of MSC-EVs to certain damaged, inflammatory or diseased tissue and organs enable targeted delivery of therapeutic agents [4-15]. This phenomenon is likely mediated by EV surface molecules, such as tetraspanins, latex adhesion proteins, and integrins [16]. As an instance, MSC-EVs showed preferential tropism to animal acute lung injury (ALI), by contrast, HEK293T cells-derived EVs were mainly accumulated in the spleen and liver [17]. The systemically infused MSC-EVs were found to penetrate and accumulate in tumors, suggesting their feasibility for delivery of tumor-targeting therapy. [4] For example, doxorubicin encapsulated MSC-EVs were revealed to home to osteosarcoma via a CXCR4-SDF1 axis, resulting in enhanced anticancer activity [18].

## GOOD BIOAVAILABILITY AND BIOCOMPATIBILITY

Compared to synthetic carriers such as liposomes or other nanoparticles, MSC-EVs demonstrated good biocompatibility and bioavailability as drug delivery systems [1,2]. As carriers, EVs can transport their cargo across cell membranes to specific intracellular locations. Importantly, the lipid membrane structure renders MSC-EVs good biological barrier penetrating capacity, *in vivo* stability, reduced immune clearance, and consequently improved drug delivery efficiency [19]. Furthermore, the low immunogenicity and good tolerability of MSC-EVs allow for their safe use in vivo, minimizing the risk of eliciting adverse reactions [4]. The desirable biocompatibility and bioavailability make MSC-EVs ideal candidates for drug delivery carriers.

## LOW IMMUNOGENICITY AND GOOD SAFETY

MSC-EVs are increasingly recognized for their low immunogenicity, a characteristic pivotal to their therapeutic potential in various diseases [20]. Certain EV surface components, such as galectins, integrins, and tetraspanins, play a masking role from the immune system leading to the low immunogenicity of MSC-EVs [21]. Additionally, the EV surface glycans and lipids also act as key signaling molecules to influence the immunogenicity, with the glycan composition dictating cellular internalization and biodistribution, while lipids contributing to intercellular communication and immune modulation [21]. It is well-known that major histocompatibility complex (MHC) molecules are crucial for antigen presentation to trigger immune responses, thus play an important role for immunogenicity. MSC-EVs have been revealed to be negative for MHC expression, indicating their low immunogenicity [22]. Actually, the systemic administration of MSC-EVs did not cause any adverse side effects on liver function, blood cell counting and organ physiology in experimental animals [4].

In the realm of safety evaluation, the administration of extracellular vesicles (EVs) has demonstrated notable superiority. Preclinical studies have revealed the superior efficacy, safety, and versatility of MSC-EV therapies compared to the MSC therapy, suggesting the satisfactory safety of MSC-EV delivery of therapeutics for disease treatment [23]. Indeed, over 20 completed or ongoing MSC-EV clinical trials have demonstrated good safety and certain efficacies in various diseases.[20] Moreover, in a phase 1 clinical trial, 24 healthy volunteers were administered of $2–16\times10^8$ allogeneic MSC-EV particles by inhalation, and all showed good tolerance to the infusion without any adverse reactions observed [24].

## IMMUNE EVASION

The application of nanomedicine faces a huge challenge, i.e., the rapid uptake and subsequent clearance of nanoparticles from the bloodstream by the mononuclear phagocyte system (MPS) [25]. Interestingly, the integrin-associated protein CD47 was found to express on MSC-EVs [4] and act as a marker of self to prevent clearance by the MPS in the liver and spleen [26]. This feature allows phagocytic evasion of MSC-EVs, and provides an approach for improving pharmacokinetics of therapeutics and thus potentially enhancing therapeutic efficacies. This advantage underscores the versatility and potential of MSC-EVs as a drug delivery vehicle for therapeutic applications [27].

