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Editorial

Trapping extracellular vesicles from biofluids by hydrogels

Extracellular vesicles (EVs), with a diameter of 30–1000 nm, are secreted by various cells and possess a lipid bilayer membrane structure [1]. EVs contain RNAs, DNAs, lipids, and proteins from the cells of origin, and play a crucial role in cell-to-cell communication [2,3]. They are considered as disease biomaker carriers, bioactive drugs, and therapeutic agent delivery platforms, which may be used in disease diagnosis, cosmeceuticals, and clinical treatments. Although the importance of EVs has become prominent, no single approach satisfies all the four aspects of efficiency, accessibility, scalability, and customizability simultaneously for efficient EV isolation, hindering the use of EVs in further investigations and practical applications. Ultracentrifugation (UC) and density-gradient UC, which are traditionally regarded as the gold standard for EV isolation [4], are primarily limited by expensive equipment and time-consuming and complicated processes [5]. Other EV isolation methods, including size-exclusion chromatography, polyethylene glycol (PEG)-based precipitation, and immunoaffinity-based isolation, are limited by complex handling steps and additional reagents or labeling [6,7]. Emerging microfluidics-based EV isolation technologies, which possess increased analysis sensitivity and provide automated and integrated platforms, are limited by low yield and risk of microfluidic channel blocking [8].

Now, writing in *Nature Nanotechnology*, Kim *et al*. designed *meso*-macroporous hydrogel particles by cryo-photocrosslinking polyethylene glycol diacrylate (PEGDA) for directly isolating EVs from diverse biofluids without pre-processing [5]. Specifically, the *meso*–macroporous hydrogel particles could capture EVs into their pores of ~400 nm, aggregate EVs by the high ionic strength of the high-concentration salt solution, and release EVs after treatment with low-concentration salt solution (Fig. 1), upgrading the EV isolation from a biofluid volume of microliters/milliliters to that of liters. In addition, the *meso*–macroporous hydrogel matrix could serve as a solid-phase carrier for achieving long-term EV storage and supporting on-demand downstream analyses. The *meso*–macroporous hydrogel technology could act as a multi-scenario EV isolation platform to assist diverse EV-related studies, ranging from fundamental research to practical applications.

The authors focused on the transport mechanism of EVs to conduct materials design. Cyro-photocrosslinked *meso*–macroporous hydrogel particles could capture the particles with sizes of <400 nm while excluding impermeable particles. The mobile PEG chains of PEGDA could actively capture EVs with a specific surface charge, and a high ionic strength environment (*i.e.*, the solution containing 1.5 mol/L NaCl and 20 mmol/L HEPES) could diminish intervesicle repulsion, inducing the aggregation and capture of EVs within the gel. More remarkably, the surface charge differences between EVs and the permeable impurities could help repel permeable non-EV impurities (*e.g.*, very low-density lipoprotein and low-density lipoprotein), improving the purity and yield of EVs relative to those obtained by conventional microporous gels. To be noted, the designed hydrogel particles possessed a relatively large diameter (5 mm), which enabled the convenient transfer of these particles between tubes without centrifugation. From fabricating hydrogel particles to EV isolation, this EV isolation procedure showed robust reproducibility under the conditions of using different batches of hydrogel particles or operating by different individuals. Next, the authors comprehensively characterized the isolated EVs using multiple experiments (including nanoparticle tracking analysis, Bradford assay, Western blot, proteomics, and RNA sequencing). Compared with the well-established EV isolation methods (*i.e.*, UC and density-gradient UC), the newly developed method exhibited higher/comparable EV isolation efficiency and EV purity. To be noted, the lipoproteins and other impurities were markedly reduced compared with the positive controls. In general, the authors demonstrated that their proposed EV isolation approach has the following advantages: (i) Efficient and pre-processing-free EV isolation from various biofluids, including whole blood, plasma, ascites, saliva, urine, bovine milk, and cell culture media, where the hydrogel outperforms UC in yield with comparable purity and shorter time consumption; (ii) Liter-scale EV isolation which was demonstrated by the experiments of extracting EVs from 1 L bovine milk and 1 L ascitic fluid, acquiring three orders of magnitude more EVs in equivalent runtime without significant changes in size distribution, yield, and purity; (iii) Custom enrichment and speed control by adjusting the size of hydrogel particles and the off-gel recovery volume); (iv) The EV preservation by *meso*-macroporous hydrogel particles can maintain a relatively stable yield at room temperature within 60 days, compared to the traditional method which shows the decline of yield by ~80% when stored at –20 °C and by ~40% after –80 °C at 8 weeks [9], extending EV application scenarios by transcending the spatiotemporal limits.

