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Letter to the Editor

Tailored Drug Delivery against Leishmaniasis: Unleashing the Potential of Engineered Extracellular Vesicles

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To Editor,

Leishmania, a protozoan parasite responsible for debilitating leishmaniasis disease, has emerged as a global health concern, with an estimated 700 000 to 1 million new cases arising annually. Traditional treatment methods for leishmaniasis face challenges like high cost, drug resistance, and toxicity (1). To address these challenges, the researchers are now exploring alternative therapeutic strategies, with one promising avenue being the utilization of extracellular vesicles (EVs). EVs are emerging as a novel drug delivery system that holds the potential to deliver the elevated drug concentrations directly into the infected host cells, thereby minimizing the off-target side effects and protection against *in vivo* degradation.

Modified EVs have been used as effective delivery vehicles for small-molecule drugs, natural products, short hairpin RNA, short interfering RNA, plasmid DNA, and microRNAs (2). *Leishmania* EVs (LEVs) are nano-sized particles secreted by the parasites in their extracellular environment, encapsulating a diverse cargo of proteins, lipids, nucleic acids, metabolites, and glycoconjugates (3). LEVs have been the subject of thorough studies including attempting to investigate their isolation and characterization, understand their cargo composition, and assess their interaction with host cells. These studies have underscored their robust roles in modulating host immunity, influencing disease progression, and facilitating the exchange of drug resistant genes (4). One key aspect of LEVs is their involvement in immune evasion, since previous studies have demonstrated their immunomodulatory effects. These include the inhibition of proinflammatory cytokines production (e.g., TNF-α) and promotion of anti-inflammatory cytokines (e.g., IL-6 and IL-10) (5,6). LEVs create an environment conducive to their survival through manipulating the host immune cells by releasing the parasitic factors (7).

Despite various challenges, researchers are making significant efforts to explore vesicles as a powerful tool for efficient drug delivery. As an avid reader with a keen interest in infectious diseases and drug development, I find the research on LEV-mediated drug delivery especially promising as it holds great promise in advancing the treatment strategies. A recent study by Davari et al highlights the utilization of LEVs for a successful delivery of Amphotericin-B into the host (8). This research illuminates the effectiveness of EVs as nanocarriers for the efficient delivery of antileishmanial drugs. Investigating the *in vitro* release kinetics of Amphotericin B from the ESVs would be intriguing to comprehend the sustained drug release profile and optimize dose regimens. Additionally, assessing the bioavailability of the drug in mouse blood holds merit and is worth exploring further.

A successful delivery of the drug-loaded EVs faces some challenges, including ensuring a targeted delivery to the infected cells, maximizing a drug release at the infection site, and minimizing the adverse effects (9). Fluorescence labeling of EVs is now in practice, which enables investigating their uptake and biodistribution as well as accessing their efficacy in real time (10,11). Utilizing high resolution imaging or flow cytometric analysis for drug-loaded and fluorescence-labeled EVs can enhance our understanding of their bioavailability, *in vitro* cellular interactions and track their bio-distribution *in vivo*. Although manufacturing EVs with therapeutic biomaterials is a promising avenue for the next generation therapeutics, a detailed evaluation of the immunogenicity of the host cells would be advantageous to develop a finely tuned, stimulus-responsive strategy. Monitoring the anti-inflammatory activity of the drug-encapsulated EVs in the host macrophages by cytokine quantification, compared to lipopolysaccharide (LPS) induced macrophages could

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be an interesting option. The EV-encapsulated drug should exhibit a higher inhibitory effect on IL-6 and TNF-α secretion compared to the naked drug. Similar studies on LPS-challenged mice could be valuable, confirming whether the EV-encapsulated drug prevents LPS-induced septic shock in mice.

Engineering EVs require precision to enhance the target specificity, mitigate the host-mediated toxicity, and minimize the transfer of undesirable biomaterials. Additionally, careful consideration of long-term outcomes and potential relapse rates in treated animals, along with pharmacokinetic studies to comprehend the distribution, metabolism, and excretion of the drug-loaded EVs, are parameters that need to be considered wisely.

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Conflict of Interests
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Ethical Issues
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