Serum exosomes mediate delivery of arginase 1 as a novel mechanism for endothelial dysfunction in diabetes

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Yu Huang's from CUHK and Associate Prof. Zhang HuiNa (张慧娜) from Beijing Anzhen Hospital and Beijing Institute of Heart, Lung and Blood Vessel Diseases corporately reported the new role and related mechanism of serum exosomes in diabetic endothelial dysfunction. This article was recently published in *PNAS* (2018, 115(29): E6922-E6936).

Endothelial dysfunction plays a crucial role in the development of diabetic vasculopathy, but the mechanisms are not fully understood. The endothelial function is always affected by blood-borne substances because of the specific location of endothelial cells as the protective screen of blood vessels. Exosomes, endosome-derived nanoscale membrane vesicles in the extracellular fluid compartment via exocytosis, always mediate the cell-cell communication through delivering various molecules (RNA, protein and lipid) from donor cells into recipient cells. Thus, exosome can effectively affect the function of recipient cells. Through this way, exosomes participate in most of the biophysical and pathological processes. Serum exosomes physiologically have high contacting frequencies with endothelial cells. Research about the effect of serum exosomes on the endothelial function shows that it is easier to mimic the physiological status, which will be of greater pathological significance and clinical value. This study found that serum exosomes from *db/db* mice (*db/db* SExos) were taken up by aortic endothelial cells, which severely impaired endothelial-dependent relaxation in non-diabetic db/m^+ mice. Comparative proteomics analysis showed significant increase of arginase 1 in *db/db* SExos. Silence or over-expression of arginase 1 revealed its essential role in *db/db* SExos-induced endothelial dysfunction through affecting NO generation.

In summary, this study confirms a new mechanism by which diabetic mouse SExos induce endothelial dysfunction through delivering exosomal Arg1 to reduce NO bioavailability in endothelial cells in diabetic mice. This research unravels a new pattern for the translocation and function of arginase 1. Meanwhile, the research proposes a previously undefined importance of serum exosomes in the regulation of endothelial function and vascular homeostasis, which may give new perspectives to improve the therapeutic strategy of diabetic endothelial dysfunction in clinical trial.

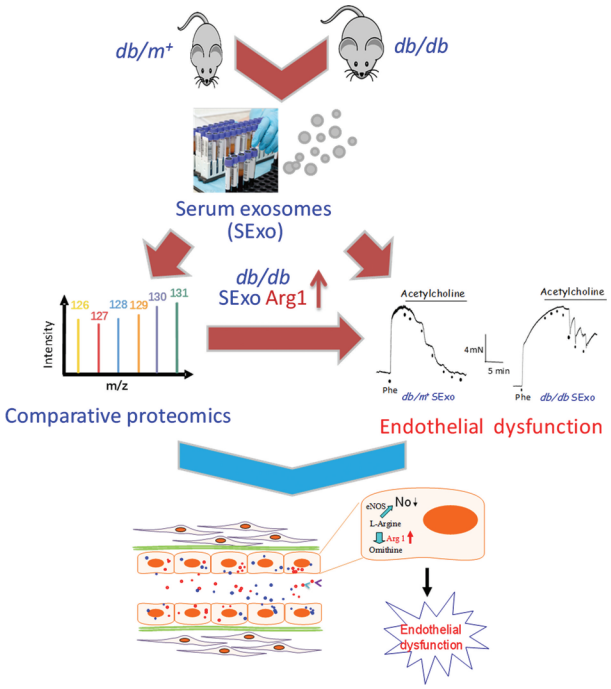

Figure The proposed role of SExos in diabetes-associated endothelial dysfunction. *db/db* mouse serum exosomes are absorbed by endothelial cells and subsequently impair endothelium-dependent relaxations through inhibiting NO generation via transfer of more exosomal Arg1 to endothelial cells.