Furthermore, the authors evaluated the application potential of the hydrogel-based EV isolation in downstream domains. For the therapeutic and cosmeceutical applications, the milk-derived EVs isolated by the hydrogel were found to be capable of stimulating human dermal fibroblast proliferation and decreasing the oxidative damage of human keratinocytes. An equal-particle-number analysis revealed that the EVs obtained from UC isolation may perform

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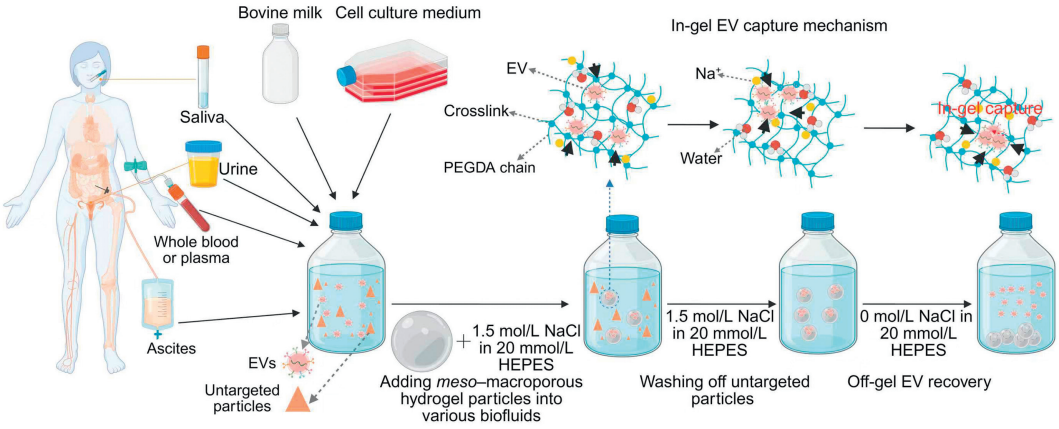


Fig. 1. Hydrogel-based EV isolation. Conventional methodologies for EV isolation require complicated pre-processing and are thus limited by productivity. To overcome these challenges, Kim and colleagues designed *meso*–macroporous hydrogel particles for directly isolating EVs. The in-gel capture mechanism (top right) of this approach is attributed to the combined effects of the PEG chains in the gel phase (forming a three-dimensional network to capture EVs with a specific surface charge) and the high Na^+ concentration (diminishing the repulsive interaction between the EVs for improved aggregation). After being washed with high salt concentration solution (containing 1.5 mol/L NaCl and 20 mmol/L *N*-2-hydroxyethylpiperazine-*N*-2-ethane sulfonic acid (HEPES)) and subsequently incubated with a low salt concentration solution (containing 0 mol/L NaCl and 20 mmol/L HEPES), the EVs can be efficiently collected from the *meso*–macroporous hydrogel particles (bottom right). This figure was created with BioRender.com.

slightly better functionality compared with those isolated by hydrogel, but the hydrogel-based isolation method yields far more EVs per unit time and volume. For the diagnostic and prognostic applications, the authors found that the urinary EVs captured by the hydrogel can support ratiometric microRNA (miRNA) detection and discriminate prostate cancer from healthy controls, illustrating how direct, high-throughput EV isolation facilitates the disease diagnosis.

