A roadmap to improve the reproducibility of extracellular vesicle research

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Extracellular vesicles (EVs), about 50 nm to 1 µm membrane-delimited particles, are released by cells into their environment. EVs are present in for example body fluids and conditioned culture media.

EVs in (human) body fluids may play a role in intercellular communication, cellular waste mangement, and protection. Since the cellular origin, concentration, biochemical composition and/or function(s) of EVs change in diseases such as cancer, EVs have become a hot topic of clinical biomarker exploration.

From the thousands of papers now published on EVs annually, one gets the impression that EVs provide biomarkers for all diseases, that EVs are carriers of all relevant biomolecules, and that EVs are omnipotent therapeutics[1]. At the same time, however, EVs are heterogeneous and difficult to study due to their physical properties and complexity of their environment. That EVs are difficult to study can be illustrated by the concentration of EVs in normal human plasma, which ranges over 10^8-fold between the lowest and highest reported concentration. Obviously, without improving the comparibility of EV measurement results, clinical applications and multi-center studies are impossible.

I will try to explain the challenges encountered when working with EVs, and how these challenges can be overcome. At present, an infrastructure is developed to improve the reproducibility of EV measurement results. This infrastructure comprises expert task forces of International Society for Extracellular Vesicles (ISEV) developing minimal requirements, guidelines and recommendations[2], procedures to calibrate instruments[3], interlaboratory comparison studies[4], standardized and transparent reporting[5], and education.

Together these developments will support the credibility of EV research by promoting reproducibility, which is a requirement for exploring the biomarker potential of EVs.