## MODIFICATION FLEXIBILITY

The enclosed lipid membrane structure and specific surface compositions enable flexible modification of MSC-EVs for either the targeted delivery of therapeutics or EV labelling and tracking within cells or tissues. There are various EV surface modification strategies available, including genetic engineering or metabolic engineering of EV-producing cells, click chemistry, ligand-receptor interaction, hydrophobic interaction, and anchoring peptide or aptamer-mediated modifications. [28] Also, different labelling approaches have been developed for EV imaging, pharmacokinetic investigation, or examination of *in vivo* biodistribution, such as bioluminescent, fluorescent, or radioactive labelling. [4-28] Furthermore, both drug pre-loading and post-loading strategies can be applied to engineer MSC-EVs for enhanced therapeutic efficacies. [4-30] Despite the aforenoted versatility and potential, one must be careful to determine MSC-EV modification strategies, considering the modifications may cause undesired immunogenicity, reduced physicochemical stability,

and the biosafety concern.[28]

In summary (Figure.2), MSC-derived extracellular vesicles offer several advantages as drug delivery systems. They exhibit high biocompatibility and low immunogenicity, ensuring safe administration. These vesicles can efficiently target specific tissues and cells, enhancing therapeutic efficacy. Additionally, they are capable of carrying a diverse range of therapeutic molecules, including proteins, RNA, and small molecules. Their nanoscale size allows for easy penetration into tissues, and they can be readily produced and stored, making them a practical option for clinical applications.

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## AUTHOR CONTRIBUTIONS

Z.Q.Y provided the theme and framework for the review, and along with C.H, he was responsible for the final proofreading and editing of the article, as well as the approval of the final version. X.B.K and J.P contributed equally to the drafting and revision, and Y.Y.P participated the writing of the manuscript.

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## CONFLICT OF INTERESTS

The authors declare no any financial, proprietary, or commercial interests in the writing of this article.

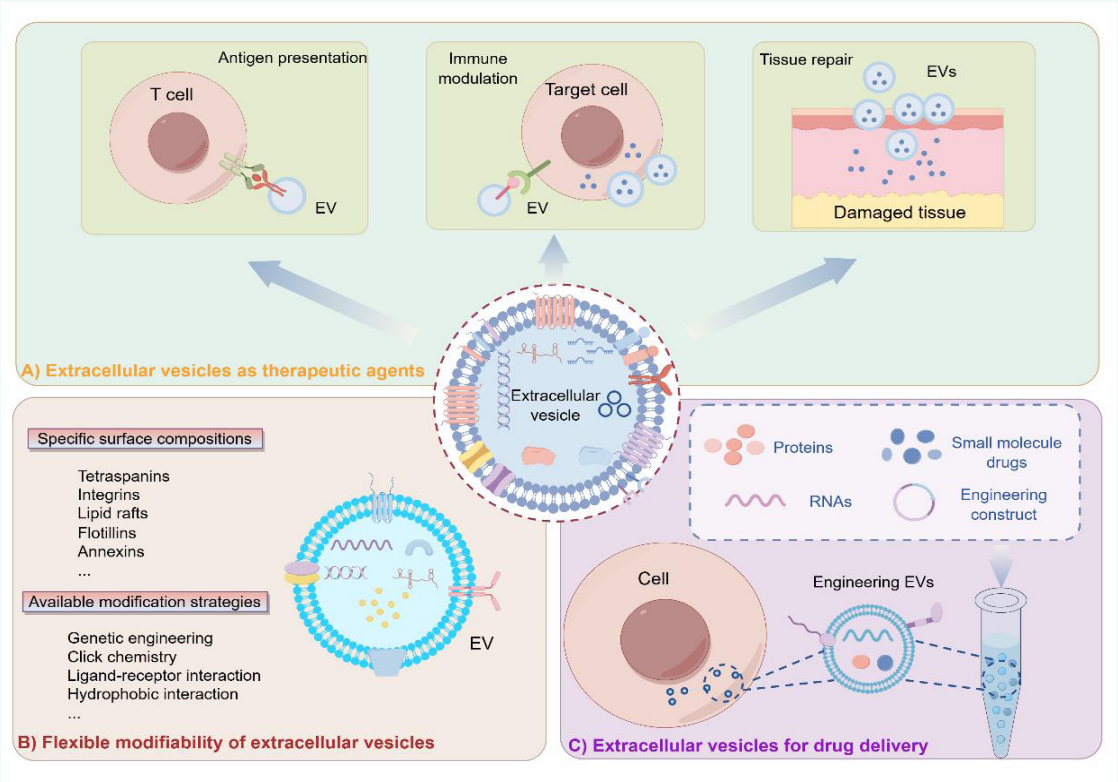


**Figure 2:** Extracellular vesicles mediate antigen presentation, immune modulation, and tissue repair. They can also be used as adaptable drug delivery vehicles and diagnostic tools.

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