As for any prospective technologies, thoughtful verification and investigation shape the road from laboratory to practical application. The actual deviation in large-scale production may reduce EV purity and amplify EV subpopulation biases. Therefore, besides changing the salt solution concentration, other strategies for EV capture and recovery with desirable biosafety and controllability can be developed to achieve EV in-gel capture and off-gel recovery. Although the authors evaluate the EV isolation capacity of the *meso*–macroporous hydrogel in whole blood, plasma, ascites, saliva, urine, bovine milk, and cell culture media, the applications of the hydrogel-based isolation method in more scenes, such as EV isolation in the cerebrospinal fluid and synovial fluid (which is from the joint cavity), bacteria- or plant-derived EV isolation, EV isolation in the high-temperature matrix, subpopulation-selective or individual EV isolation during high-throughput analysis, and *in-situ* EV isolation from living organisms, deserve further confirmation. The viscosity and protein loads between diverse biofluids are different, and setting biofluid-specific standard operation procedures (*e.g.*, capture time, salt solution concentration, wash time, and recovery volume) will be essential for clinical and practical applications. If these concerns can be addressed in the authors' manufacturing roadmap, *meso*–macroporous hydrogels may break the limitation caused by complicated operations in current EV isolation, realize the upgrade from batch EV isolation process to column-based continuous EV isolation process, and facilitate the transition from laboratory to industrial applications.

In addition to the viewpoints above, the researchers who focus on cancer neurotherapy and immunotherapy pay more attention to whether this *meso*–macroporous hydrogel that can directly isolate EVs from biofluids can be applied to collect/release EVs *in situ* in the tumors to block/enhance cell-to-cell communication. Increasing evidences have shown that cell-to-cell communication between nerve cells and tumor cells can promote the occurrence and development of cancer [10]. Therefore, developing tools to capture specific EVs (*e.g.*, the tumor-secreted EVs) *in situ* may help block the tumor–nerve interaction and achieve efficient suppression of tumor growth and invasion. In addition, the lack of therapeutic effect of immunotherapy on solid tumors and "cold" tumors may be caused by insufficient interaction between immune cells and tumor cells [11]. Thus, we propose that presenting tumor cell EVs to immune cells *in situ* (achieved by rational design of EV-capturing tools and/or suitable guidance under external stimuli) may facilitate the initiation of anticancer immune responses. Moreover, many other diseases, such as the autoimmune diseases which may be caused by the overly close interaction between normal cells and immune cells, the neurological disorders possibly induced by irregular communication between normal cells and neurons [12], and regenerative dysfunction attributed to insufficient contact between damaged cells and various functional cells (*e.g.*, vascular cells, neutrophils, and stem cells), may benefit from the *in-situ* EV capture/release therapy by regulating the communication between these different cells. However, the advancement of *in-situ* EV capture/release therapy is still challenged by several important issues (including the capture of specific EVs, controllability of EV delivery and release, and material biosafety), and therefore more comprehensive consideration and careful evaluation are further required. Overall, we believe that the development of efficient and safe strategies for *in-situ* extracellular vesicle manipulation may significantly promote the clinical application of next-generation disease therapies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yang Liu: Writing – original draft, Conceptualization. **Zi-Xi Wang:** Writing – review & editing. **Fu-Gen Wu:** Writing – review & editing, Conceptualization.

Yang Liu
Zi-Xi Wang
Fu-Gen Wu*
State Key Laboratory of Digital Medical Engineering, Jiangsu Key Laboratory for Biomaterials and Devices, School of Biological Science and Medical Engineering, Southeast University, Nanjing 211189, China

*Corresponding author.
E-mail address: wufg@seu.edu.cn (F.-G. Wu).

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