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Opinion

Plant-Derived Extracellular Vesicles as a Platform for Drug Delivery

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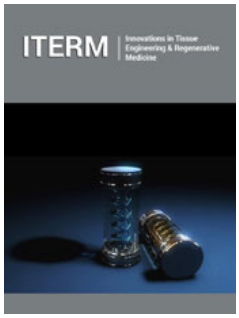

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Submission: January 19, 2023
Published: January 26, 2023

Volume 1 - Issue 5

How to cite this article: Pomatto MAC, and Camussi G. Plant-Derived Extracellular Vesicles as a Platform for Drug Delivery. Innovations Tissue Eng Regen Med. 1(5). ITERM.000523.2023.

Opinion

Originally described in mammalians, extracellular membrane vesicles were found to be present not only in eukaryotes but also in all life kingdoms including prokaryotes and plants [1]. In eukaryotes, these vesicles were found to be secreted by cells as exosomes when derived from the multivesicular bodies or as ectosomes (also called microvesicles) when derived by budding of plasma membrane [2]. The same cell can originate both types of vesicles and since several of their features (including biogenesis, size, and mechanism of action) are largely superimposable and difficult to distinguish, it has been suggested to collectively call them as Extracellular Vesicles (EVs) [3]. EVs are constituted by a bilayer lipid membrane derived from the cell of origin incorporating molecular messages that can be shared with cells in a paracrine way [4]. Of interest, the membrane of EVs provides protection from enzyme-mediated degradation of their molecular content, including nucleic acids. It has been shown that EVs may allow a horizontal transfer of functional mRNA naturally carried by EVs as well as exogeneous mRNA incorporated in EVs [5]. Subsequent studies extensively investigated native or engineered EVs as carriers for mRNA, noncoding RNA, and DNA for regenerative purposes [4]. In particular, stem cell-derived EVs were shown to mimic the pro-regenerative activity of the cell of origin based on the transfer of transcripts that target pathways in the injured recipient cells [6]. In order to generate EVs specifically targeting defined pathways, their cargo modification was obtained by genetically engineering of the cell of origin or by various methods of chemically/mechanically induced modification of EV membrane [3,7-10]. Multiloading methods have been also developed enhancing the exploitation of EVs for drug delivery [11] but the manufacturing yield of EVs still represents a limitation to overcome.

EVs have been described also in plant kingdom [12]. Little is known about the mechanism of biogenesis and function, but their structures and sizes are very similar to the ones of eukaryotes [13] (Figure 1). Plant-derived EVs can be extracted from different parts of plants and they are particularly enriched in plant-derived juices. Plant EVs, being an extractive product, can be a good option for scalable EV production for drug delivery purposes. In particular, EVs derived from edible plants are non-toxic and, due to the mechanism of oral tolerance, they are also not immunogenic [13-15]. Edible plant-derived EVs have been shown to play a role in a crosstalk between the plant and eukaryotes kingdoms [16]. In humans, plant EVs absorbed through the intestinal tract may transfer molecules that modulate pathways in the recipient organisms with influence on health [16]. The properties of plant EVs to protect nucleic acids (microRNAs, small interfering RNAs, RNAs, DNAs), to reduce toxicity of drugs as well as to improve the absorption of poorly soluble compounds (for instance curcumin and liposoluble vitamins) represent key factors to make them an optimal drug delivery platform [17-21].

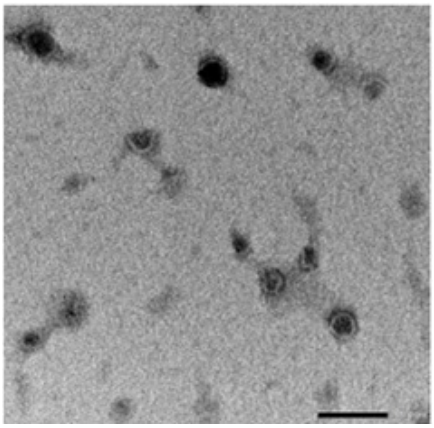

Figure 1: Transmission electron microscopy of EVs derived from edible plant (Citrus sinensis). Scale bar 100nm.

Using a proprietary technique of EvoBiotech (WO2022152771A1), we engineered EVs obtained from Citrus sinensis juice with SARS-CoV-2 mRNA coding for S1 subunit, Full Spike and N proteins to develop nucleic acid based vaccines. Our data demonstrated the functionality of edible plant-derived EVs as drug carrier for mRNA vaccines and their ability to induce immune stimulation direct against the specific antigen. Previous studies supported the use of EVs as possible vaccine carrier demonstrating that EVs derived from engineered cell lines may express a recombinant S protein on their surface suitable for inducing an immune response [22]. Despites difficulties in manufacturing scalability, EV-based vaccines have advantages in conferring long lasting immunization and lower toxicity than synthetic nanoparticles. In addition, EVs may present the viral antigens in their natural configuration to the immune system [23]. In this context, plant-derived EVs are superior to those derived from cultured cells being a natural, abundant and easily extractable product, more suitable for mRNA delivery in clinic. We found that, after incorporation into plant EVs, mRNA was stable in chemical stress condition and storable at room temperature after lyophilization. Plant EVs conferred resistance to mRNA molecules against RNA degradation and simulated gastric juice. The immunization of multiple rodent models (mice and rats) via different routes including intramuscular, oral and intranasal elicited a humoral and T cell mediated immune response. Of interest, the oral and intranasal administration not only triggered IgM and IgG but also an IgA mucosal immune response.

Conclusion

In conclusion, the development of an EV based anti-COVID mRNA vaccine may represent a prototype for a platform of therapeutic delivery of nucleic acids. The stability and bioavailability of nucleic acids incorporated in edible plant EVs suggest that this natural extractable product may represent a good option for drug delivery, especially suitable for oral administration.

Conflict of Interest

Authors are associated with EvoBiotech s.r.l. and named as inventors in EV related patents.

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